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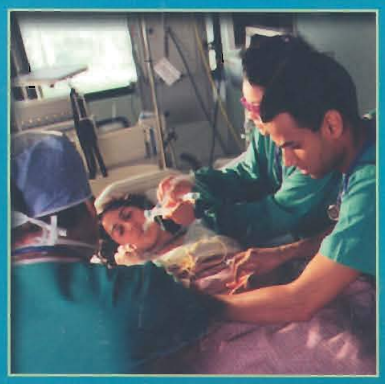
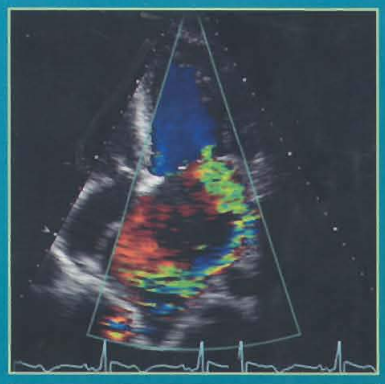
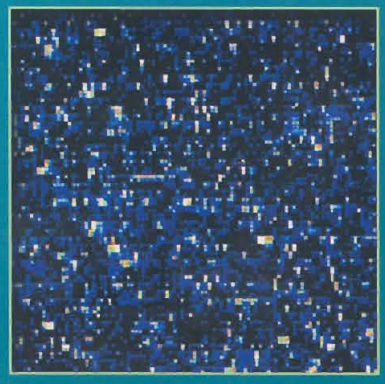
Textbook of CRITICAL CARE

FIFTH EDITION







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همگام با توسعه علمی و فرهنگی جهان معاصر و استفاده روزافزون کامپیوتر در بین جوامع بشری خصوصاً رشته‌های مختلف علوم و استفاده بهینه از آخرین یافته‌های پزشکی دنیا و ارائه این یافته‌ها در قالب نرم‌افزارهای پزشکی (*ebook* ، *VCD* ، *DVD* ، *VHS* و ...) ما را بر آن داشت که با گردآوری و ارائهٔ این یافته‌ها گامی کوچک در راه ارتقاء سطح علمی متخصصین کلیه رشته‌های پزشکی کشور به صورت سمعی و بصری برداریم. امید است مشوق ما در این راه باشید.

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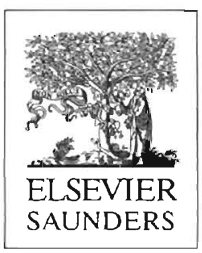

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DEDICATION

To my beloved wife, Jan, and my two wonderful children, Emily and Matt, for tolerating my long hours away from home; and to my wonderful parents, Walter and Betty Fink, for providing me with a stable and supportive environment during my formative years.

–Mitchell P. Fink

To Norma-May, the love of my life, and to Claire and Erin, who bring me the greatest joy each day.

–Edward Abraham

To Hac and Amélie, hoping for better care of the critically ill throughout the world.

–Jean-Louis Vincent

To my parents, Stella and Julius Kochanek, for leading by example on the value of hard work; to my wife, Denise, and my children, Ashley, Stanton, and Jillian, for their many sacrifices; and to the late Dr. Peter Safar, for encouraging each of us to bring promising new therapies to the bedside of the critically ill.

–Patrick M. Kochanek

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The Neutrophil: Balancing Antimicrobial Effectiveness and the Potential for Damage to the Host

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Balloon Tamponade

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Metabolic Acidosis and Alkalosis

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Acute Bacteremia

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Receptor Physiology

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Agitation and Delirium; Management of Pain, Anxiety, and Delirium

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Hepatic Encephalopathy

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Sudden Cardiac Death: Implantable Cardioverter-Defibrillators

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Cannulation for Extracorporeal Membrane Oxygenation

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Nosocomial Pneumonia; Bronchoalveolar Lavage and Protected Specimen Bronchial Brushing

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Glomerulonephritis and Interstitial Nephritis in the ICU

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Prostaglandins, Thromboxanes, Leukotrienes, and Other Products of Arachidonic Acid

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Key Issues in Pediatric Neurointensive Care

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Indications for and Management of Tracheostomy

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Clinical Use of Immunosuppressants

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Burns and Inhalation Injury

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Acute Coronary Syndromes: Pathophysiology and Diagnosis

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Infectious Endocarditis

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Infections in the Immunocompromised Patient

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Mechanical Support in Cardiogenic Shock

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Cardiac Surgery: Indications and Complications

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Difficult Airway Management for Intensivists

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Ventricular Arrhythmias

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Low Systemic Arterial Blood Pressure

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Anemia of Critical Illness

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Management of Acute Pain in the Intensive Care Unit

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Anemia and Red Blood Cell Transfusion in Critically Ill Patients

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Noninvasive Positive-Pressure Ventilation

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Acute Coronary Syndromes: Management and Complications

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Arterial Cannulation and Invasive Blood Pressure Measurement; Beyond Technology: Caring for the Critically Ill

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The Hematopoietic Stem Cell Transplantation Patient

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Sudden Cardiac Death: Implantable Cardioverter-Defibrillators

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Anticonvulsants in the Intensive Care Unit

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Inotropic Therapy in the Critically Ill

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Toxic Megacolon in Critically Ill Patients

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Disorders of Calcium and Magnesium Metabolism

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The Pursuit of Performance Excellence

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Fulminant Hepatic Failure Including Acetaminophen Toxicity

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Metronidazole and Other Antibiotics for Anaerobic Infections

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Key Issues in Pediatric Neurointensive Care

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Poisoning: Overview of Approaches for Evaluation and Treatment

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Aortic Dissection

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Beyond Technology: Caring for the Critically Ill

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The Neutrophil: Balancing Antimicrobial Effectiveness and the Potential for Damage to the Host

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PREFACE

The fifth edition of the *Textbook of Critical Care* continues the tradition of excellence established by the earlier editions but embodies a number of new features that should make it easier to use by both trainees and experienced clinicians and more likely to remain up-to-date. Several features of the fifth edition warrant special comment.

- Because critical care medicine is now a mature specialty that is practiced all over the world, the experts selected to write chapters for the fifth edition are an international group.
- The opening section of the book consists of short chapters that provide a brief overview of clinical problems, such as acute respiratory failure or diarrhea, that are commonly encountered in the management of patients with critical illness.
- Although the book contains extensive citations to the medical literature, both the bulk and the cost of the resulting volume have been decreased by providing most of the references on a CD-ROM rather than in the text per se. The most important citations are provided in the text with some annotation to help readers understand why the selected references are particularly noteworthy.
- Most chapters include a list of key points. A quick glance at this list will help readers remember the "take home" messages for the chapter.
- New pediatric content of the textbook is also international in scope and addresses key topics within each area of pediatric critical care that are germane to the broader readership of the book.
- Because the basic science that underlies the practice of critical care medicine is advancing rapidly, the editors have included an entire section devoted to key topics in areas of fundamental biology that are relevant to the field.

A new feature of the fifth edition is a dedicated website, www.criticalcaretext.com, which has been launched at the same time the book published. This website will be updated every week throughout the life of this edition. The website features the full text and illustrations of the fifth edition of the *Textbook of Critical Care* and is fully searchable. You can even download the illustrations to PowerPoint to enhance your presentations or lectures. Another added-value feature on the website is the inclusion of critical care calculators. References are linked to Medline or directly to full-text articles where available, which will expand your search capabilities. However, the absolute key feature of the website is the regular weekly updates from experts in the field, so that the text is consistent with the best information available in the scientific literature. The latest issues of the major medical journals might contain an article that will fundamentally change the standard of care for the management of a disease or syndrome encountered in the care of critically ill patients. If this happens, the relevant chapter(s) will be updated immediately, so that this work can stay current year after year. The book and the website can be purchased either separately or together as an **e-dition** package, giving you unprecedented reference power.

The fifth edition of this textbook would not have been possible without the enormous contributions made by the prior editors. We express our gratitude to Will Shoemaker, Steve Ayers, Ake Grenvik, and Peter Holbrook for the opportunity and great honor to follow in their footsteps.

We want to thank the many people who were instrumental in helping us assemble the text you are now holding in your hands. Specifically, we wish to thank Ms. Janice Knapp, editorial assistant to Dr. Fink; Marci Provins, editorial assistant to Dr. Kochanek; Dr. Karen Pickett and Ms. Marie-Rose Andre, who assisted Dr. Vincent; and Kelly Kast and Katie Overdier, who assisted Dr. Abraham.

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Section I

COMMON PROBLEMS

Chapter 1
SUDDEN DETERIORATION IN NEUROLOGIC STATUS

Joseph M. Darby • Anupam Anupam

Patients admitted to the intensive care unit (ICU) with critical illness or injury are at risk for neurologic complications.[1-5] A sudden or unexpected change in the neurologic condition of a critically ill patient often heralds a complication that may cause direct injury to the central nervous system (CNS). Alternatively, such changes may simply be neurologic manifestations of the underlying critical illness or treatment that necessitated ICU admission (e.g., sepsis). These complications can occur in patients admitted to the ICU without neurologic disease and in those admitted for the management of primary CNS problems (e.g., stroke). Neurologic complications also can occur as a result of invasive procedures and therapeutic interventions performed. Commonly, the recognition of neurologic complications is delayed or missed entirely because ICU treatments (e.g., intubation, drugs) interfere with the physical examination or confound the clinical picture. In other cases, neurologic complications are not recognized because of a lack of sensitive methods to detect the problem (e.g., delirium). Morbidity and mortality are increased among patients who develop neurologic complications; therefore, the intensivist must be vigilant in the evaluation of all critically ill patients for changes in neurologic status.

Despite the importance of neurologic complications of critical illness, few studies have specifically assessed their incidence and impact on outcome among ICU patients. Available data are limited to medical ICU patients; data regarding neurologic complications in general surgical and other specialty ICU populations must be extracted from other sources. In studies of medical ICU patients, the incidence of neurologic complications is 12.3% to 33%.[1,2] Patients who develop neurologic complications have increased morbidity, mortality, and ICU length of stay. Sepsis is the most common problem associated with the development of neurologic complications (sepsis-associated encephalopathy). In addition to encephalopathy, other common neurologic complications associated with critical illness include seizures and stroke. As the complexity of ICU care has increased, so has the risk of neurologic complications. Neuromuscular disorders are now recognized as a major source of morbidity in severely ill patients.[6] Recognized neurologic complications occurring in selected medical, surgical, and neurologic ICU populations are shown in Table 1–1.[7-41]

TABLE 1–1. NEUROLOGIC COMPLICATIONS IN SELECTED SPECIALTY POPULATIONS

Medical	
Bone marrow transplantation[7,8]	CNS infection, stroke, subdural hematoma, brainstem ischemia, hyperammonemia, Wernicke's encephalopathy
Cancer[9]	Stroke, intracranial hemorrhage, CNS infection
Fulminant hepatic failure[10]	Encephalopathy, coma, brain edema, increased ICP
HIV/AIDS[11,12]	Opportunistic CNS infection, stroke, vasculitis, delirium, seizures, progressive multifocal leukoencephalopathy
Pregnancy[13,14]	Seizures, ischemic stroke, cerebral vasospasm, intracranial hemorrhage, cerebral venous thrombosis, hypertensive encephalopathy, pituitary apoplexy
Surgical	
Cardiac surgery[15-19]	Stroke, delirium, brachial plexus injury, phrenic nerve injury
Vascular surgery[20,21]	
Carotid	Stroke, cranial nerve injuries (recurrent laryngeal, glossopharyngeal, hypoglossal, facial), seizures
Aortic	Stroke, paraplegia
Peripheral	Delirium
Transplantation[10,22-25]	
Heart	Stroke
Liver	Encephalopathy, seizures, opportunistic CNS infection, intracranial hemorrhage, Guillain-Barré syndrome, central pontine myelinolysis
Renal	Stroke, opportunistic CNS infection, femoral neuropathy
Urologic surgery (TURP)[26]	Seizures and coma (hyponatremia)
Otolaryngologic surgery[27,28]	Recurrent laryngeal nerve injury, stroke, delirium
Orthopedic surgery[29]	
Spine	Myelopathy, radiculopathy, epidural abscess, meningitis
Knee and hip replacement	Delirium (fat embolism)
Long bone fracture/nailing	Delirium (fat embolism)
Neurologic	
Stroke[30-34]	Stroke progression or extension, reocclusion after thrombolysis, bleeding, seizures, delirium, brain edema, herniation
Intracranial surgery[35]	Bleeding, edema, seizures, CNS infection
Subarachnoid hemorrhage[32,36-38]	Rebleeding, vasospasm, hydrocephalus, seizures
Traumatic brain injury[32,39,40]	Intracranial hypertension, bleeding, seizures, stroke (cerebrovascular injury), CNS infection

Continued

IMPAIRMENT IN CONSCIOUSNESS

Global changes in CNS function, best described in terms of impairment in consciousness, are generally referred to as encephalopathy or altered mental status. An acute change in

TABLE 1–1. NEUROLOGIC COMPLICATIONS IN SELECTED SPECIALTY POPULATIONS—CONT'D

Cervical spinal cord injury[41]	Ascension of injury, stroke (vertebral artery injury)

CNS, central nervous system; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; ICP, intracranial pressure; TURP, transurethral prostatic resection.

the level of consciousness undoubtedly is the most common neurologic complication that occurs after ICU admission. Consciousness is defined as a state of awareness (arousal or wakefulness) and the ability to respond appropriately to changes in environment.[42] For consciousness to be impaired, global hemispheric dysfunction or dysfunction of the brainstem reticular activating system must be present.[43] Altered consciousness may result in a sleeplike state (coma) or a state characterized by confusion and agitation (delirium) (Table 1–2).

When an acute change in consciousness is noted, the patient should be evaluated, keeping in mind the patient's age, the presence or absence of coexisting organ system dysfunction, the patient's metabolic status and medication list, and the presence or absence of infection (Table 1–3). In patients with a primary CNS disorder, deterioration in the level of consciousness (e.g., from stupor to coma) frequently represents the development of brain edema, increasing intracranial pressure, new or worsening intracranial hemorrhage, hydrocephalus, CNS infection, or cerebral vasospasm. In patients without a primary CNS diagnosis, an acute change in consciousness is often due to the development of infectious complications (i.e., sepsis-associated encephalopathy), drug toxicities, or the development or exacerbation of organ system failure. Nonconvulsive status epilepticus is increasingly being recognized as a cause of impaired consciousness in critically ill patients.[44-53]

States of altered consciousness manifesting as impairment in wakefulness or arousal (i.e., coma and stupor) and their causes are well defined.[42,43,54,55] Much confusion remains, however, regarding the diagnosis and management of delirium, perhaps the most common state of impaired CNS functioning in critically ill patients at large. When dedicated instruments are used, delirium can be diagnosed in more than 80% of critically ill patients, making this condition the most common neurologic complication of critical illness.[56-58] Much of the difficulty in establishing the diagnosis of delirium stems from the belief that delirium is a state characterized mainly by confusion and agitation and that such states are expected consequences of the unique environmental factors and sleep deprivation that characterize the ICU experience. Terms previously used to describe delirium in critically ill patients include ICU

TABLE 1–2. STATES OF ACUTELY ALTERED CONSCIOUSNESS

State	Description
Coma	Closed eyes, sleeplike state with no response to external stimuli (pain)
Stupor	Responsive only to vigorous or painful stimuli
Lethargy	Drowsy, arouses easily and appropriately to stimuli
Delirium	Acute state of confusion with or without behavioral disturbance
Catatonia	Eyes open, unblinking, unresponsive

TABLE 1–3. GENERAL CAUSES OF ACUTELY IMPAIRED CONSCIOUSNESS IN THE CRITICALLY ILL

Infection
Sepsis encephalopathy
CNS infection
Drugs
Narcotics
Benzodiazepines
Anticholinergics
Anticonvulsants
Tricyclic antidepressants
Selective serotonin uptake inhibitors
Phenothiazines
Steroids
Immunosuppressants (cyclosporine, FK506, OKT3)
Anesthetics
Electrolyte and Acid-Base Disturbances
Hyponatremia
Hypernatremia
Hypercalcemia
Hypermagnesemia
Severe acidemia and alkalemia
Organ System Failure
Shock
Renal failure
Hepatic failure
Pancreatitis
Respiratory failure (hypoxia, hypercapnea)
Endocrine Disorders
Hypoglycemia
Hyperglycemia
Hypothyroidism
Hyperthyroidism
Pituitary apoplexy
Drug Withdrawal
Alcohol
Opiates
Barbiturates
Benzodiazepines
Vascular Causes
Shock
Hypotension
Hypertensive encephalopathy
CNS vasculitis
Cerebral venous sinus thrombosis
CNS Disorders
Hemorrhage
Stroke
Brain edema
Hydrocephalus
Increased intracranial pressure
Meningitis
Ventriculitis
Brain abscess
Subdural empyema
Seizures
Vasculitis
Seizures
Convulsive and nonconvulsive status epilepticus

Continued

TABLE 1–3. GENERAL CAUSES OF ACUTELY IMPAIRED CONSCIOUSNESS IN THE CRITICALLY ILL—CONT'D

Miscellaneous
Fat embolism syndrome
Neuroleptic malignant syndrome
Thiamine deficiency (Wernicke's encephalopathy)
Psychogenic unresponsiveness

CNS, central nervous system.

psychosis, acute confusional state, encephalopathy, and postoperative psychosis. It is now recognized that ICU psychosis is a misnomer; delirium is a more accurate term.[59]

The currently accepted criteria for the diagnosis of delirium include an abrupt onset of impaired consciousness, disturbed cognitive function, fluctuating course, and the presence of a medical condition that could impair brain function.[60] Subtypes of delirium include hyperactive (agitated) delirium and the more common hypoactive or quiet delirium.[58] Impaired consciousness may be apparent as a reduction in awareness, psychomotor retardation, agitation, or impairment in attention (increased distractability or vigilance). Cognitive impairment can include disorientation, impaired memory, and perceptual aberrations (hallucinations or illusions).[61] Autonomic hyperactivity and sleep disturbances may be features of delirium in some patients (e.g., those with drug withdrawal syndromes, delirium tremens). Delirium in critically ill patients is associated with increased morbidity, mortality, and ICU length of stay.[62-64] In general, sepsis and drugs should be the primary etiologic considerations in critically ill patients who develop delirium.

As has been noted, nonconvulsive status epilepticus is increasingly recognized as an important cause of impaired consciousness in critically ill patients. Although the general term can encompasses other entities, such as absence and partial complex seizures, in critically ill patients, nonconvulsive status epilepticus is often referred to as "status epilepticus of epileptic encephalopathy."[53] It is characterized by an alteration in consciousness or behavior associated with electroencephalographic evidence of continuous or periodic epileptiform activity without overt motor manifestations of seizures. In one study of comatose patients without overt seizure activity, nonconvulsive status epilepticus was evident in 8%.[51] Nonconvulsive status epilepticus can precede or follow an episode of generalized convulsive status epilepticus; it can also occur in patients with traumatic brain injury, subarachnoid hemorrhage, global brain ischemia or anoxia, sepsis, and multiple organ failure. Despite the general consensus that nonconvulsive status epilepticus is a unique entity responsible for impaired consciousness in some critically ill patients, there is no general consensus on the electroencephalographic criteria for its diagnosis or the optimal approach to treatment.[65]

STROKE AND OTHER FOCAL NEUROLOGIC DEFICITS

The new onset of a major neurologic deficit that manifests as a focal impairment in motor or sensory function (e.g., hemiparesis) or results in seizures usually indicates a primary problem referable to the cerebrovascular circulation. In a study evaluating the value of computed tomography (CT) in medical ICU patients, ischemic stroke and intracranial bleeding were the most common abnormalities associated with the new onset of a neurologic deficit or seizures.[66] Overall, the frequency of new-onset stroke is between 1% and 4% in medical ICU patients.[1,2] Among general surgical patients, the frequency of perioperative stroke ranges from 0.3% to 3.5%.[67] Patients undergoing cardiac or vascular surgery and surgical patients with underlying cerebrovascular disease can be expected to have an increased risk of perioperative stroke.[19]

The frequency of new or worsening focal neurologic deficits in patients admitted with a primary neurologic or neurosurgical disorder varies. For example, as many as 30% of patients with aneurysmal subarachnoid hemorrhage develop delayed ischemic neurologic deficits.[36] Patients admitted with stroke often develop worsening or new symptoms as a result of stroke progression, bleeding, or reocclusion of vessels previously opened with interventional therapy. In patients who have undergone elective intracranial surgery, postsurgical bleeding or infectious complications are the main causes of new focal deficits. In trauma patients, unrecognized injuries to the cerebrovascular circulation can cause new deficits. Patients who have sustained spinal cord injuries, and those who have undergone surgery of the spine or of the thoracic or abdominal aorta, can develop worsening or new symptoms of spinal cord injury. Early deterioration of CNS function after spinal cord injury usually occurs as a consequence of medical interventions to stabilize the spine, whereas late deterioration is usually due to hypotension and impaired cord perfusion. Occasionally, focal weakness or sensory symptoms in the extremities occur as a result of occult brachial plexus injury or compression neuropathy. New cranial nerve deficits in patients without primary neurologic problems can occur after neck surgery or carotid endarterectomy.

SEIZURES

The new onset of motor seizures occurs in 0.8% to 4% of critically ill medical ICU patients.[1,2,68] The new onset of seizures in general medical-surgical ICU patients is typically caused by narcotic withdrawal, hyponatremia, drug toxicities, or previously unrecognized structural abnormalities.[3,68] New stroke, intracranial bleeding, and CNS infection are other potential causes of seizures after ICU admission. The frequency of seizures is higher in patients admitted to the ICU with a primary neurologic problem, such as traumatic brain injury, aneurysmal subarachnoid hemorrhage, stroke, or CNS infection.[69] Because nonconvulsive status epilepticus may be more common than was previously appreciated, this problem should also be considered in the differential diagnosis of patients developing new, unexplained, or prolonged alterations in consciousness.

GENERALIZED WEAKNESS AND NEUROMUSCULAR DISORDERS

Generalized muscle weakness often becomes apparent in ICU patients as previous impairments in arousal are resolving or sedative and neuromuscular blocking agents are being discontinued or tapered. Polyneuropathy and myopathy associated

with critical illness are now well recognized as the principal causes of new-onset generalized weakness among ICU patients being treated for non-neuromuscular disorders.[5,70-73] These disorders also may be responsible for prolonged ventilator dependency in some patients. Patients at increased risk for these complications include those with sepsis, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome, as well as those who require prolonged mechanical ventilation. Other risk factors include treatment with corticosteroids or neuromuscular blocking agents. In contrast to demyelinating neuropathies (e.g., Guillain-Barré syndrome), critical illness polyneuropathy is primarily an axonal condition. Critical illness polyneuropathy is diagnosed in a high percentage of patients undergoing careful evaluation for weakness acquired while in the ICU. Because primary myopathy coexists in a large number of patients with critical illness polyneuropathy, ICU-acquired paresis[72] or critical illness neuromuscular abnormalities[5] may be better terms to describe this problem. Although acute Guillain-Barré syndrome and myasthenia gravis are rare complications of critical illness, these diagnoses should also be considered in patients who develop generalized weakness in the ICU.

NEUROLOGIC COMPLICATIONS OF PROCEDURES AND TREATMENTS

Routine procedures performed in the ICU or in association with the evaluation and treatment of critical illness can result in neurologic complications.[4] The most obvious neurologic complications are those associated with intracranial bleeding secondary to the treatment of stroke and other disorders with thrombolytic agents or anticoagulants. Other notable complications are listed in Table 1–4.

TABLE 1–4. NEUROLOGIC COMPLICATIONS ASSOCIATED WITH ICU PROCEDURES AND TREATMENTS

Procedure	Complication
Angiography	Cerebral cholesterol emboli syndrome
Anticoagulants/ antiplatelet agents	Intracranial bleeding
Arterial catheterization	Cerebral embolism
Bronchoscopy	Increased ICP
Central venous catheterization	Cerebral air embolism, carotid dissection, Horner's syndrome, phrenic nerve injury, brachial plexus injury, cranial nerve injury
DC cardioversion	Embolic stroke, seizures
Dialysis	Seizures, increased ICP (dialysis disequilibrium syndrome)
Endovascular procedures (CNS)	Vessel rupture, thrombosis, reperfusion bleeding
Epidural catheter	Spinal epidural hematoma, epidural abscess
ICP monitoring	CNS infection (ventriculitis), hemorrhage
Intra-aortic balloon pump	Lower extremity paralysis
Intubation	Spinal cord injury
Left ventricular assist devices	Stroke, seizures
Lumbar puncture or/drain	Meningitis, herniation
Mechanical ventilation	Cerebral air embolism, increased ICP (high PEEP and hypercapnea), seizures (hypocapnea)
Nasogastric intubation	Intracranial placement

CNS, central nervous system; DC, direct current; ICP, intracranial pressure; ICU, intensive care unit; PEEP, positive end-expiratory pressure.

EVALUATION OF SUDDEN NEUROLOGIC CHANGE

A new or sudden change in the neurologic condition of a critically ill patient necessitates a focused neurologic examination, a review of the clinical course and the medications administered before the change, a thorough laboratory assessment, and appropriate imaging or neurophysiologic studies when indicated. The type and extent of the evaluation depend on the clinical context and the general category of neurologic change occurring. The history and physical examination should lead the clinician to the diagnostic approach best suited to the individual patient.

The essential elements of the neurologic examination include an assessment of the level and content of consciousness, pupillary size and reactivity, and motor function. Additional evaluation of the cranial nerves and peripheral reflexes and a sensory examination are conducted as indicated by the clinical circumstances. If the patient is comatose on initial evaluation, a more detailed coma examination should be performed to help differentiate structural from metabolic causes of coma.[43,55] When the evaluation reveals only a change in arousal, without evidence of a localizing lesion in the CNS, a search for infection, discontinuation or modification of drug therapy, and a general metabolic evaluation may be indicated. Lumbar puncture to aid the diagnosis of CNS infection may be warranted in selected neurosurgical patients and immunocompromised individuals. Lumbar puncture to rule out nosocomially acquired meningitis in other patients is generally not rewarding.[74] Electroencephalography should be performed in patients with clear evidence of seizures, as well as when the diagnosis of nonconvulsive status epilepticus is being entertained. Continuous electroencephalography should be considered when the index of suspicion for nonconvulsive status epilepticus remains high and the initial electroencephalographic studies are unrevealing.

CT is indicated for non-neurologic patients with new focal deficits, seizures, or otherwise unexplained impairments in arousal.[66] In patients with primary neurologic disorders, CT is indicated if worsening brain edema, herniation, bleeding, and hydrocephalus are considerations when new deficits or worsening neurologic status occurs. In some cases, when the basis for a change in neurologic condition remains elusive, magnetic resonance imaging (MRI) may be helpful. In particular, the diffusion-weighted MRI technique can reveal structural abnormalities, such as hypoxic brain injury, fat embolism, vasculitis, cerebral venous thrombosis, or multiple infarcts following cardiopulmonary bypass, that are not apparent by standard CT or conventional MRI.[75-80] MRI may be the imaging modality of choice in patients with human immunodeficiency virus (HIV) and new CNS complications.[75] For patients who develop signs and symptoms of spinal cord injury complicating critical illness, MRI or somatosensory evoked potentials can be used to further delineate the nature and severity of the injury. For patients who develop generalized muscle weakness or unexplained ventilator dependency,

electromyography and nerve conduction studies can confirm the presence of critical illness polyneuropathy or myopathy.

MONITORING FOR NEUROLOGIC CHANGES

The common occurrence of neurologic changes in critically ill patients emphasizes the need for vigilant monitoring. A variety of clinical techniques, such as the Glasgow Coma Scale, National Institutes of Health Stroke Scale, Ramsay Sedation Scale, Richmond Agitation-Sedation Scale, and Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) can be used to monitor clinical neurologic status.[57,58,81-86] Neurophysiologic methods such as the bispectral index may provide more objective neurologic monitoring in the future for patients admitted to the ICU with and without primary neurologic problems.[87-89] For patients admitted to the ICU with a primary neurologic disorder, a variety of monitoring techniques, including measurements of intracranial pressure, near infrared spectroscopy, brain tissue Po_2, transcranial Doppler, and electroencephalography, are available.[90]

ANNOTATED REFERENCES

De Jonghe B, Sharshar T, Lefaucheur JP, et al: Paresis acquired in the intensive care unit. A prospective multicenter study. JAMA 2002;288:2859-2867.

This prospective multicenter study of critically ill patients was the first to assess the clinical incidence, risk factors, and outcomes of mechanically ventilated patients developing ICU acquired weakness, emphasizing a central role for corticosteroid use in its genesis and prolonged mechanical ventilation as a relevant ICU outcome.

Ely EW, Inouye SK, Bernard GR, et al: Delirium in mechanically ventilated patients. Validity and reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). JAMA 2001;286:2703-2710.

Recognizing that the diagnosis of delirium is often difficult in the critically ill patient receiving mechanical ventilation, the authors adapted a common method for assessing delirium using the Confusion Assessment Method to critically ill patients receiving mechanical ventilation. This prospective evaluation revealed high sensitivity, specificity, and interrater reliability in detecting delirium in 80% of the patient population they studied.

McGuire BE, Basten CJ, Ryan CJ, et al: Intensive care unit syndrome. A dangerous misnomer. Arch Intern Med 2000;160:906-909.

In an effort to dispel the myth that environmental conditions lead to "ICU psychosis," the authors of this article argue that ICU psychosis is more appropriately described as delirium. The etiology and management of delirium in critically ill patients are reviewed.

Naik-Tolani S, Oropello JM, Benjamin E: Neurologic complications in the intensive care unit. Clin Chest Med 1999;20:423-434.

The authors of this article present an overview of central nervous system (CNS) complications of critical illness and ICU procedures in critically ill patients without primary disorders of the CNS.

Sundgren PC, Reinstrup P, Romner B, et al: Value of conventional diffusion- and perfusion-weighted MRI in the management of patients with unclear cerebral pathology, admitted to the intensive care unit. Neuroradiology 2002;44:674-680.

This retrospective study of 21 critically ill patients undergoing MR imaging because of a disparity in clinical neurologic findings and CT imaging revealed that additional useful diagnostic and prognostic information can be obtained, especially when diffusion and perfusion weighted MR sequences are obtained.

Chapter 2
AGITATION AND DELIRIUM

Eric B. Milbrandt • E. Wes Ely

Agitation and delirium are commonly encountered in the intensive care unit (ICU). They are more than an inconvenience; these conditions can have deleterious effects on patient and staff safety and contribute to poor outcomes. It is important for clinicians to have an organized approach for the evaluation and management of agitation and delirium.

AGITATION

Agitation is a state of extreme arousal, irritability, and motor restlessness that results from an internal sense of discomfort or tension. It is the behavioral response to physical or emotional distress, including pain, dyspnea, and anxiety, although the most common cause of agitation in the ICU is probably delirium.[1] Agitation is characterized by repetitive, nonproductive movements that may appear purposeless, although careful observation of the patient sometimes reveals an underlying intent. Agitation may be mild, characterized by increased movements and an apparent inability to get comfortable. Severe agitation can be life-threatening, leading to removal of life-saving devices as well as hypoxia, barotrauma, and hypotension due to patient-ventilator asynchrony. Indeed, recent studies have shown that agitation contributes to ventilator asynchrony, increased oxygen consumption, and inadvertent removal of devices and catheters.[2-5]

DELIRIUM

Delirium is an acute, fluctuating change in mental status, with inattention and altered level of consciousness. Delirium is an objective sign of cerebral insufficiency or acute cognitive dysfunction. It should be thought of as a form of organ dysfunction, much like shock and hypoxemia are considered evidence of dysfunction of the cardiovascular and pulmonary systems, respectively. Delirium has myriad causes, including pain and anxiety, medications, toxins, and metabolic derangements. Also known as acute encephalopathy[6] or ICU psychosis,[7] delirium occurs in as many as 80% of mechanically ventilated ICU patients and has recently been shown to be associated with increased length of stay, medical complications, and poor outcomes, including an increased 6-month mortality.[8-12] Furthermore, delirium can adversely affect the quality of life in survivors of critical illnesses, because a significant percentage of individuals who develop delirium in the hospital continue to demonstrate symptoms of delirium after discharge.[13-16] These patients manifest decreased cerebral activity and increased cognitive deterioration, and they are more likely to develop dementia than are patients without delirium. Finally, patients who develop delirium have a greater rate of decline on cognitive tests than do nondelirious patients.[13-16]

Delirium can be hypoactive or hyperactive. Patients with hypoactive delirium are calm but inattentive, and they manifest decreased mobility. Patients with hyperactive delirium are agitated and combative. Inattention is the hallmark feature of both types of delirium. Patients with hyperactive delirium are at risk for self-extubation, loss of catheters, and patient-ventilator asynchrony. Because of these risks, patients are often given high doses of sedatives that commit them to continued mechanical ventilation. Despite the dangers of hyperactive delirium, hypoactive delirium may actually be associated with a worse prognosis.[17-20]

Because the majority of patients manifest hypoactive delirium instead of the more obvious hyperactive type,[18,21-25] delirium frequently goes unrecognized in the ICU. Furthermore, up to 40% of alert or easily arousable patients who are usually assumed to be "cognitively intact" by ICU personnel may actually be delirious.[10] Even when ICU delirium is recognized, most clinicians consider it an expected event that is often iatrogenic and without consequence.[26]

CAUSES AND RISK FACTORS

The list of causes and risk factors for agitation and delirium is long, and the causes of the two conditions overlap to a large extent (Table 2–1). Fortunately, there are several mnemonics that can aid clinicians in recalling the list; two common ones are IWATCHDEATH and DELIRIUM (Table 2–2). In practical terms, the risk factors can be divided into three categories: the acute illness itself, patient factors, and iatrogenic or environmental factors. Importantly, a number of medications that are commonly used in the ICU are associated with the development of agitation and delirium (Table 2–3). A thorough approach to the treatment and support of the acute illness (e.g., controlling sources of sepsis and giving appropriate antibiotics), as well as minimizing the iatrogenic component (e.g., avoiding excessive sedation), can help reduce the incidence and magnitude of delirium and its attendant complications.

ASSESSMENT

There are many scales available for the assessment of agitation and sedation, including the Ramsay Scale,[27] the Riker Sedation-Agitation Scale (SAS),[28] the Motor Activity Assessment Scale (MAAS),[29] and the Richmond Agitation-Sedation Scale (RASS).[30] Each has good reliability and validity

TABLE 2–1. CAUSES OF AND RISK FACTORS FOR AGITATION AND DELIRIUM

Age >70 years	BUN/creatinine ratio ≥18
Transfer from a nursing home	Renal failure, creatinine >2.0 mg/dL
History of depression	Liver disease
History of dementia, stroke, or epilepsy	Congestive heart failure
Alcohol abuse within past month	Cardiogenic or septic shock
Tobacco use	Myocardial infarction
Drug overdose or illicit drugs	Infection
HIV infection	Central nervous system pathology
Medications	Urinary retention or fecal impaction
Hypo- or hypernatremia	Tube feeding
Hypo- or hyperglycemia	Rectal or bladder catheters
Hypo- or hyperthyroidism	Physical restraints
Hypothermia or fever	Central line catheters
Hypertension	Malnutrition or vitamin deficiencies
Hypoxia	Procedural complications
Acidosis or alkalosis	Visual or hearing impairment
Pain	Sleep disruption
Fear and anxiety	

BUN, blood urea nitrogen; HIV, human immunodeficiency virus.

among adult ICU patients and can be used to set targets for goal-directed sedative administration. The SAS, which scores agitation and sedation using a 7-point system, has excellent interrater reliability (kappa = 0.92), and it is highly correlated (r^2 = 0.83 to 0.86) with other scales. The RASS (Table 2–4), however, is the only method that has been shown to detect variations in the level of consciousness over time or in response to changes in sedative and analgesic drug use.[31,32] The 10-point Richmond scale has discrete criteria to distinguish levels of agitation and sedation. Patient evaluation consists of a three-step process. First, a patient is observed to determine whether he or she is alert, restless, or agitated (0 to +4). If the patient is not spontaneously alert, the patient's name is called and the duration of eye contact is measured (−1 to −3). If there is no eye contact with verbal stimulation,

TABLE 2–2. MNEMONICS FOR REMEMBERING CAUSES OF DELIRIUM AND AGITATION: IWATCHDEATH AND DELIRIUM

IWATCHDEATH	DELIRIUM
Infection	**D**rugs
Withdrawal	**E**lectrolyte and physiologic abnormalities
Acute metabolic	**L**ack of drugs (withdrawal)
Trauma/pain	**I**nfection
Central nervous system pathology	**R**educed sensory input (blindness, deafness)
Hypoxia	**I**ntracranial problems (CVA, meningitis, seizure)
Deficiencies (vitamin B_{12}, thiamine)	**U**rinary retention and fecal impaction
Endocrinopathies (thyroid, adrenal)	**M**yocardial problems (MI, arrhythmia, CHF)
Acute vascular (hypertension, shock)	
Toxins/drugs	
Heavy metals	

CHF, congestive heart failure; CVA, cerebrovascular accident; MI, myocardial infarction.

TABLE 2–3. COMMONLY USED DRUGS ASSOCIATED WITH DELIRIUM AND AGITATION

Benzodiazepines	Antibiotics
Opiates (especially meperidine)	Corticosteroids
Anticholinergics	Metoclopramide
Antihistamines	Muscle relaxants
H_2 blockers	Lidocaine

the shoulder is shaken or the sternum is rubbed, and the response is noted (−4 or −5). This assessment takes less than 20 seconds and correlates well with other measures of sedation (e.g., Glasgow Coma Scale, bispectral electroencephalography, neuropsychiatric ratings).

Until recently, there was no valid and reliable way to assess delirium in critically ill patients, many of whom are nonverbal owing to sedation or mechanical ventilation. The Confusion Assessment Method for the ICU (CAM-ICU) (Table 2–5) is a delirium measurement tool that was developed by a team of specialists in critical care, psychiatry, neurology, and geriatrics.[8-12] Administered by a nurse, the evaluation takes only 1 to 2 minutes to conduct and is 98% accurate for detecting

TABLE 2–4. RICHMOND AGITATION-SEDATION SCALE

+4	Combative	Combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent nonpurposeful movement; fights ventilator
+1	Restless	Anxious, apprehensive, but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert but has sustained (>10 sec) awakening (eye opening/contact) to voice
−2	Light sedation	Drowsy; briefly (<10 sec) awakens to voice or physical stimulation
−3	Moderate sedation	Movement or eye opening (but no eye contact) to voice
−4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Procedure for Assessment

1. Observe patient
   Is patient alert, restless, or agitated? **(Score 0 to +4)**
2. If not alert, state patient's name and tell him or her to open eyes and look at speaker.
   Patient awakens, with sustained eye opening and eye contact. **(Score −1)**
   Patient awakens, with eye opening and eye contact, but not sustained. **(Score −2)**
   Patient does not awaken (no eye contact) but has eye opening or movement in response to voice. **(Score −3)**
3. Physically stimulate patient by shaking shoulder and/or rubbing sternum.
   No response to voice, but response (movement) to physical stimulation. **(Score −4)**
   No response to voice or physical stimulation **(Score −5)**

From Sessler CN, Gosnell MS, Grap MJ, et al: The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166:1338-1344; Ely EW, Truman B, Shintani A, et al: Monitoring sedation status over time in ICU patients: Reliability and validity of the Richmond agitation-sedation scale (RASS). JAMA 2003;289:2983-2991.

TABLE 2–5. CONFUSION ASSESSMENT METHOD FOR THE INTENSIVE CARE UNIT

1. Acute Onset or Fluctuating Course	Absent	Present
A. Is there evidence of an acute change in mental status from baseline?		
OR		
B. Did the (abnormal) behavior fluctuate during the past 24 hours, that is, tend to come and go or increase and decrease in severity, as evidenced by fluctuation on a sedation scale (e.g., Richmond Agitation-Sedation Scale), Glasgow Coma Scale, or previous delirium assessment?		

2. Inattention	Absent	Present
Did the patient have difficulty focusing attention, as evidenced by a score of less than 8 on either the auditory or visual component of the Attention Screening Examination?		

3. Disorganized Thinking	Absent	Present
Is there evidence of disorganized or incoherent thinking, as evidenced by incorrect answers to 2 or more of the 4 questions or the inability to follow commands?		

Questions (use either set A or set B):

Set A	Set B
1. Will a stone float on water?	1. Will a leaf float on water?
2. Are there fish in the sea?	2. Are there elephants in the sea?
3. Does 1 pound weigh more than 2 pounds?	3. Do 2 pounds weigh more than 1 pound?
4. Can you use a hammer to pound a nail?	4. Can you use a hammer to cut wood?

Other:

1. Are you having any unclear thinking?
2. Hold up this many fingers. (Examiner holds two fingers in front of patient.)
3. Now do the same thing with the other hand. (Do not repeat the number of fingers.)

4. Altered Level of Consciousness	Absent	Present
Is the patient's level of consciousness anything other than alert, such as vigilant, lethargic, or stuporous (i.e., Richmond agitation-sedation score other than 0 at time of assessment)?		

Alert: spontaneously fully aware of environment and interacts appropriately

Vigilant: hyperalert

Lethargic: drowsy but easily aroused; unaware of some elements in the environment or not spontaneously interacting appropriately with the interviewer; becomes fully aware and appropriately interactive when prodded minimally

Stuporous: becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli, and as soon as the stimulus ceases, lapses back into the unresponsive state

Overall Assessment: Presence of Features 1 and 2 and Either Feature 3 or Feature 4?	Yes	No

delirium as compared with a full *Diagnostic and Statistical Manual of Mental Disorders* IV assessment by a geriatric psychiatrist.[8,10] Delirium is diagnosed when a patient demonstrates an acute change or fluctuating changes in mental status, inattention, and either disorganized thinking or altered level of consciousness. National guidelines recommend the routine use of this method for delirium assessment in all critically ill patients.[32]

MANAGEMENT

Agitation is expected in a newly intubated patient. However, when agitation or delirium develops in a previously comfortable patient, a search for the underlying cause should be undertaken before attempting pharmacologic intervention. A rapid assessment should be performed, including vital signs and physical examination, to rule out life-threatening problems (e.g., hypoxia, self-extubation, pneumothorax, hypotension) or other acutely reversible physiologic causes (e.g., hypoglycemia, metabolic acidosis, stroke, seizure, pain). The previously mentioned IWATCHDEATH and DELIRIUM mnemonics can be particularly helpful in guiding this initial evaluation.

After correcting any identifiable contributing factors, pharmacologic treatment is often required. If pain is present, an analgesic should be the initial drug of choice. Although benzodiazepines are the most commonly used drugs for the treatment of agitation, they are not recommended for the management of delirium because they can paradoxically exacerbate confusion. Patients who manifest delirium should be treated with a traditional antipsychotic medication (e.g., haloperidol). When given intravenously, these medications exert a calming effect, flattening the affect and diminishing psychomotor agitation without suppressing respiratory drive or affecting hemodynamics. Haloperidol and related drugs achieve this effect by blocking dopamine receptors in the central nervous system. With acute delirium, haloperidol should be given in doses of 2 to 10 mg i.v. every 20 to 30 minutes until delirium is controlled. Subsequently, 25% of the total loading dose should be administered every 6 hours.[32] The dose should then be tapered over several days. Despite their favorable safety profile, antipsychotic medications can cause extrapyramidal reactions, neuroleptic malignant syndrome, and QT interval prolongation leading to torsades de pointes. These adverse effects are thought to be dose related, leading some experts to question the safety of the rapid-loading approach. According to this view, patients should receive no more than 20 mg/day of haloperidol.[33] Anecdotally, the use of atypical antipsychotics, such as risperidone, olanzapine, or ziprasidone,[34] is in vogue. However, their effectiveness in treating ICU delirium has not been evaluated systematically and, like haloperidol, these agents have the potential for QT interval prolongation.

For nondelirious agitated patients, benzodiazepines and propofol are the drugs of choice in the ICU. These agents are most effectively administered using standardized nurse-driven protocols with a clearly stated target level for sedation. Benzodiazepines bind to gamma-aminobutyric acid receptors in the central nervous system, leading to sedation, anxiolysis, hypnosis, muscle relaxation, anticonvulsant activity, and amnesia.[35] Benzodiazepines do not relieve pain, but their anxiolytic and amnestic properties may improve pain tolerance by moderating the anticipatory pain response.[36] Benzodiazepines can cause hypotension when given as a bolus dose, particularly in hypovolemic patients who may not tolerate the reduction in sympathetic vascular tone associated with benzodiazepine-induced anxiolysis. Further, by reducing inhibitions, these agents can sometimes cause paradoxical increases in agitation and aggressiveness. Of the benzodiazepines that are currently available, diazepam, midazolam, and lorazepam are the preferred agents in the ICU. The onset of action of diazepam is 2 to 5 minutes, making it useful for rapidly sedating acutely agitated patients. However, its long half-life makes prolonged sedation a risk with repeated use, particularly in patients with renal or hepatic dysfunction. To control acute agitation, it is given in doses of 2 to 6 mg every 5 to 15 minutes until the event is controlled. Continuous infusions are not recommended. Midazolam is also useful for acute agitation because it has a rapid onset (2 to 5 minutes) and short duration of action. It is given as bolus injections of 2 to 5 mg every 5 to 15 minutes. When used for long-term sedation (>48 to 72 hours), it tends to produce unpredictable awakening times, especially in patients who are obese or who have low serum albumin concentrations or renal failure.[32] Lorazepam has a slower onset of action (5 to 20 minutes), making it less helpful for acute agitation; however, it is less lipid-soluble and has no active metabolite, making it the preferred agent for long-term administration in most critically ill patients. Intermittent doses of 1 to 4 mg are given every 2 to 6 hours, or continuous infusions may be used.

Propofol is an intravenous anesthetic whose mechanism of action is not known. It is quite popular in the ICU owing to its rapid onset of action (1 to 2 minutes) and short duration of action (2 to 8 minutes). It is the preferred sedative when rapid awakening is important, such as for neurologic assessment or pending extubation.[32] When used for long-term (>48 to 72 hours) sedation, the short duration of action does not translate into a reduced duration of mechanical ventilation or a shorter ICU stay.[37] Propofol can cause hypotension due to vasodilatation-related loss of preload and myocardial depression.[38] High-dose continuous infusions have been associated with lactic acidosis in children and with metabolic acidosis, arrhythmias, and cardiac arrest in adults.[39-41] Consequently, providers should consider alternative sedative agents for any patient receiving high-dose propofol infusions who develops unexplained metabolic acidosis, arrhythmias, or cardiac failure.

At times, mechanical restraints may be needed to ensure patient and staff safety while waiting for medications to take effect. It is important to keep in mind, however, that restraints can actually increase agitation and delirium, and their use may have adverse consequences, including strangulation, nerve injury, skin breakdown, and other complications of immobilization.

SUMMARY

Agitation and delirium are very common in the ICU, where their occurrence puts patients at risk for self-injury and poor clinical outcomes. Through a systematic approach, life-threatening problems and other acutely reversible physiologic causes can be rapidly identified and remedied. Recognizing and treating agitated delirium with antipsychotic medications may reduce the use of sedative medications and decrease the risk of prolonging the ICU stay due to oversedation.

Chapter 3

MANAGEMENT OF ACUTE PAIN IN THE INTENSIVE CARE UNIT

Paul Jodka • Stephen O. Heard

Acute pain often occurs in patients who are cared for in the intensive care unit (ICU). Acute pain and discomfort can have multiple causes in this setting, including surgical and post-traumatic wounds and injuries, the use of invasive monitoring devices and mechanical ventilators, prolonged immobilization, and routine nursing care (e.g., dressing changes, airway suctioning).[1-4] Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage."[5] The experience of pain and any related suffering differs among patients,[6,7] but the physiologic sequelae of inadequately treated pain are relatively predictable and potentially deleterious. Such physiologic responses to acute pain and stress are mediated by neuroendocrine activation and increased sympathetic tone. As a consequence, the patient develops tachycardia, increased myocardial oxygen consumption, immunosuppression, hypercoagulability, persistent catabolism, and numerous other metabolic alterations.[8,9] Additional morbidity may be incurred by pain-related functional limitations affecting, for example, pulmonary mechanics[10] and the timing of ambulation.

ACUTE PAIN ASSESSMENT

A variety of scales, such as the visual analog scale and the numeric rating scale, have been used as pain assessment tools in the ICU, although they have not been formally validated for such use (Fig. 3–1). Unfortunately, many ICU patients cannot provide full (or even partial) information regarding their pain. As a consequence, caregivers must sometimes use signs of heightened sympathetic activity (e.g., hypertension, tachycardia, lacrimation, diaphoresis, restlessness) as surrogate markers for the presence of pain; trends in such signs provide a measure of the success of a given intervention. Behavioral-physiologic scales have been described and compared with the visual analog and numeric rating scales.[11,12] These scales, however, are not specific enough to eliminate the subjective component of pain assessment in ICU patients. Thus, pain assessment in critically ill patients remains an inexact science requiring an individualized approach. Assessments must be made consistently and repeatedly and documented in the medical record.

OPTIONS FOR ACUTE PAIN THERAPY

Acute pain is triggered by stimulation of peripheral nociceptors in the skin or deeper structures and is a complex process, involving multiple mediators at various levels of the neuraxis (Fig. 3–2).[5] Different parts of the pain pathway can be targeted either individually or as part of a comprehensive strategy aimed at multiple sites for additive or synergistic effects. Thus, nociception can be influenced peripherally by the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and nerve blocks, at the spinal cord level by the use of epidural or intrathecal medications, and centrally by the use of systemic medications.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Drugs in this class inhibit cyclooxygenase (COX) enzymes, which are involved in prostaglandin synthesis and related inflammation in response to injury. COX-1 is a constitutive enzyme that is present in most tissues and, through the production of prostaglandins E_2 and I_2, serves homeostatic and protective functions.[13] COX-2 is an inducible enzyme that is expressed in response to inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in conjunction with other agents, such as opioids, to take advantage of different side effect profiles and possible synergistic efficacy. As a class, NSAIDs may cause adverse effects that include nausea, gastrointestinal bleeding, inhibition of platelet function, operative site bleeding, renal insufficiency, and bronchospasm in aspirin-sensitive patients (triad of asthma, nasal polyposis, and aspirin allergy).[1,5,14,15]

Currently, ketorolac tromethamine (Toradol) is the only parenteral NSAID available in the United States. It has been

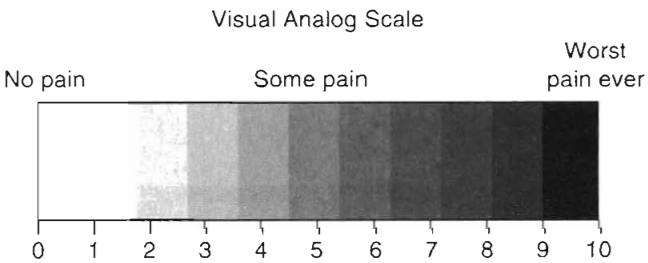

FIGURE 3–1. Visual analog scale. Pain can be rated between 0 (no pain) and 10 (extreme pain). Use of a graphic such as this allows an intubated patient to indicate his or her level of discomfort by pointing. Other scales use cartoon faces that are either smiling or frowning. (From Higgins TL, Jodka PG, Farid A: Pharmacologic approaches to sedation, pain relief and neuromuscular blockade in the intensive care unit. Part II. Clin Intensive Care 2003;14[3-4]:91-98.)

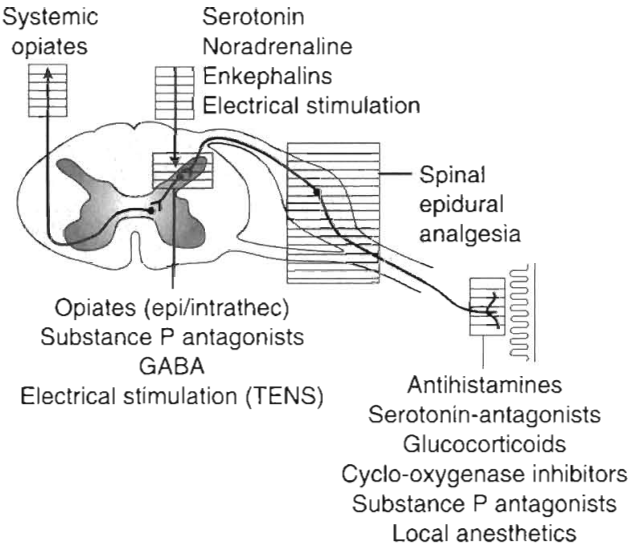

FIGURE 3–2. A "map" of the path of nociceptive information from the periphery to the central nervous system. Modification of that information can occur at any point of information transfer. GABA, gamma-aminobutyric acid; stim, stimulation; TENS, transcutaneous electric nerve stimulation. (From Kehlet H: Modification of responses to surgery by neural blockade: Clinical implications. In Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Pain Management, 2nd ed. Philadelphia, Lippincott, 1988, p 145.)

shown to reduce postoperative opioid requirements and does not cause respiratory depression.[16,17] However, prolonged use has been associated with a significant incidence of the aforementioned side effects (primarily bleeding and renal failure)[18,19]; consequently, ketorolac therapy should be limited to a maximum of 5 days.[1] In addition, ketorolac should be used at decreased dosages, or avoided altogether, in patients at higher risk of such complications owing to advanced age, hypovolemia, and preexisting renal insufficiency. This caution also applies to enterally administered NSAIDs.

Selective COX-2 inhibitors such as celecoxib (Celebrex) and rofecoxib (Vioxx) are available for enteral administration, and injectable COX-2 agents are being studied primarily for the management of acute postoperative pain.[13] The main advantage of these agents over their nonselective relatives lies in the promise of decreased gastrointestinal side effects. However, because COX-2 inhibitors reduce the formation of prostaglandin I_2 (a vasodilating prostaglandin) without affecting the production of thromboxane A_2 (a vasoconstricting prostaglandin), the potential for cardiovascular toxicity exists.[13] Clinical trials are under way to determine the efficacy, cost-effectiveness, and safety of these drugs in the perioperative arena. As with NSAIDs overall, this class of drugs has yet to be formally evaluated in the ICU setting.

OPIOID ANALGESICS

A number of opioids are available(Table 3–1), and this drug class remains the mainstay of ICU analgesia. Morphine, hydromorphone (Dilaudid), and fentanyl are commonly used in ICUs in the United States and have been recommended as first-line narcotic analgesic agents.[1] Opioids bind to a variable degree with various opioid receptor subtypes (μ, δ, κ) located in the brain, spinal cord, and peripheral sites and modulate the transmission and processing of nociceptive signals.[5] The clinical and pharmacologic properties of opioids depend on several variables, such as chemical and solubility properties, dosing regimen (dose, route, and duration of administration), patient characteristics (Table 3–2), and presence of active metabolites. Drugs that are often thought of as short-acting (e.g., fentanyl) actually have a markedly prolonged duration of action if given repeatedly or as an infusion (Fig. 3–3).

Opioids are excellent analgesics, but they are not amnestic agents. As a class, opioids can suppress respiratory drive and promote sedation, gastrointestinal symptoms (ileus, nausea and vomiting, constipation), urinary retention, pruritus, or hypotension. Morphine can cause hypotension by triggering the release of histamine. High doses of meperidine can cause myocardial depression and lead to hypotension on this basis. Hypotension can also be caused by the ablation of pain-mediated sympathetic stimulation, or it may be multifactorial.[20] In actual practice, however, opioids are relatively neutral regarding their hemodynamic effects, if they are used judiciously in euvolemic patients. Of note, coadministration of other central nervous system–active agents (such as benzodiazepines) tends to accentuate opioid-induced side effects, specifically those of sedation, respiratory depression, and hypotension.

Opioids are most commonly administered intravenously in critically ill patients and titrated to effect, either on a scheduled, intermittent basis or as a continuous infusion following a loading dose to achieve analgesia.[1] This strategy avoids concerns regarding unpredictable bioavailability associated with intramuscular, enteral, or transdermal administration and favors more stable analgesic drug concentrations. The benefits of administering analgesics (and sedatives) in such a fashion are several, but they must be balanced against the possibility of inadvertent excess dosing, which may result in prolonged mechanical ventilation and longer hospital stays.[21] It has been reported, however, that scheduled daily interruption of sedative-analgesic drug infusions can help minimize this problem and may actually lead to a shorter duration of mechanical ventilation and a shorter ICU stay.[22]

Morphine is a naturally occurring narcotic analgesic.[1,20] It is metabolized mainly by the liver to an active compound (morphine-6-glucuronide) that can cause a prolonged drug

TABLE 3–1. COMMONLY USED OPIOIDS

Agent	Intermittent Dose	Continuous Dose	Metabolism	Precautions
Fentanyl	0.35–1.5 μg/kg i.v. q 0.5–1 h	0.7–10 μg/kg/h	Oxidation	Rigidity with high doses
Hydromorphone	10–30 μg/kg i.v. q 1–2 h	7–15 μg/kg/h	Glucuronidation	
Morphine	0.01–0.15 mg/kg i.v. q 1–2 h	0.07–0.5 mg/kg/h	Glucuronidation	Histamine release
Meperidine	Not recommended	Not recommended	Demethylation and hydroxylation	Avoid with MAOIs and SSRIs

MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor.

TABLE 3–2. FACTORS INFLUENCING NARCOTIC PHARMOCOKINETICS

Age (increased sensitivity in elderly)
Acid-base status (increased arterial pH increases brain penetration)
Cardiopulmonary bypass (prolongs elimination half-life)
Liver disease
Renal disease (active metabolites may accumulate)
Other central nervous system depressants
Acute and chronic tolerance

effect in patients with renal insufficiency. Onset of action after intravenous administration is relatively slow (5 to 10 minutes) owing to low lipid solubility, and the duration of clinical effect is long enough to permit its use as either an intermittent injection or an infusion. Morphine can cause histamine release and vasodilatation, resulting in hypotension, so it should be used with caution in hypovolemic and hemodynamically unstable patients. Dosing requirements vary significantly from patient to patient and must be individualized (see Table 3–1).

Hydromorphone is a semisynthetic narcotic that, compared with morphine, has a similar duration of action, is a more potent analgesic, does not release histamine, and lacks an active metabolite. These properties make it an attractive alternative to morphine in patients with hemodynamic instability or significant renal impairment.[1] Hydromorphone is also best administered by either infusion or intermittent injection.

Fentanyl is a synthetic narcotic with a potency about 100 times that of morphine. Fentanyl does not cause histamine release, has no active metabolites, and generally has minimal effects on hemodynamics. It is very lipophilic, leading to a rapid onset of action. Fentanyl can accumulate in fat, however, giving rise to a prolonged drug effect if it is given in very high doses or for a lengthy period, even in patients without significant renal or hepatic dysfunction.[1] Rapid high-dose fentanyl injection can cause chest rigidity that may interfere with ventilation, even in intubated patients, necessitating temporary use of a paralytic agent. On balance, however, fentanyl is a good choice for the analgesic needs of unstable ICU patients, provided the aforementioned pharmacokinetic properties are kept in mind.[1]

Meperidine (Demerol) is a synthetic opioid that is about one tenth as potent as morphine. Meperidine is metabolized by the liver into several compounds that are cleared by the kidneys; these compounds tend to accumulate in the setting of renal insufficiency or after repeated administration in patients with normal renal function. Normeperidine is a primary and neuroexcitatory metabolite of meperidine that has been reported to cause seizures.[23] Additionally, meperidine can cause tachycardia[24] due to anticholinergic effects and also may cause myocardial depression at higher doses. Given these concerns and the ready availability of alternative agents, it is difficult to justify the use of meperidine in the ICU.

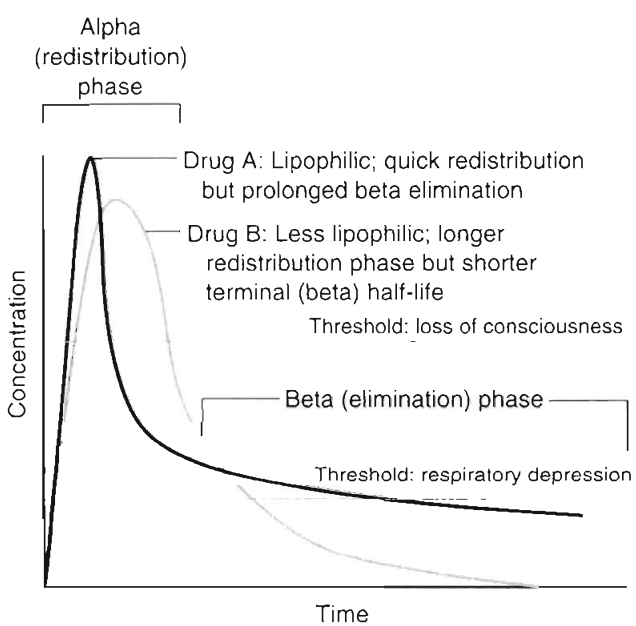

FIGURE 3–3. Pharmacokinetics. A lipophilic drug (drug A) may have a rapid onset and an initially quick distribution but a prolonged beta-elimination (metabolism) phase, resulting in respiratory depression with repeated doses or constant infusion. A less lipophilic drug (drug B) may take longer to redistribute, giving the impression of a prolonged initial duration of action, but does not accumulate, owing to a shorter elimination half-life. Fentanyl is like drug A, whereas morphine is more similar to drug B. (From Higgins TL, Jodka PG, Farid A: Pharmacologic approaches to sedation, pain relief and neuromuscular blockade in the intensive care unit. Part II. Clin Intensive Care 2003;14[3-4]:91-98.)

OTHER NARCOTIC ANALGESICS

Many other opioids are available for clinical use, such as alfentanil, sufentanil, and remifentanil. Comparative data on the use of these drugs in critically ill patients are lacking, and the use of a given agent is determined largely by a given practitioner's experience and practice patterns.

NEURAXIAL ANALGESIC TECHNIQUES

The administration of narcotics, local anesthetics, and other agents via intrathecal or epidural catheters targets the processing of pain signals at the level of the spinal cord or nerve root.[5,25] Intrathecal analgesic techniques are most appropriate for the acute perioperative setting, with limited applicability to the general ICU population. The use of epidural catheters for regional analgesia in ICU patients may be quite useful, assuming that the pain pattern is regionalized and that there are no contraindications to catheter placement (e.g., coagulopathy, uncontrolled infection, unstable spinal skeletal structures). In some patients, epidural analgesia may be preferable to intravenously administered medications, because this approach affords dense regional pain control[5] while largely avoiding the sedative and respiratory side effects of systemic medications. Because there are multiple factors related to the feasibility and utility of neuraxial techniques in ICU patients, consultation with a pain management specialist is advised when such an approach is being considered.

ANNOTATED REFERENCES

Carroll KC, Atkins PJ, Herold GR, et al: Pain assessment and management in critically ill postoperative and trauma patients: A multisite study. Am J Crit Care 1999;8:105-117.

A descriptive, correlational study of pain management in 213 patients in 13 ICUs. The authors found that patients were generally satisfied with their pain management, despite being in pain. They concluded that patient satisfaction alone is not a reliable means of gauging the effectiveness of pain management.

Desbiens NA, Wu AW, Broste SK, et al: Pain and satisfaction with pain control in seriously ill hospitalized adults: Findings from the SUPPORT research investigations. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment. Crit Care Med 1996;24:1953-1961.

In the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT), approximately 50% of patients experienced pain, 15% reported extreme or moderate amounts of pain, and 15% were dissatisfied with their pain management. Patients were more likely to be dissatisfied if they had severe pain, greater anxiety, depression, and alteration of mental status.

Gilron I, Milne B, Hong M: Cyclooxygenase-2 inhibitors in postoperative pain management: Current evidence and future directions. Anesthesiology 2003; 99:1198-1208.

An up-to-date review of COX-2 inhibitors for analgesia in the postoperative period.

Jacobi J, Fraser GL, Coursin DB, et al: Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002;30:119-141.

A review of pain assessment and analgesic therapy in the critically ill patient promulgated by a task force of the American College of Critical Care Medicine of the Society of Critical Care Medicine. Recommendations are made (and graded), based on a critical evaluation of the literature.

Kress JP, Pohlman AS, O'Connor MF, Hall JB: Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342:1471-1477.

A classic study showing that the daily interruption of sedatives and analgesics can decrease the duration of mechanical ventilation.

Novaes MA, Knobel E, Bork AM, et al: Stressors in ICU: Perception of the patient, relatives and health care team. Intensive Care Med 1999;25: 1421-1426.

The ICU environmental stressor scale was administered to patients, families, and ICU professionals during a patient's first week of care. Pain, inability to sleep, and having tubes in the mouth were the most important stressors identified by the three groups.

Chapter 4
FEVER AND HYPOTHERMIA

Mitchell P. Fink

Fever is defined as an increase in body temperature. Normal body temperature is 36.8 ± 0.4° C. Normally, body temperature varies in a circadian fashion by about 0.6° C, being lowest in the morning and highest in the late afternoon or early evening. Fever is triggered by the release of various cytokines—notably, interleukin-1 beta, tumor necrosis factor, and interleukin-6—that are capable of causing secretion of prostaglandin E_2 in the hypothalamus. Prostaglandin E_2 binds to prostaglandin receptors on neurons in the ventromedial preoptic area and the median preoptic nucleus.[1,2] Activation of these receptors triggers a number of neurohumoral and physiologic changes that lead to increased body temperature.

Body temperature can be measured using an oral, axillary, or rectal mercury-filled glass thermometer. These traditional approaches, however, have been largely replaced by a variety of safer and more environmentally friendly methods. These approaches use thermistors located on catheters or probes situated in the pulmonary artery, distal esophagus, urinary bladder, or external ear canal.[3] Infrared detectors can also be used to measure tympanic membrane temperature. Forehead skin temperature can be measured using a temperature-sensitive patch. A core (i.e., rectal, pulmonary artery, esophageal, bladder, or tympanic membrane) temperature greater than 38.3° C should be regarded as evidence of fever.

Fever is a cardinal sign of infection. Accordingly, the new onset of fever should trigger a careful diagnostic evaluation, looking for a source of infection. The diagnostic evaluation should be thorough and tailored to the recent history of the patient. For example, the possibility of a central nervous system infection should receive greater attention in a patient with recent or ongoing central nervous system instrumentation. By the same token, if a patient recently underwent a gastrointestinal surgical procedure, the clinician should have a high index of suspicion for an intra-abdominal source of infection. Key elements in the assessment of new-onset fever in the intensive care unit (ICU) are listed in Table 4–1. Common sources of infection in ICU patients are listed in Table 4–2.

Although fever in the ICU is most commonly due to infection, myriad noninfectious causes of systemic inflammation can also result in hyperthermia. Important noninfectious causes of fever in ICU patients are listed in Table 4–3. Some authors claim that noninfectious causes of fever rarely result in a core temperature greater than 38.9° C,[4,5] although rigorous data in support of this view are lacking. By the same token, infections are rarely, if ever, associated with core temperatures greater than 41.1° C. When the core temperature is this high, the clinician should suspect malignant hyperthermia, neuroleptic malignant syndrome, or heat stroke.

In general, fever should not be treated using antipyretics. This view is based on data that suggest that hyperthermia is an adaptive response that enhances the host's ability to fight infection.[6,7] In addition, body temperature is an unreliable clinical parameter when patients are receiving antipyretic therapy. These considerations notwithstanding, antipyretic therapy should be administered to selected patients with fever. Among such patients are those with acute coronary syndromes (i.e., myocardial infarction or unstable angina), because the tachycardia that usually accompanies the febrile response can exacerbate imbalances between myocardial oxygen delivery and demand. Febrile patients with head trauma, subarachnoid hemorrhage, or stroke should receive antipyretics to prevent temperature-related increases in cerebral oxygen utilization. Children with temperatures greater than 40° C or a history of seizures should also be treated.

Hypothermia blankets are often used to lower the core temperature in febrile ICU patients; however, hypothermia

TABLE 4–1. KEY ELEMENTS IN THE EVALUATION OF NEW-ONSET FEVER IN ICU PATIENTS

Be familiar with the patient's history. Pay particular attention to possible predisposing causes of fever.
Perform a careful physical examination. Pay particular attention to surgical wounds and vascular access sites. Look for evidence of pressure-induced skin ulceration. In patients with recent median sternotomy, evaluate the stability of the chest closure. Perform a careful abdominal examination.
Obtain or review a recent chest x-ray, looking for evidence of new infiltrates or effusions.
Obtain appropriate laboratory studies. At a minimum, these studies should include a peripheral white blood cell count and cultures of blood and urine. If the patient is endotracheally intubated or has a tracheotomy, obtain a sample of sputum for Gram stain. In some centers, sputum is routinely cultured. In other centers, bronchoalveolar lavage or bronchial brushing for quantitative microbiology is performed using blind or bronchoscopic methods.
Central venous catheters that have been in place for longer than 96 h should be removed. The tip should be submitted for semiquantitative microbiology.
In patients receiving antibiotics for more than 3 days, a stool sample should be analyzed for the presence of *Clostridium difficile* toxin.
More extensive diagnostic evaluation should be considered in a graded fashion based on history, physical examination findings, laboratory results, persistence of fever despite presumably appropriate antimicrobial chemotherapy, or clinical instability. These additional tests and procedures include diagnostic thoracentesis, paracentesis, and lumbar puncture. Imaging studies should be considered, including abdominal or cardiac ultrasonography and head, chest, or abdominal computed tomography.

TABLE 4–2. COMMON INFECTIOUS CAUSES OF FEVER

- Central nervous system
  - Meningitis
  - Encephalitis
  - Brain abscess
  - Epidural abscess
- Head and neck
  - Acute suppurative parotitis
  - Acute sinusitis
  - Parapharyngeal and retropharyngeal space infections
  - Acute suppurative otitis media
- Cardiovascular
  - Catheter-related infection
  - Endocarditis
- Pulmonary and mediastinal
  - Pneumonia
  - Empyema
  - Mediastinitis
- Hepatobiliary and gastrointestinal
  - Diverticulitis
  - Appendicitis
  - Peritonitis (spontaneous or secondary)
  - Intraperitoneal abscess
  - Perirectal abscess
  - Infected pancreatitis
  - Acute cholecystitis
  - Cholangitis
  - Hepatic abscess
  - Acute viral hepatitis
- Genitourinary
  - Bacterial or fungal cystitis
  - Pyelonephritis
  - Perinephric abscess
  - Tubo-ovarian abscess
  - Endometritis
  - Prostatitis
- Breast
  - Mastitis
  - Breast abscess
- Cutaneous and muscular
  - Cellulitis
  - Suppurative wound infection
  - Necrotizing fasciitis
  - Bacterial myositis or myonecrosis
  - Herpes zoster
- Osseous
  - Osteomyelitis

TABLE 4–3. NONINFECTIOUS CAUSES OF FEVER

- Central nervous system
  - Subarachnoid hemorrhage
  - Intracerebral hemorrhage
  - Infarction
- Cardiac
  - Myocardial infarction
  - Pericarditis
- Pulmonary
  - Atelectasis
  - Pulmonary embolism
  - Fibroproliferative phase of acute respiratory distress syndrome
- Hepatobiliary and gastrointestinal
  - Acalculous cholecystitis
  - Acute pancreatitis
  - Active Crohn's disease
  - Toxic megacolon
  - Alcoholic hepatitis
- Rheumatologic syndromes
  - Vasculitides (e.g., polyarteritis nodosa, temporal arteritis, Wegener's syndrome)
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Goodpasture's syndrome
- Endocrine
  - Hyperthyroidism
  - Adrenal insufficiency
  - Pheochromocytoma
- Other
  - Drug reactions ("drug fever")
  - Transfusion reactions
  - Neoplasms (especially lymphoma, hepatoma, renal cell carcinoma)
  - Malignant hyperthermia
  - Neuroleptic malignant syndrome
  - Serotonin syndrome
  - Opioid withdrawal syndrome
  - Ethanol withdrawal syndrome
  - Transient endotoxemia or bacteremia associated with procedures
  - Devitalized tissue secondary to trauma
  - Hematoma

blankets are no more effective in cooling patients than are antipyretic agents.[8] Hypothermia blankets can cause large temperature fluctuations and are associated with rebound hyperthermia when removed.[8] Additionally, external cooling can augment hypermetabolism and actually promote persistent fever. Lenhardt and colleagues demonstrated that active external cooling in volunteers with induced fever increased oxygen consumption by 35% to 40% and was associated with a significant increase in circulating epinephrine and norepinephrine concentrations.[9]

In view of the preceding, when treatment of fever is warranted, administration of an antipyretic agent is the recommended approach. Commonly used antipyretics include isoform nonselective cyclooxygenase inhibitors, such as ibuprofen or aspirin, or acetaminophen. Although acetaminophen is not a cyclooxygenase inhibitor, it is converted in the central nervous system to a metabolite with activity against this enzyme. Cyclooxygenase inhibitors treat fever by inhibiting the formation of prostaglandin E_2. Because corticosteroids, such as hydrocortisone or methylprednisolone, are potent anti-inflammatory agents, these drugs can suppress the febrile response to infection. Other anti-inflammatory agents have a similar effect. Therefore, absence of fever should not be used to rule out infection, especially in patients receiving corticosteroids or other potent anti-inflammatory drugs.

A reasonable approach for evaluating fever in ICU patients was described by Marik.[4] As depicted in Figure 4–1, blood cultures should be obtained whenever an ICU patient develops a new fever. A comprehensive physical examination should be carried out, and a chest x-ray obtained and reviewed. Noninfectious causes of fever should be excluded. In patients with an obvious focus of infection, a directed diagnostic evaluation is necessary. However, if there is no obvious source of infection and the patient is not deteriorating clinically, it is reasonable to obtain blood cultures and observe the patient for 48 hours before ordering additional diagnostic studies or starting empirical antibiotics. This approach is not reasonable, however, if new fever is accompanied by other signs of worsening clinical status such as arterial hypotension, oliguria, increasing confusion, rising serum lactate concentration, falling platelet count, or worsening coagulopathy. Nor is this approach reasonable if the core temperature is greater than 39° C but less than 41.1° C. Patients in this category should receive empirical antimicrobial chemotherapy while aggressive attempts are made to diagnose the source of infection. All febrile neutropenic patients should receive broad-spectrum empirical antimicrobial chemotherapy after appropriate cultures are obtained.

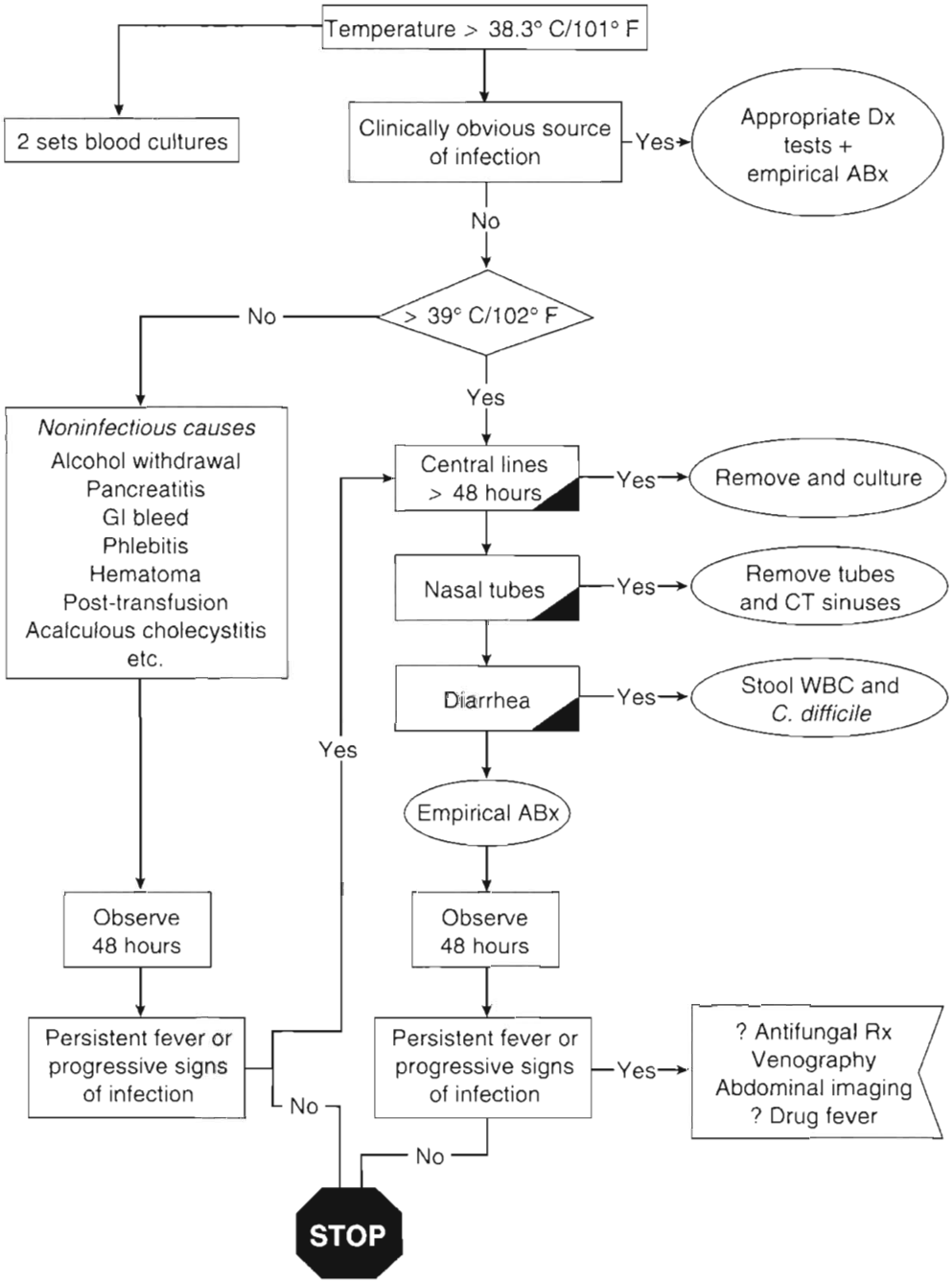

FIGURE 4–1. Approach to evaluating patients with fever in the intensive care unit. ABx, antibiotics; CT, computed tomography; Dx, diagnostic; GI, gastrointestinal; Rx, prescription; WBC, white blood cell. (From Marik PE: Fever in the ICU. Chest 2000;117:855-869.)

Chapter 5

VERY HIGH SYSTEMIC ARTERIAL BLOOD PRESSURE

Michael Donahoe

Very high systemic arterial blood pressure is a common problem in the ICU. The intensivist must distinguish conditions requiring prompt intervention from clinical situations in which aggressive blood pressure control could lead to an adverse outcome. This distinction cannot be based solely on the level of arterial blood pressure elevation.

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure described two acute conditions of elevated systemic arterial pressure.[1] A *hypertensive emergency* is a rare clinical situation that requires immediate blood pressure reduction (not necessarily to normal ranges) within minutes to hours. Hypertensive emergencies are defined by the presence of new or progressive end-organ damage of the neurologic, cardiovascular, or renal systems (Table 5-1).

In contrast, *hypertensive urgencies* are characterized by elevated systemic arterial pressure without evidence of end-organ damage. In these cases, a gradual reduction of blood pressure over several hours to days is the goal because there is no proven benefit to more rapid reduction of blood pressure in asymptomatic patients. Cerebral or myocardial ischemia or infarction can be induced by aggressive antihypertensive therapy if the blood pressure decreases to less than a level that supports adequate tissue perfusion.[2] Hypertensive urgencies are not to be ignored, however, because they can progress to end-organ damage if blood pressure remains uncontrolled over a sustained interval.

Another term, *accelerated hypertension*, also implies end-organ damage. In this case, the clinical markers of damage are pathophysiologic changes involving the retina of the eye, including exudates, hemorrhages, arteriolar narrowing, and spasm. The term *malignant hypertension* is characterized by the additional retinal finding of papilledema. Both of these conditions are often associated with vascular injury to the kidney, termed *malignant nephrosclerosis*, and to other target organs. Two large series confirmed that specific retinal findings do not predict the outcome in patients with elevated systemic arterial pressure.[3,4] This chapter uses the term *hypertensive emergency* to identify acute increases in systemic blood pressure that mandate prompt intervention by the intensivist.

PATHOPHYSIOLOGY

An acute elevation in systemic arterial blood pressure most frequently results from increased systemic vascular resistance. Increased vascular resistance can be precipitated by increased circulating concentrations of catecholamines, increased activity of the sympathetic nervous system, or activation of the renin-angiotensin system. Less commonly, hypertension occurs in the setting of significant volume expansion or augmented contractility of the left ventricle or both.

Two crucial components in the pathophysiology of organ dysfunction associated with accelerated hypertension include the development of obliterative vascular lesions and disordered vasoregulation. The vascular changes of the retina, in accelerated and malignant hypertension, are mirrored by similar changes in the kidney and other organs, leading to a proliferative arteritis and, in advanced stages of the process, fibrinoid necrosis. Presumably, vasoactive mediators play a key role in this process, but the mechanisms underlying these pathologic changes due to severe hypertension remain to be elucidated. A state of relative ischemia is produced in affected organs, resulting in end-organ dysfunction. Early recognition and control of elevated blood pressure are crucial to prevent progression to this more advanced stage of disease.

Aggressive control of elevated systemic arterial blood pressure must be undertaken with caution. There is a rightward shift of the pressure-flow relationship in the central nervous system in patients with long-standing hypertension.[5] Normally, cerebrovascular arteriolar tone is adjusted over a range of perfusion pressures to maintain a constant blood flow. In normal individuals, normal flow is maintained over a range of mean arterial pressure from approximately 60 to 150 mm Hg. A rightward shift in this relationship results in the loss of autoregulation at higher mean arterial pressure values. Aggressive lowering of the blood pressure in patients with an altered autoregulation curve can lead to compromised organ perfusion and ischemia. These pathophysiologic observations are supported by numerous clinical observations. The lower limit of autoregulation is about 20% to 25% below the resting mean arterial pressure. A safe level of blood pressure reduction in the acute setting has been proposed as a 25% reduction of mean arterial pressure or a diastolic blood pressure in the 100 to 110 mm Hg range. This regulated level of blood pressure reduction should maintain critical organ perfusion even in patients with long-standing hypertension.

CEREBROVASCULAR DISEASE

HYPERTENSIVE ENCEPHALOPATHY

Acute elevations in systemic arterial blood pressure can lead to hypertensive encephalopathy. The most common presenting

TABLE 5–1. HYPERTENSIVE EMERGENCIES

Cerebrovascular

Hypertensive encephalopathy
Acute stroke
Subarachnoid hemorrhage

Cardiovascular

Acute coronary syndrome
Acute left ventricular dysfunction
Acute aortic dissection
Accelerated/malignant hypertension

Renovascular

Acute glomerulonephritis
Scleroderma renal crisis
Post–kidney transplantation

Excess Catecholamine States

Pheochromocytosis
Pharmacologically mediated
  Monoamine oxidase inhibitor–tyramine interaction
  Antihypertensive withdrawal
  Alpha-stimulant intoxication
Autonomic hyperreflexia post–spinal cord injury

Miscellaneous Conditions

Eclampsia/preeclampsia
Postoperative hypertension

clinical manifestations include headache, nausea and vomiting, visual disturbances, focal neurologic findings, and seizures. If left untreated, the condition can progress to coma and death. Most patients with hypertensive encephalopathy have a mean arterial pressure significantly greater than the patient's baseline blood pressure, although not in the range typically associated with hypertensive emergency. Retinal findings, including arteriolar spasm, exudates or hemorrhages, and papilledema, are often present. Absence of these findings does not exclude the diagnosis of hypertensive encephalopathy, however. Neuroimaging studies suggest that edema involving the subcortical white matter of the parieto-occipital regions is a characteristic feature of hypertensive encephalopathy; this finding is termed *posterior leukoencephalopathy*.[6] Although the exact mechanism is debated, disordered regulation of vascular flow is believed to contribute to the clinical and radiographic findings. Hypertensive encephalopathy must be distinguished from other acute neurologic conditions associated with hypertension by a thorough evaluation. In general, the neurologic symptoms of stroke or intracranial hemorrhage have a more acute onset than the symptoms associated with hypertensive encephalopathy. The diagnosis of hypertensive encephalopathy is confirmed by the absence of other conditions and the prompt resolution of symptoms with effective blood pressure control. The failure of a patient to improve within 6 to 12 hours of blood pressure reduction should prompt an investigation for an alternative cause of the mental status changes. In most cases, the condition is entirely reversible with no observable adverse outcomes.

ACUTE STROKE

Hypertension is reportedly present in 80% of patients with an acute stroke.[7] The incidence of hypertension is higher in patients with primary intracerebral hemorrhage compared with ischemic disorders.[8,9] Current data suggest that hypertension in the setting of acute stroke is associated with a poor functional outcome.[8,10] Despite this knowledge, the treatment of elevated systemic arterial pressure in acute stroke is poorly investigated and complex.

Two important clinical features complicate the management of hypertension in acute stroke. First, during acute stroke, cerebral autoregulation may be compromised, and lowering of blood pressure may compromise cerebral blood flow further and extend ischemic injury.[11] Second, medications used to treat hypertension may lead to cerebral vasodilation, resulting in increased cerebral blood flow and progression of cerebral edema.[12] Ideally a "correct" level of mean arterial pressure should be maintained in each patient to maintain cerebral perfusion pressure without risking worsening cerebral edema or progression of the lesion, but the clinical determination of this "ideal" value is difficult.

Data are lacking from randomized clinical trials to guide antihypertensive therapeutic decisions in acute stroke. Only a few drug classes have been investigated in this condition, and the total number of patients studied is small. Published guidelines are not based on solid evidence. Using available information, only modest reductions in mean arterial pressure (10% to 15%) are advised in the acute setting of an ischemic stroke. The natural history is for the blood pressure to begin declining shortly after the onset of the acute event and to stabilize within the first 24 hours. Agents that allow titration of therapy (i.e., intravenous medications) may be preferred over oral agents when treatment is necessary, provided that the patient can be monitored carefully in a stroke unit. Also, many patients are unable to tolerate oral medications because of stroke-induced swallowing dysfunction.

For patients with hemorrhagic strokes, the general recommendation is that blood pressure should be reduced to prevent hematoma progression and rebleeding. Even this recommendation is not based on carefully controlled clinical trials, however. Similar cautions to limit the extent of blood pressure reduction (i.e., 15% to 20%) are advised.

SUBARACHNOID HEMORRHAGE

A patient with aneurysmal subarachnoid hemorrhage provides the challenge of an acute neurologic syndrome secondary to an initial insult, followed by the ongoing risk of additional insults over time. These additional insults can include hydrocephalus, rebleeding, and vasospasm. Hemodynamic management is complicated by the competing goals of lowering blood pressure to minimize the rebleeding risk and elevating blood pressure to minimize the risk of cerebral vasospasm and infarction.[13] In general, hypertension is not treated aggressively in this population for fear of precipitating cerebral ischemia. Treatment can be guided by the neurologic condition. For a patient with a normal neurologic picture, small reductions in blood pressure can be accomplished to minimize the risk of rebleeding. For a neurologically impaired patient, aggressive control of blood pressure is avoided to maintain cerebral perfusion pressure.

CARDIOVASCULAR DISEASE

ACUTE CORONARY SYNDROME

Patients presenting with acute myocardial ischemia or infarction frequently have elevated systemic arterial pressure.

The increased afterload increases myocardial oxygen demand. A reduction in myocardial work, achieved by decreasing heart rate and blood pressure, favorably reduces myocardial oxygen demand and infarct size in these patients. A reduction of high systemic arterial pressure in this setting should be done cautiously, however. Potent systemic vasodilation, without coronary vasodilation, can lead to a reduced coronary artery perfusion pressure and infarct extension. For this reason, nitroglycerin, a potent coronary and arterial vasodilator, is often the antihypertensive agent of choice in acute coronary syndromes. In combination with beta-blocker therapy, this approach to reduction in arterial pressure can reduce cardiac workload significantly in the setting of ischemia. Careful monitoring of hemodynamic indices during treatment is paramount.

ACUTE LEFT VENTRICULAR DYSFUNCTION

High systemic arterial blood pressure in a patient with acute pulmonary edema contributes to an increased myocardial workload and diastolic dysfunction. The hypertension may be a primary event with secondary myocardial dysfunction or secondary to the sympathoadrenal response to hypoxemia, increased work of breathing, and anxiety in the setting of acute left ventricular dysfunction. Regardless of the cause, efforts to control elevated systemic arterial pressure are essential. For a critically ill patient, infusion of sodium nitroprusside permits rapid titration of blood pressure. Angiotensin-converting enzyme (ACE) inhibitors, which are available in oral and intravenous forms, are associated with acute and long-term beneficial effects in patients with left ventricular failure.[14,15] Aggressive diuresis before blood pressure control may not be advised. Patients with hypertensive emergencies in particular may have had a natriuresis resulting in elevated levels of renin production by the kidney and increased circulating levels of the potent endogenous vasoconstrictor angiotensin II. Further reduction in renal perfusion can lead to increased production of angiotensin II. Medications that increase cardiac work (e.g., hydralazine) or impair cardiac contractility (e.g., labetalol) also may be contraindicated in this setting.

In contrast, nicardipine, a calcium antagonist, has been associated with reduced systemic arterial pressure with preservation of coronary blood flow, favoring the use of this medication in acute left ventricular dysfunction.[16] Likewise, fenoldopam, a dopamine-1 receptor antagonist, has been associated with preservation of coronary blood flow during treatment to reduce systemic arterial pressure.[17]

ACUTE AORTIC DISSECTION

Aortic dissection is believed to result from an intimal tear in the aortic wall. The primary morbidity and mortality result from extension of that tear. This extension is promoted by factors that increase the rate of change of aortic pressure (dP/dt), including elevation in blood pressure, heart rate, and myocardial stroke volume. Blood pressure should be reduced promptly to near-normal levels. Aggressive control of blood pressure with a vasodilator could precipitate a reflex tachycardia, increasing dP/dt. Combined-modality therapy to promote vasodilation (sodium nitroprusside) and control cardiac contractility (beta blocker) is advocated for this disorder. Alternatively, drugs that do not increase dP/dt, such as trimethaphan, can be used effectively to control blood pressure.

RENOVASCULAR DISEASE

The kidney is a source of the mediators that promote hypertension (i.e., angiotensin II) and a target of high systemic arterial pressure. Chronic hypertension is secondary only to diabetes mellitus as a cause of renal insufficiency. In younger patients, the presence of severe hypertension suggests the possibility of intrinsic renal disease, such as poststreptococcal glomerulonephritis and IgA nephropathy. Renovascular disease is noted in 30% of white patients with severe hypertension and retinopathy.[18]

Elevated systemic arterial pressure should be regulated in patients with underlying renal insufficiency, and a comprehensive workup should be initiated to determine the cause-and-effect relationship. Traditional vasodilator medications, such as labetalol and sodium nitroprusside, are preferred to ACE inhibitors in the acute setting because ACE inhibitors can compromise renal function.[19] The risk of ACE inhibitor–induced renal dysfunction is particularly great in patients with hyperkalemia and acute uremia.[19]

SCLERODERMA RENAL CRISIS

Scleroderma renal crisis is characterized by the development of acute renal failure associated with moderate-to-severe hypertension and a normal to minimally abnormal urine sediment. The most significant risk factor for scleroderma renal crisis is the presence of the diffuse skin involvement characteristic of the disease. The disorder results in marked activation of the renin-angiotensin system. Aggressive control of blood pressure using ACE inhibitors, particularly early in the disease process, can control blood pressure in 90% of patients and promote a greater rate of recovery in renal function.[20] Captopril has been the most extensively studied agent used for treatment of this hypertensive emergency.

POST–KIDNEY TRANSPLANTATION

Hypertension after renal transplantation occurs in a high percentage of patients. In the immediate post-transplantation period, hypertension usually is a manifestation of graft rejection, ischemia, or medication toxicity. Corticosteroids and calcineurin inhibitors promote the development of hypertension. In addition, renal artery stenosis can complicate allograft function and should be evaluated in any patient with resistant hypertension. In the immediate post-transplant period, blood pressure should be regulated at the upper limits of normal to preserve graft function. In the later post-operative period, even more strict control of blood pressure is preferred.[21] The therapy of choice for post–kidney transplantation hypertension is controversial. Calcium channel blockers may reverse cyclosporine-induced renal vasoconstriction; however, outcome trials in this area showed conflicting results.[22,23] ACE inhibitors have the potential to exacerbate renal dysfunction and augment the hyperkalemia induced by calcineurin inhibitors. Either category of medication for blood pressure control could be used with careful monitoring for toxicity.

EXCESS CATECHOLAMINE STATES

PHEOCHROMOCYTOMA

Pheochromocytoma can result in the production of circulating mediators leading to catecholamine excess. These mediators result in hypertension, diaphoresis, tachycardia, and paresthesias of the hands and feet. These attacks can last minutes to days and occur several times a day or once per month. Operative manipulation of the tumor can result in perioperative hypertension. The treatment of hypertension in this disorder must avoid the use of isolated therapy with a beta blocker, a strategy that can lead to unopposed alpha-adrenergic stimulation with the risk of further vasoconstriction and blood pressure elevation. The preferred agent for treatment of hypertension due to pheochromocytoma is phentolamine, a potent alpha-adrenergic antagonist. If necessary, this medication can be combined with a beta blocker, or a combined alpha/beta blocker, such as labetalol, can be used safely.

PHARMACOLOGICALLY MEDIATED

Clonidine withdrawal can mimic the crisis of pheochromocytoma. Clonidine is a centrally acting stimulant of alpha-adrenergic receptors that reduces peripheral adrenergic system activation. Rapid withdrawal or tapering of therapy with this agent has been associated with a hyperadrenergic state, characterized by hypertension, diaphoresis, headache, and anxiety.[24] The syndrome can best be treated by restarting treatment with clonidine. If the symptoms are extreme, treatment can be initiated as outlined for patients with pheochromocytoma. Hypertension also can occur during the withdrawal phase of alcohol abuse[25] and beta-blocker therapy.

Monoamine oxidase inhibitor use can be associated with a marked elevation in the systemic arterial blood pressure, if the patient consumes foods or medications containing tyramine or other sympathomimetic amines. Tyramine-containing foods include champagne, avocados, smoked or aged meats, and fermented cheeses. The monoamine oxidase inhibitor interferes with degradation of the tyramine in the intestine, leading to excess absorption and tyramine-induced catecholamine activity in the circulation. Other medications, including metoclopramide, a dopamine agonist; the calcineurin inhibitors cyclosporine and tacrolimus; and drugs of abuse, such as cocaine, phenylpropanolamine, phenylcyclidine, and methamphetamine, must be considered as possible factors in an ICU patient with elevated systemic arterial pressure.

After spinal cord injury, hypertensive states may occur particularly with stimulation of dermatomes and muscles below the level of the spinal cord injury. Patients with hypertension in this setting typically have lesions above the level of the thoracolumbar sympathetic neurons. Blood pressure elevation is believed to result from excess stimulation of sympathetic neurons. Hypertension is accompanied by bradycardia through stimulation of the baroreceptor reflex. Treatment is focused on minimizing stimulation and providing medical therapy as necessary. Patients with Guillain-Barré syndrome can manifest a similar syndrome.

MISCELLANEOUS CONDITIONS

PREECLAMPSIA/ECLAMPSIA

Preeclampsia/eclampsia is the second most common cause of maternal death in the United States after thromboembolic disease. Hypertension occurs as one manifestation of preeclampsia in a pregnant patient; the other key features are proteinuria and edema. Hypertension in pregnancy also can be seen secondary to chronic hypertension and transient or gestational hypertension. The new onset of hypertension after 20 weeks of gestation is most characteristic of a patient with preeclampsia.

When possible, the optimal treatment of preeclampsia is delivery of the fetus, an approach that prevents progression to eclampsia. Blood pressure should be regulated, however, to prevent end-organ damage. Hydralazine generally is considered the agent of choice in pregnant patients. Sodium nitroprusside (fetal defects), ACE inhibitors (renal dysfunction in fetus), and trimethaphan (meconium ileus) should be avoided because of associated toxicities in pregnant patients. In addition to hydralazine, alternative agents that can be used in this population include labetalol and nicardipine.

POSTOPERATIVE HYPERTENSION

Poorly controlled hypertension preoperatively and intraoperatively is associated with an increased rate of postoperative complications.[26,27] Hypertension in the postoperative period can be seen in 75% of patients, and the risk seems to be greater for vascular surgical procedures, including abdominal aortic aneurysm repair, carotid endarterectomy, and coronary artery revascularization.[28] Postoperative hypertension in these patients can lead to complications, including bleeding from suture lines, intracerebral hemorrhage, and left ventricular dysfunction. Postoperative hypertension can be caused by elevated systemic vascular resistance in response to circulating stress hormones, activation of the renin-angiotensin-aldosterone system, or altered baroreceptor function after certain types of surgery.

Patients with postoperative hypertension must be investigated thoroughly to rule out reversible causes before the institution of drug therapy. Factors such as pain, anxiety, hypervolemia, hypoxemia, hypercarbia, and nausea can contribute to postoperative hypertension. Postoperative hypertension often is limited in duration (i.e., 2 to 12 hours), and aggressive attempts to lower blood pressure acutely can lead to delayed hypotension.

Postoperative hypertension typically is treated by the administration of vasodilators, including sodium nitroprusside and nitroglycerin. Beta blockers can be added for additional control.

ANTIHYPERTENSIVE MEDICATIONS

The goal of antihypertensive therapy in the emergent situation is to lower blood pressure to a safe range as quickly as possible. In general, intravenous medications are preferred, allowing titration of dosing to minimize the risk of excessive hypotension. The precise level of blood pressure reduction necessary to reduce the risk of organ ischemia is not defined. A commonly proposed goal is to lower the mean arterial pressure by approximately 20%, or to reduce diastolic blood pressure to 100 to 110 mm Hg. To monitor carefully the effect of antihypertensive therapy, these patients are best monitored in the ICU.

For hypertensive urgencies, oral therapy generally can be used to lower the blood pressure to safer levels over a 24-hour interval. These patients in general do not require monitoring in an ICU.

TABLE 5–2. INTRAVENOUS ANTIHYPERTENSIVE THERAPY

Medication (Route)	Mechanism	Dosing	Indication	Contraindication
Nitroprusside (i.v. infusion)	Arteriolar and venous vasodilator	0.25-10 µg/kg/min i.v. infusion	Most hypertensive emergencies	Contraindicated in pregnancy. Caution with use in cerebral edema, acute coronary syndrome, or azotemia
Labetalol (i.v. infusion, oral)	Alpha/beta-adrenergic blocker	i.v. bolus 20 mg initially followed by 20-80 mg every 10 min Infusion: 0.5-2 mg/min	Most hypertensive emergencies	Contraindicated in acute heart failure or in patients nontolerant of beta blockers
Nicardipine (i.v. infusion)	Calcium channel blocker	Initial: 5 mg/h Maximum: 15 mg/h	Most hypertensive emergencies	Contraindicated in acute heart failure and caution with use in acute coronary syndrome
Fenoldopam (i.v. infusion)	Peripheral dopamine-1 antagonist	Initial: 0.1 µg/kg/min	Most hypertensive emergencies	Caution in patients with glaucoma
Nitroglycerin (i.v. infusion)	Venodilator	Initial: 0.25-0.5 µg/kg/min Maximum: 8-10 µg/kg/min	Acute coronary syndromes	
Phentolamine (i.v.)	Alpha-adrenergic blocker	5-10 mg every 5-15 min	Pheochromocytoma, catecholamine withdrawal, catecholamine excess	
Enalaprilat	Angiotensin-converting enzyme inhibitor	1.25-5 mg every 6 h	Scleroderma crisis and acute left ventricular dysfunction	Caution with use in acute coronary syndrome
Hydralazine (i.v., oral)	Arteriolar vasodilator	Initial: 10 mg every 20-30 min Maximum: 20 mg	Pregnancy	

Medications available for the treatment of elevated systemic arterial pressure are summarized in Table 5-2. Sodium nitroprusside has been the gold standard for the treatment of hypertensive emergencies because of its short duration of action allowing careful titration. Sodium nitroprusside acts as a direct vasodilator of arterioles and veins. The blood pressure response to nitroprusside infusion is rapid and mandates the use of this medication in a well-monitored environment. The infusion must be provided by a calibrated pump with frequent blood pressure recording. Typically, intra-arterial blood pressure recording is preferred owing to the need for rapid and frequent monitoring, particularly during the initial titration. An accurate noninvasive system may offer equal efficacy, however.

The major concern with sodium nitroprusside is the rare risk of cyanide, or thiocyanate, toxicity. Cyanide intoxication is manifested by alterations in mental status, gastrointestinal complaints, arrhythmias, seizures, or lactic acidosis. The last finding occurs in the setting of a reduced systemic oxygen uptake and a narrow arterial-venous oxygen gradient. Cyanide is liberated during the combination of nitroprusside with sulfhydryl groups in red blood cells and tissues. The circulating cyanide is converted rapidly in the liver to thiocyanate with subsequent excretion by the kidney. Cyanide toxicity from nitroprusside is uncommon and occurs primarily in patients receiving infusions for greater than 24 to 48 hours, in patients with underlying renal insufficiency, and in patients in whom the dose used exceeds the capacity of the body to detoxify cyanide (>2 µg/kg/min increases the risk of cyanide accumulation).

The treatment of cyanide intoxication involves the administration of sodium thiosulfate. Sodium thiosulfate donates its sulfane sulfur atom in a reaction catalyzed by the enzyme rhodanese to convert cyanide to the much less toxic thiocyanate ion, which is excreted in the urine. For severe cases, sodium nitrite also may be administered. The nitrites exert their effect by oxidizing hemoglobin to methemoglobin, with attraction of the cyanide molecule to the ferric ion; this results in displacement of the cyanide from the cytochrome aa_3 to form a ferricyanide complex. The onset of action of sodium nitrite is rapid, but the induction of methemoglobinemia decreases the oxygen-carrying capacity of blood and may be harmful in patients with anemia or significant carboxyhemoglobinemia.

Hydroxocobalamin (vitamin B_{12a}) is another safe and effective antidote for cyanide intoxication that does not effect oxygen-carrying capacity. This compound reacts with circulating cyanide to form cyanocobalamin, with subsequent urinary excretion. Hydroxocobalamin has been shown to minimize the risk of cyanide accumulation during nitroprusside use in surgery.[29]

Thiocyanate toxicity in association with nitroprusside infusion also is rare. Clinical manifestations include fatigue, gastrointestinal complaints, and mental status changes. The symptoms most typically appear with plasma thiocyanate levels that exceed 5 to 10 ng/dL and occur with higher dose nitroprusside infusion in renal impairment.

Intravenous fenoldopam is a postsynaptic dopamine-1 receptor antagonist with short-acting vasodilator properties. In contrast to sodium nitroprusside, fenoldopam administration is not associated with a risk of toxic metabolite accumulation. Similar to sodium nitroprusside, fenoldopam lowers blood pressure by decreasing peripheral vascular resistance. The medication causes slight elevation in heart rate and an increase in renal blood flow. The preservation of renal blood flow is attributed to the drug's mechanism as a dopamine-1 receptor agonist.

The hemodynamic effects of fenoldopam have been compared with nitroprusside in a multicenter investigation of patients with acute hypertension.[30] This prospective, randomized trial in 153 patients at 24 centers showed that fenoldopam was as effective as nitroprusside in controlling acute systemic hypertension. The average decreases in systolic and diastolic blood pressure at 6 hours of infusion were similar in the two study groups. The average maintenance infusion rate of fenoldopam was 0.41 µg/kg/min (range 0.1 to 1.62 µg/kg/min), and the average maintenance infusion rate of nitroprusside was 1.67 µg/kg/min (range 0.3

to 8 μg/kg/min) when target blood pressure control was achieved. The time required to reach the maintenance infusion rate also was similar in the two groups (85 minutes for patients who received fenoldopam and 94 minutes for patients who received nitroprusside). In a subset of the population studied, renal indices, including creatinine clearance, urinary output, and sodium excretion, were better in the group randomized to fenoldopam treatment. The study sample is too small to draw definitive conclusions, however. Both drugs were equally well tolerated.

The use of fenoldopam in patients with hypertensive emergencies was evaluated in 107 patients with a diastolic blood pressure greater than 120 mm Hg and clinical evidence of acute vasculopathy.[31] Infusion rates of 0.01 μg/kg/min, 0.03 μg/kg/min, 0.1 μg/kg/min, or 0.3 μg/kg/min for 24 hours were compared. The time required to reduce diastolic blood pressure by 20 mm Hg ranged from an average of 55 minutes among the patients given the highest dose to 133 minutes among the patients given the lowest dose. Within this range of doses, fenoldopam was safe and found to provide a flexible dose-titration regimen that is effective when the blood pressure must be reduced rapidly.

Labetalol is an oral and parenteral agent that acts as an alpha-adrenergic and nonselective beta-adrenergic blocker. The blood pressure–lowering effect is produced through a reduction in systemic vascular resistance without a compensatory increase in heart rate. The drug has been used effectively in patients with end-organ dysfunction and acute neurologic injury, pheochromocytoma, cocaine intoxication, dissecting aneurysm, and eclampsia. The primary contraindication to the use of labetalol relates to its nonselective beta-blocking properties. Labetalol is approximately one fifth as potent as propranolol as a nonselective beta blocker. Despite this knowledge, the drug should be used cautiously in patients with reactive airways disease, heart block, or decompensated left ventricular failure.

Nitroglycerin is a direct vasodilator that is known to promote coronary vascular dilation. When administered intravenously, the medication has a relatively short duration of action. Nitroglycerin has favorable effects for patients with acute coronary syndromes, including reducing myocardial oxygen demand via its effects on preload and afterload and augmenting myocardial oxygen delivery through its effects on the coronary circulation.

Nicardipine hydrochloride is a calcium channel blocker that acts primarily as a systemic and coronary artery vasodilator. The greater water solubility of this drug compared with other calcium channel blockers (e.g., nifedipine) allows intravenous administration with a short onset and duration of action and easy titration of therapeutic effect. The medication has no significant effect on cardiac inotropy and promotes afterload reduction. The medication has been reported most extensively in the preoperative and postoperative patient environments.

Comparative investigations of nicardipine and nitroprusside for postoperative hypertension have suggested the agents are equally effective.[32-34] Nicardipine offers the advantage of avoiding the issues related to cyanide and thiocyanate intoxication. Nicardipine is metabolized by the liver, and excretion can be impaired in these patients.

Enalapril is an intravenously administered ACE inhibitor. The medication reduces renin-dependent vasopressor activity and reduces aldosterone production. Similar to other ACE inhibitors, the medication is effective in patients with low-to-normal renin levels and hypertension.

Phentolamine is a rapid-acting, alpha-adrenergic blocker. Phentolamine is the drug of choice for hypertensive emergencies secondary to pheochromocytoma, monoamine oxidase–tyramine interactions, and clonidine rebound hypertension.

SUMMARY

The treatment of high systemic arterial blood pressure in the ICU must be incorporated into a comprehensive assessment of the patient. Clinical situations that are associated with progressive end-organ damage require urgent intervention, most frequently with a titratable medication and careful ongoing monitoring. In contrast, aggressive antihypertensive therapy in asymptomatic patients without immediate risk of organ dysfunction can be harmful. The intensivist is routinely challenged to recognize this distinction in a hypertensive patient.

Chapter 6
LOW SYSTEMIC ARTERIAL BLOOD PRESSURE

Kyle J. Gunnerson

When initially assessing a critically ill patient, it is essential to perform a rapid, focused physical examination (the ABCs of resuscitation). After ensuring that the patient has a patent airway (A) and is effectively breathing (B), the next step is to assess the adequacy of the circulation (C).

INITIAL EVALUATION

The initial evaluation should be a global assessment (Fig. 6–1). When walking into a patient's room, the clinician should think, "What do I see?" Quickly determine whether the patient is in distress or has problems related to the airway or breathing. Look for obvious evidence of external hemorrhage, and assess the adequacy of intravenous access. Look for evidence of hypoperfusion. Do not rely only on blood pressure readings, as there is no "normal" blood pressure applicable to every patient, and a blood pressure value in the normal range does not always equate with adequate tissue perfusion. A patient with a history of poorly controlled chronic hypertension may have signs of hypoperfusion even when the blood pressure is within the normal range (for nonhypertensive patients). Conversely, a patient with cirrhosis may be adequately perfused despite having a lower-than-normal blood pressure. A quick assessment of perfusion should include evaluation of mental status, urine output, and skin findings (temperature plus presence or absence of diaphoresis, mottling, and adequate capillary refill). If any of these parameters are abnormal, a more urgent approach to treatment must be taken.

A focused cardiac and pulmonary examination is essential. The examiner should seek evidence of jugular venous distention, presence of an S_3 or S_4 heart sound, new or worsening murmurs, or muffled heart sounds. The examiner should check for the presence of rales. It is also important to note whether there are absent breath sounds, a finding suggestive of pneumothorax.

During the initial evaluation, pay close attention to pulse pressure, diastolic pressure, and surrogates of systemic vascular resistance (SVR), such as capillary refill. These basic concepts of cardiac physiology will be useful in determining the cause and devising a treatment plan.

WHAT IS THE CAUSE?

To help focus the differential diagnosis of a hypotensive patient, it is important to review basic cardiovascular physiology. The first concept to remember is that *pressure = flow × resistance*, where flow is cardiac output and resistance is SVR. Because cardiac output is determined by stroke volume (SV) × heart rate, the presence of hypotension means that at least one of these parameters (i.e., SV, SVR, or heart rate) is abnormal.[1] Disturbances in heart rate are discussed in Chapter 7 and should be obvious by feeling the peripheral pulse or looking at the electrocardiogram monitor; the focus here is on conditions associated with decreased SV or SVR. By properly measuring pulse pressure and diastolic pressure, the clinician can determine whether the cause is a change in SVR or SV.

During systole, the SV is ejected into the proximal arterial conduits. Because more blood is being ejected than the peripheral circulation can accommodate in the arterioles, the arterial walls distend, increasing systolic blood pressure (SBP) in a way that is directly proportional to the SV and indirectly proportional to the capacitance (C) of the arterial wall. This relationship is represented by the formula $SBP = SV \div C$.[1] That is, for a fixed SV, if capacitance is higher, the SBP is lower.

During diastole, the portion of the SV that was "stored" by the distention of the arterial walls during systole fills the peripheral arterioles, leading to a progressive decrease in blood pressure until the next systolic phase. This is the diastolic pressure, a parameter that is directly related to the SVR and capacitance (i.e., low diastolic pressure = low SVR and/or capacitance).[1] When using these basic cardiovascular principles to understand the cause of hypotension, it is important to remember the following: (1) capacitance does not change from heartbeat to heartbeat, and (2) SV depends on preload, afterload, and contractility.

Numerous problems can be associated with low SVR, including sepsis (see Chapter 147), adrenal insufficiency (see Chapter 176), vasodilating medications (see Section XII), neurogenic shock (see Section III), and severe liver dysfunction (see Chapter 120). Decreased SVR is suggested by the presence of a widened pulse pressure and low diastolic pressure.[2,3]

Reduced SV can be due to decreased preload, decreased contractility, or increased afterload. The most common cause of inadequate preload is hypovolemia (see Chapter 229). Other causes of inadequate preload include increased intrathoracic pressure due to dynamic hyperinflation in mechanically ventilated patients (see Chapter 64)[4,5] or tension pneumothorax, pulmonary embolism,[6] mitral valve stenosis,[7,8] cardiac tamponade,[9] and right ventricular failure.[10] Decreased contractility can be caused by myocardial ischemia or infarction, cardiomyopathy, myocarditis, negative inotropic drugs, and direct myocyte toxins such as chemotherapeutic agents and inflammatory mediators (tumor necrosis factor and interleukin-1 beta).[11] A reduction in SV can be identified by decreased systolic blood pressure and normal or narrow pulse pressure.

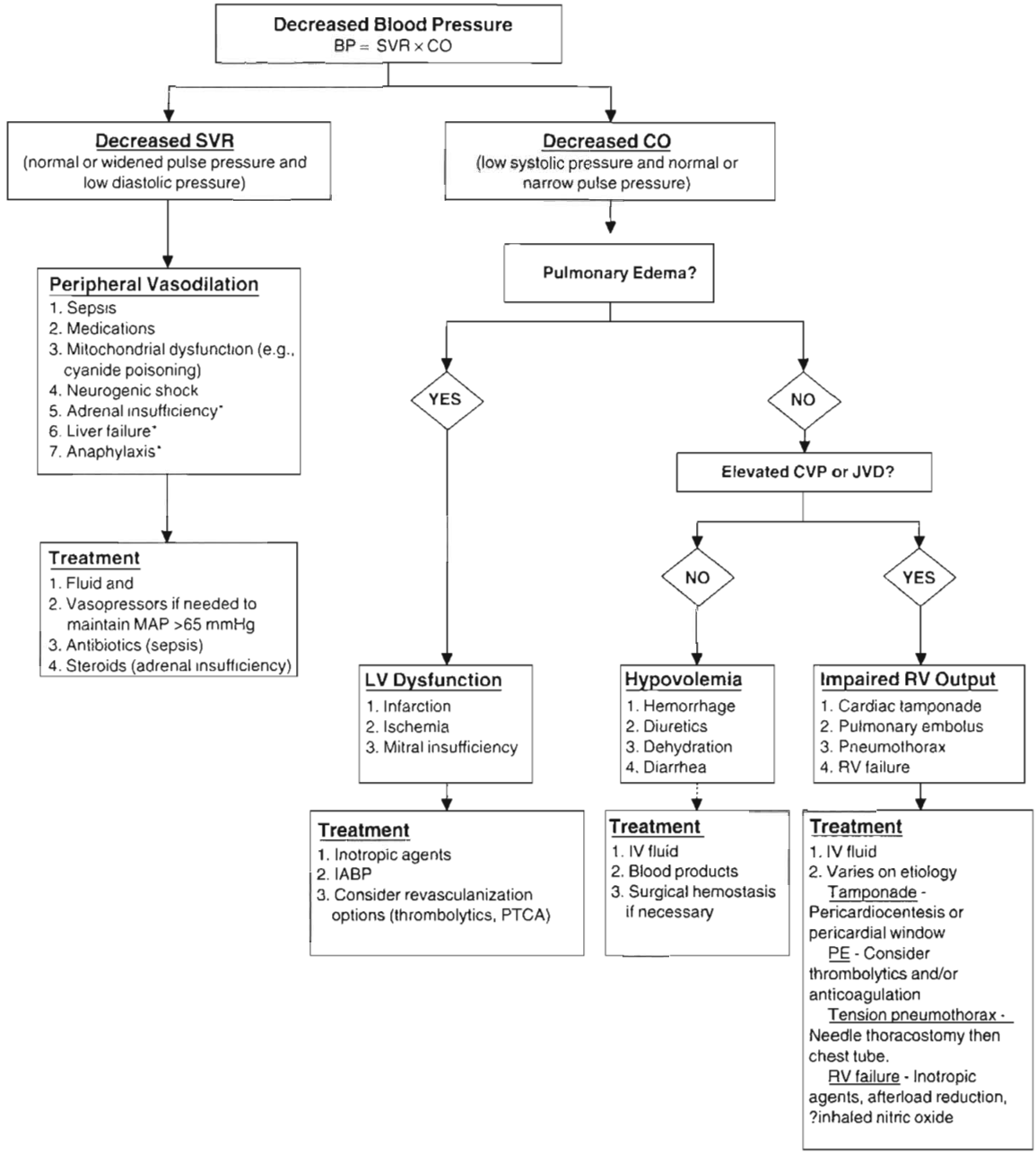

FIGURE 6–1. Initial approach to a patient with low systemic arterial blood pressure. *Adrenal insufficiency, liver failure, and anaphylaxis are sometimes listed as vasodilatory shock; however, data are inconclusive. BP, blood pressure; CO, cardiac output; CVP, central venous pressure; IABP, intra-aortic balloon pump; IV, intravenous; JVD, jugular venous distention; LV, left ventricle; MAP, mean arterial pressure; PE, pulmonary embolism; PTCA, percutaneous transluminal coronary angioplasty; RV, right ventricle; SVR, systemic vascular resistance.

TREATMENT

Until proved otherwise, hypotension should be considered synonymous with hypoperfusion and thus treated aggressively. This initial treatment includes monitoring *and* therapeutic measures. All patients should have adequate intravenous access, preferably two patent 18-gauge or larger catheters. The patient should be monitored using a standard electrocardiogram monitor and pulse oximetry, and a 12-lead electrocardiogram should be performed to look for evidence of myocardial ischemia. Supplemental oxygen should be given as needed to keep oxygen saturation greater than 92%. A 1-L fluid bolus of an isotonic crystalloid solution should be infused as rapidly as possible while data are being gathered. The history, focused examination, and assessment of pulse pressure and diastolic pressure will aid in the formulation of a more specific treatment strategy.

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Chapter 7
TACHYCARDIA AND BRADYCARDIA

Arthur Boujoukos

Bradycardia (heart rate <60 beats/min) and tachycardia (heart rate >100 beats/min) are encountered frequently in the intensive care unit (ICU). Evaluation and management should proceed concurrently.

Bradycardia with or without hypotension should prompt a consideration of metabolic disturbances, drug effects, and myocardial ischemia. If bradycardia is of abrupt onset, hypoxemia or acidosis can be quickly excluded by obtaining an arterial blood gas measurement. If the patient is unresponsive, intubate him or her and institute mechanical ventilation. If the patient is already intubated, disconnect the ventilator and manually ventilate the patient (using an Ambu bag) to ensure adequate ventilation and oxygenation. Mucous plugging of the endotracheal tube or airways should be excluded in an acutely hypoxemic patient. Once these conditions are excluded, evaluate the electrocardiogram (ECG) for evidence of second- or third-degree heart block or ischemic changes. Aminophylline (100 mg i.v.) has been reported to correct ischemic heart block.[1] Insertion of a temporary transvenous pacemaker may be indicated in the setting of ischemic heart block, because further deterioration can occur unpredictably. Medications that can cause bradycardia include beta-adrenergic blockers, amiodarone, diltiazem, verapamil, digoxin, and propofol. Severe toxicity due to overdose with a beta-adrenergic antagonist leading to bradycardia, hypotension, and shock can be treated with glucagon (5 to 10 mg i.v., followed by an infusion of 1 to 10 mg/h diluted in D5W). Moderate drug-induced bradycardia (heart rate >40 beats/min) can be observed until the offending drug is metabolized, as long as peripheral perfusion appears to be adequate. Dopamine (starting at 3 μg/kg/min and titrated upward as needed) can be used to provide temporary support for bradycardic hypotensive patients. Atropine (1-mg i.v. bolus; repeat × 1 as necessary) is occasionally beneficial. Bradycardia in the setting of preexisting shock and refractory acidosis is an ominous sign, and transcutaneous or transvenous pacing is generally futile.

When acute-onset tachycardia occurs, the degree of resulting hemodynamic instability must be assessed. It is critical to differentiate hypotension leading to tachycardia (e.g., rapid atrial fibrillation due to increasing dopamine titration in sepsis or hypovolemic shock causing sinus tachycardia) from hypotension caused by tachycardia (e.g., ventricular tachycardia after myocardial infarction). In the former situation, intravascular volume loading or decreasing the dose of a beta-adrenergic agonist is indicated. In the latter circumstance, rapid conversion of the rhythm should bring about hemodynamic stability.

Sustained regular tachycardia (heart rate >160 beats/min) associated with a narrow QRS complex on the ECG is often reentrant. These dysrhythmias can often be converted with carotid sinus massage. Adenosine can be administered (6 mg i.v., followed by 12 mg i.v. if no response to the lower dose) if sequential carotid sinus massage fails or is contraindicated. Patients presenting with reentrant supraventricular tachycardia in the ICU often have a past history of this dysrhythmia. Beta-adrenergic blockers or calcium channel blockers are reasonable choices for both acute conversion and maintenance therapy. Specific beta blockers include metoprolol 5 mg i.v. every 5 minutes or an esmolol infusion of 500 μg/kg/min over 1 minute, then a 50 μg/kg/min infusion. Esmolol can be rebolused and the drip titrated to a maximum of 400 μg/kg/min. For diltiazem, use 5- to 10-mg boluses titrated upward if the patient's blood pressure tolerates the increase.

Sinus tachycardia is probably the most common dysrhythmia encountered in the ICU. Its meaning, importance, and management vary, depending on the clinical circumstances. In trauma and postsurgical patients, tachycardia can be a sign of bleeding and hypovolemia. It is usually reasonable to administer an intravascular volume challenge (e.g., 500 mL of colloid solution in adults) and check the hemoglobin concentration. Sinus tachycardia and hypertension can be manifestations of opioid withdrawal, failure of a ventilator weaning trial, or inadequate sedation. Most patients at high risk for coronary disease warrant prophylactic treatment with a beta-adrenergic blocker to prevent myocardial ischemia secondary to a high "rate-pressure product" and high myocardial oxygen demand.[2,3] In particular, perioperative patients with significant cardiac risk should have titrated therapy with a beta-adrenergic blocker to maintain the heart rate at less than 80 beats/min unless significant contraindications exist.[4]

Sustained tachycardia associated with hemodynamic instability (i.e., arterial hypotension) and a wide QRS complex on the ECG should be treated as ventricular tachycardia (Fig. 7–1). Unsynchronized cardioversion should proceed expeditiously. Sustained and nonsustained ventricular tachycardia without hemodynamic instability typically occurs in patients with cardiomyopathy or acute myocardial infarction. Initial interventions should include correction of hypokalemia or hypomagnesemia (if present), reduction in the dose of beta-adrenergic agonists (if being infused), and removal of physical stimuli such as pulmonary artery catheters. Amiodarone (150-mg i.v. bolus, then 1 mg/min infusion for 6 hours, then infusion at a rate of 0.5 mg/min) is the preferred therapy in this setting. Consider myocardial ischemia as the cause of monomorphic ventricular tachycardia, and perform the appropriate diagnostic workup. Polymorphic ventricular tachycardia should prompt a

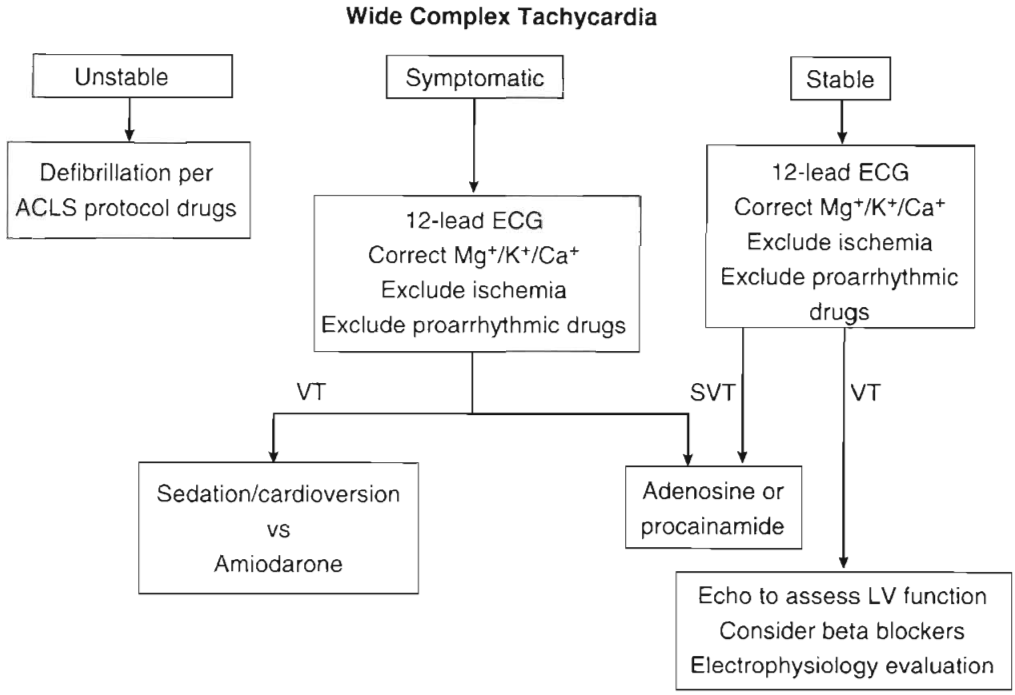

FIGURE 7–1. Algorithm for the diagnosis and testing of wide-complex tachycardia. ACLS, advanced cardiac life support; ECG, electrocardiogram; LV, left ventricle; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

thorough evaluation of the medication list, searching for agents that prolong the QTc (Table 7–1).

Atrial fibrillation with rapid ventricular response can cause significant hemodynamic instability requiring emergent electrical cardioversion. The initial attempt should be synchronized, using 100 J of energy. If unsuccessful, subsequent cardioversion attempts should use escalating energy levels (i.e., 200, 300, 360 J). Atrial fibrillation with rapid ventricular response in the absence of hemodynamic instability can be managed initially by using drugs or other interventions to provide rate control. The goal should be to reduce heart rate to less than 120 beats/min. First, minimize adrenergic stimulation by instituting mechanical ventilation, if high work of breathing and respiratory failure appear to be contributing factors. Reduce the rate of catecholamine (epinephrine, dobutamine, dopamine) infusions, if possible. If the patient is not currently receiving treatment with inotropes or vasopressors, consider beta-adrenergic blockade as the first-line therapy. Metoprolol (5 mg i.v. every 5 minutes) or esmolol (500 μg/kg over 1 minute, then 50 μg/kg/min infusion) is a reasonable choice. If the patient requires treatment with inotropic agents to support cardiac output, a trial of diltiazem (5- to 10-mg i.v. bolus, followed by an infusion of 5 to 20 mg/h) is warranted. Amiodarone (see previous dosing recommendations) is a reasonable choice for both rate control and conversion therapy. There have been multiple reports about amiodarone lung toxicity, even with short-term therapy, so caution is warranted, particularly in critically ill patients with underlying lung pathology.[5] Digoxin is the least effective option acutely; it is relatively ineffective for controlling ventricular rate when endogenous or exogenous adrenergic tone is high.[6] With new-onset atrial fibrillation, conversion to sinus rhythm is desirable in patients who are poor candidates for anticoagulation. Conversion to sinus rhythm is also beneficial for patients with profound left ventricular dysfunction, because coordinated atrial contraction can contribute substantially to cardiac output under these conditions. In other patients, the primary goal should be to achieve rate control.[7,8] Conversion is significantly more likely to occur during rate control with beta blockers (e.g., esmolol) than diltiazem, but this may actually reflect a reduction in the spontaneous conversion rate when diltiazem is used.[9,10]

TABLE 7–1. COMMON MEDICATIONS THAT MAY PROLONG THE QTc

Antibiotics
Ciprofloxacin
Clarithromycin
Erythromycin
Ketoconazole
Itraconazole
Antiarrhythmics
Procainamide
Amiodarone
Sotalol
Ibutilide
Dofetilide
Quinidine
Flecainide
Propafenone
Psychiatric
Tricyclic antidepressants
Tetracyclic antidepressants
Ziprasidone
Droperidol
Haloperidol
Phenothiazines
Other
Methadone
Bepridil

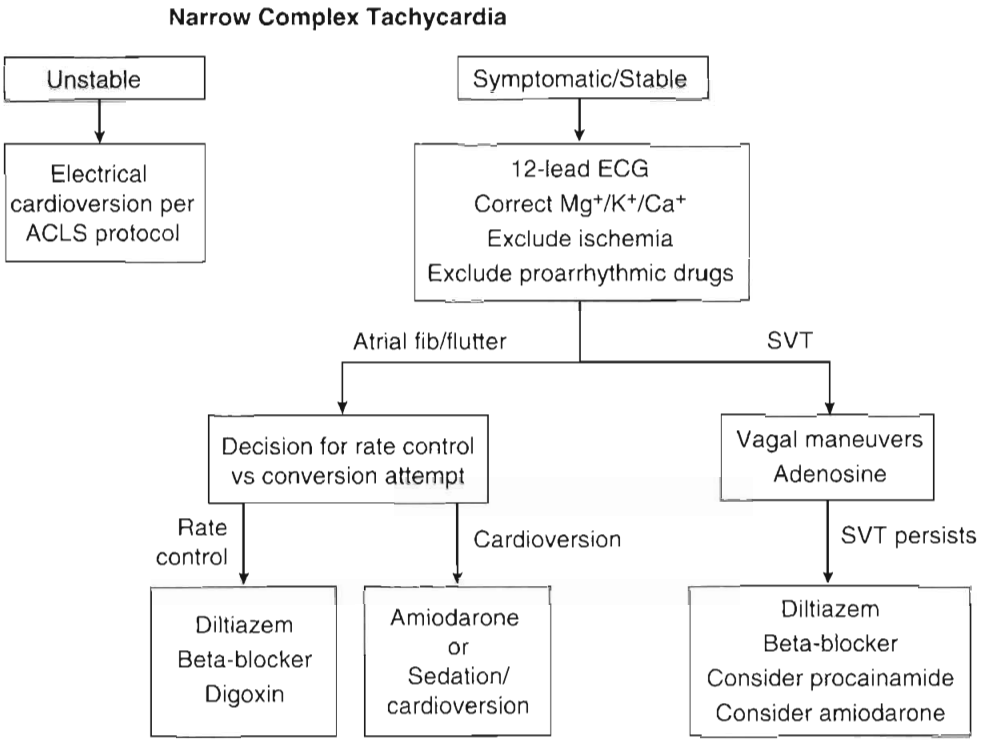

FIGURE 7–2. Algorithm for the diagnosis and testing of narrow-complex tachycardia. ACLS, advanced cardiac life support; ECG, electrocardiogram; fib, fibrillation; SVT, supraventricular tachycardia.

Amiodarone, particularly in patients with impaired ventricular function, is generally the drug of choice to achieve conversion.

Regular narrow-complex tachycardia with a heart rate between 145 and 155 beats/min is typically due to atrial flutter. Carotid sinus massage or adenosine can unmask this diagnosis, if it is in doubt from the 12-lead ECG (Fig. 7–2). Ventricular rate control is difficult to achieve pharmacologically when the dysrhythmia is atrial flutter; accordingly, conversion to sinus rhythm is the goal. Synchronized cardioversion should be tried starting at 50 J, using appropriate conscious sedation. If cardioversion converts the rhythm to atrial fibrillation, use synchronized electrical cardioversion again, starting with 100 J. If atrial fibrillation persists, treat with a rate-controlling agent and anticoagulation. If refractory or recurrent atrial flutter is the problem, attempt rate control with beta-adrenergic blockers or diltiazem, as for atrial fibrillation.

Chapter 8

RESPIRATORY DISTRESS WITH ARTERIAL HYPOXEMIA

Paul Rogers

Respiratory distress with hypoxemia is a common reason for patients to be admitted to the ICU. Because a patient's arterial oxygen saturation can be monitored easily using a continuous pulse oximeter, nurses and physicians are alerted immediately to changes in a patient's oxygen saturation. For these reasons, it is important for health care providers to understand the meaning of this measurement, recognize its limitations, and outline a plan for diagnosing and managing patients with hypoxemia.

Arterial hypoxemia is defined as a partial pressure of oxygen in arterial blood (PaO_2) less than 80 mm Hg while breathing room air. The PaO_2 represents the amount of oxygen in physical solution, whereas the oxygen saturation represents the fractional amount of oxyhemoglobin relative to total hemoglobin concentration. Oxygen saturation varies with the PaO_2 in a nonlinear relationship and is affected by temperature, partial pressure of carbon dioxide in arterial blood ($PaCO_2$), pH, and 2,3-diphosphoglycerate concentration (Fig. 8-1).

Falsely low saturations can be recorded if there is a poor waveform or if the light absorption is decreased by dark blue or black nail polish. Patients with methemoglobinemia may have a falsely low oxygen saturation, whereas patients with carboxyhemoglobinemia may have a falsely elevated oxygen saturation because the pulse oximeter cannot differentiate carboxyhemoglobin from oxyhemoglobin.[1] Finally, because the oxygen hemoglobin dissociation curve is affected by temperature, pH, partial pressure of carbon dioxide (PCO_2), and 2,3-diphosphoglycerate concentration, patients may have a higher or lower saturation for a given PaO_2.

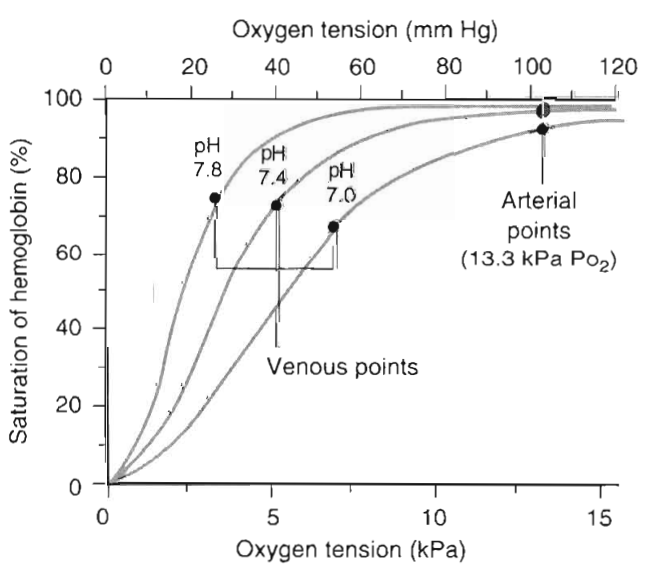

FIGURE 8–1. Oxygen saturation varies with the PaO_2 in a nonlinear relationship and is affected by temperature, $PaCO_2$, pH, and 2,3-diphosphoglycerate (2,3-DPG) concentration.

Patients who have significant decreases in oxygen saturation attempt to maintain oxygen delivery by increasing cardiac output. Although patients with normal left ventricular function and normal coronary vasculature can tolerate lower oxygen saturation, patients with coronary artery disease or decreased contractility may not be able to tolerate the compensatory tachycardia. The decision to begin mechanical or noninvasive ventilation should be based on the patient's cardiopulmonary physiology and not a specific oxygen saturation. A PaO_2 less than 40 mm Hg or an oxygen saturation less than 75% results in tissue hypoxemia, however, even if cardiac output increases. Generally, saturations in the low 90s on escalating levels of inspired oxygen concentration indicate impending respiratory failure, and invasive or noninvasive mechanical ventilation is necessary.

Etiologies for hypoxemia are best understood if approached from a physiologic point of view rather than by referring to a list of possible differential diagnoses. Simply stated, hypoxemia results from an imbalance between pulmonary ventilation and pulmonary capillary blood flow.[2] There is inadequate oxygen tension in the alveoli, the oxygen is unable to get to the alveoli because of reduced ventilation, or there is a diffusion abnormality preventing oxygen from entering the capillaries.

REDUCED ALVEOLAR OXYGENATION

Alveolar oxygenation is defined by the equation: $PalvO_2 = FiO_2 (BP - BP_{H_2O}) - PaCO_2/RQ$, where FiO_2 is the concentration of inspired oxygen, BP is the barometric pressure, BP_{H_2O} is the partial pressure of water, and RQ is the respiratory quotient. The respiratory quotient represents the amount of oxygen consumed relative to the amount of carbon dioxide produced when nutrients are metabolized and is generally assumed to be 0.8. The normal alveolar oxygenation is 100 mm Hg. According to the equation, factors that contribute to lower alveolar oxygenation are a reduction in barometric pressure or an increase in $PaCO_2$. Clinically, significant increases in $PaCO_2$ are explained by the relationship: $PaCO_2$ = carbon dioxide production/respiratory rate (tidal volume – dead space). Accordingly, the $PaCO_2$ increases with either an increase in production or a decrease in alveolar ventilation.

Alveolar ventilation represents that portion of the minute ventilation undergoing blood-gas exchange and is represented by the product of respiratory rate and tidal volume minus dead space.

Medications, such as narcotics and sedatives, and processes that reduce tidal volume, such as neuromotor weakness, are common causes of hypercarbia. If the alveolar oxygen tension is reduced, the arterial hypoxemia is due to factors that reduce the alveolar oxygen tension. If alveolar oxygen tension is normal, the hypoxemia is the result of either a ventilation/perfusion imbalance or a diffusion abnormality.

DIFFUSION ABNORMALITIES

Diffusion abnormalities are the least likely cause of hypoxemia in the ICU, but can occur as a result of an increase in the thickness of the capillary membrane, a reduction in total alveolar surface area, or a reduction in the capillary transit time. Increases in sympathetic tone because of fever, anemia, work of breathing, or sepsis can increase cardiac output and heart rate, resulting in faster transit times. With less opportunity for alveolar oxygen to diffuse into red blood cells, diffusing capacity is reduced. When capillary transit time is faster, the mean capillary arterial oxygen partial pressure decreases, and the diffusing capacity is reduced.

VENTILATION/DIFFUSION MISMATCH

The most common cause of hypoxemia is ventilation/perfusion mismatch. When perfusion is reduced as a result of a decrease in cardiac output or obstruction from pulmonary emboli, the percent of alveoli with adequate blood flow is reduced, increasing the dead space. If minute ventilation remains constant, the primary blood gas abnormality is an increase in carbon dioxide (PCO_2 = carbon dioxide production/respiratory rate × tidal volume – dead space).

When ventilation is reduced relative to perfusion, alveolar oxygenation decreases and results in arterial hypoxemia. This problem occasionally occurs with bronchospasm or bronchitis. Patients with ventilation/perfusion abnormalities generally respond to increasing the FIO_2. When there is no ventilation (as opposed to reduced ventilation), increasing the FIO_2 is not beneficial.

The portion of cardiac output that does not participate in gas exchange is called the *shunt fraction*. The normal shunt fraction is approximately 3% and is due to the bronchial arterial circulation. When alveoli are not ventilated, such as occurs with pulmonary edema, pneumonia, or atelectasis, the shunt fraction increases. As the shunt fraction increases, PaO_2 decreases (Fig. 8-2), and there is a blunted response to increasing the FIO_2, such that a patient with a shunt fraction greater than 50% has little response to increasing FIO_2 (Fig. 8-3).

Patients with refractory hypoxemia and a clear chest radiograph are often evaluated for a pulmonary embolus. In patients with otherwise previously normal lungs, pulmonary emboli are associated with modest decreases in arterial oxygenation; however, the major pathophysiology is an increase in dead space, which results in hypercarbia unless minute ventilation increases. The hypoxemia caused by pulmonary emboli is due to regional ventilation/perfusion abnormalities and responds to supplemental oxygen. If a patient with a pulmonary embolus has refractory hypoxemia unresponsive

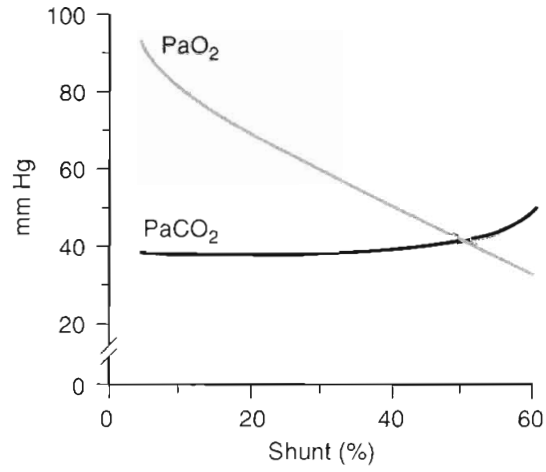

FIGURE 8–2. Decrease in PaO_2 with increasing shunt fraction.

to supplemental oxygenation, an echocardiogram should be performed to rule out a patent foramen ovale, which creates a right-to-left intracardiac shunt in response to the acute increase in pulmonary artery pressure.

Other causes of refractory hypoxemia with a clear chest radiograph are intracardiac shunts and intrapulmonary shunts resulting from either arterial-venous malformations or end-stage liver disease. Often the cause of refractory hypoxemia without radiographic findings on the plain chest film is atelectasis, which is not seen on the typical anteroposterior portable study obtained in the ICU.

It also is relatively common for patients to develop significant hypoxemia when they are started on an intravenous vasodilator, such as sodium nitroprusside. Infusion of sodium nitroprusside interferes with normal hypoxic vasoconstriction, leading to increased perfusion of poorly ventilated areas of the lung. As a result, shunt fraction increases.

Because calculating the shunt fraction, $QsCQ_t = CcO_2/C_{CO_2} - CV_{O_2}$, requires arterial and mixed venous blood gases for calculation of C_{CaO_2} (arterial) and C_{VO_2} (venous) oxygen contents, and because capillary oxygen cannot be directly measured, other indices have been used to estimate the extent of pulmonary gas exchange abnormality. These indices

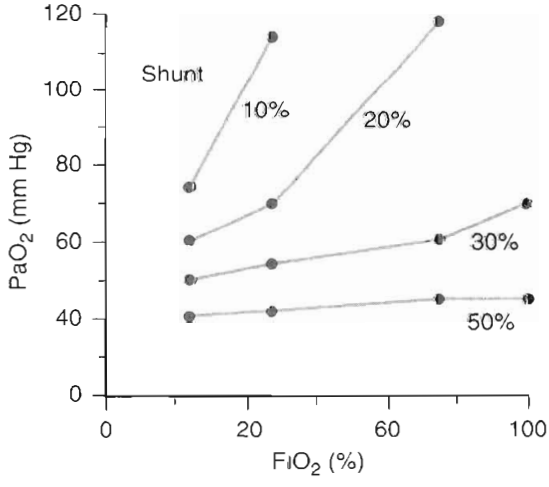

FIGURE 8–3. Blunted response to increasing the inspired oxygen concentration. A patient with a shunt greater than 50% has little response to increasing FIO_2.

include the alveolar-to-arterial (A-a) PO_2 gradient and the arterial/alveolar PO_2 ratio.

ALVEOLAR-ARTERIAL PARTIAL PRESSURE OF OXYGEN GRADIENT

The difference between the alveolar PO_2 and the arterial PO_2 (i.e., the A-a gradient) often is used to estimate the extent of pulmonary pathophysiology and to rule out hypoxemia due to low alveolar PO_2 as the cause of arterial hypoxemia.[3,4] A patient with a reduced alveolar PO_2 (e.g., secondary to breathing room air at high altitude) would have a normal A-a gradient, whereas a patient with ventilation/perfusion mismatching would have a widened A-a gradient. A patient with a PaO_2 of 48 mm Hg and a $PaCO_2$ of 80 mm Hg would have an alveolar PO_2 on room air of 50 mm Hg; the normal A-a gradient of 2 mm Hg is consistent with reduced alveolar PO_2, and causes of hypercarbia need to be ruled out and reversed.

The A-a gradient increases with age or increasing FiO_2, making it an unreliable predictor of the degree of pulmonary dysfunction.[4,5] The PaO_2/FiO_2 ratio also correlates with shunt fraction, but is influenced by increasing FiO_2.[3] The arterial/alveolar ratio is not influenced by FiO_2.[5]

These gradients and ratios are not a substitute for thorough bedside assessment. If a patient has low arterial oxygen saturation by pulse oximetry and is tolerating the reduced saturation without tachycardia or chest pain, adding supplemental oxygen and observing for an appropriate response is reasonable. If there is no increase in saturation, the patient has at least a 40% to 50% shunt and requires intubation or noninvasive ventilation to improve ventilation. Additional oxygen would not increase saturation. If the saturation responds to increasing the FiO_2, the patient has a shunt fraction less than 0.4 or ventilation/perfusion mismatching, and there is time to obtain a chest radiograph and arterial blood gas measurements. If the patient has low saturation and is unstable, immediate bag-and-mask ventilation and securing the airway take precedence over establishing a diagnosis.

REDUCED MIXED VENOUS OXYGEN

A final contribution to hypoxemia may be a reduced mixed venous oxygen content ($CmvO_2$) or saturation. In patients with normal lung function, reducing $CmvO_2$ has little influence on arterial oxygenation; however, in patients with a significant shunt fraction, reducing $CmvO_2$ contributes to arterial hypoxemia.[6] In patients with a widened A-a gradient and abnormally low $CmvO_2$, oxygenation can be improved by increasing venous saturation either by increasing oxygen delivery (increased hemoglobin concentration or cardiac output or both) or reducing oxygen consumption (e.g., induction of hypothermia or using neuromuscular blocking agents).

Chapter 9
ACUTE RESPIRATORY FAILURE

Lakshmipathi Chelluri

Acute respiratory failure is one of the leading causes of admission to an intensive care unit (ICU). In a recent study of cases in the United States, the reported incidence of acute respiratory failure requiring hospitalization was 137 in 100,000 population and the median age of the patients was 69 years.[1] Acute respiratory failure is secondary either to a failure of oxygenation (hypoxic respiratory failure) or to a failure of elimination of carbon dioxide (hypercarbic respiratory [ventilatory] failure). Chronic obstructive pulmonary disease (COPD) with acute exacerbation is the most common cause of ventilatory failure requiring ICU admission.

PATHOPHYSIOLOGY

Oxygenation and elimination of carbon dioxide are the primary gas exchange functions of the lung, and a failure of either one results in acute respiratory failure.[2]

CAUSES OF HYPOXIC RESPIRATORY FAILURE

HYPOVENTILATION

Arterial partial pressure of carbon dioxide ($PaCO_2$) increases with decrease in minute ventilation. An increase in $PaCO_2$ decreases alveolar partial pressure of oxygen (PAO_2) because the carbon dioxide displaces oxygen in the alveoli. Narcotics, anesthetics, and other medications that induce respiratory depression are the usual causes of primary hypoventilation.

VENTILATION-PERFUSION MISMATCH

Gas exchange is optimal when ventilation and perfusion in the lung are matched. A decrease in perfusion relative to ventilation (dead space) or a decrease in ventilation relative to perfusion (shunt) results in ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch. Hypoxia occurs as a result of $\dot{V}/\dot{Q}$ mismatch because of admixture of venous and arterial blood at the capillary level. $\dot{V}/\dot{Q}$ mismatch is the most common cause of hypoxia in hospitalized patients. In contrast to hypoxemia caused by an anatomic shunt, hypoxemia caused by $\dot{V}/\dot{Q}$ mismatching can be improved by administration of supplemental oxygen.

SHUNT

Hypoxia secondary to shunt occurs as a result of a direct mixture of venous and arterial blood in patients with a right-to-left shunt secondary to congenital cardiac disease or trauma. Oxygenation cannot be improved with supplemental oxygen in patients with an anatomic shunt.

DIFFUSION IMPAIRMENT

Thickening of the alveolar endothelial barrier or a decrease in transit time in the pulmonary capillary bed impairs diffusion of oxygen from the alveoli into the blood.

HIGH ALTITUDE

Barometric pressure decreases with increasing altitude, and, as a result, the partial pressure of oxygen in the ambient atmosphere decreases as well. Consequently, unless supplemental oxygen is provided, hypoxia is an inevitable consequence of respiration at high altitude.

IMPAIRED TISSUE PERFUSION

When tissue perfusion is impaired, the cells attempt to maintain normal oxygen consumption by extracting more oxygen from the available blood supply. As a consequence, venous oxygen tension decreases. Unless fractional pulmonary shunt flow is zero, decreased mixed venous oxygen tension inevitably decreases arterial oxygen tension. Although low tissue cardiac output or impaired blood flow to tissues can cause hypoxia, hypoperfusion is rarely a primary cause of clinically significant hypoxia. Nevertheless, hypoperfusion is a common factor exacerbating the degree of hypoxia caused by other problems.

If the circulating concentration of carboxyhemoglobin or methemoglobin increases, then the oxygen-carrying capacity of the blood decreases. Although arterial oxygen tension may be normal, arterial oxygen saturation is abnormally low because of the presence of hemoglobin derivatives that are incapable of transporting oxygen.

HYPERCARBIC RESPIRATORY FAILURE

Partial pressure of carbon dioxide in the arterial blood ($PaCO_2$) is inversely proportional to alveolar ventilation. $PaCO_2$ increases when the elimination of carbon dioxide is decreased because of a decrease in minute ventilation. $PaCO_2$ also increases if minute ventilation remains constant but carbon dioxide production increases. Primary pulmonary diseases are the most common cause of hypercarbia, although nonpulmonary causes contribute to hypoventilation, increased $PaCO_2$, and the need for mechanical ventilatory support.

Minute ventilation can be decreased due to pulmonary or nonpulmonary factors. Pulmonary causes of impaired minute ventilation include large airway obstruction (e.g., due to the presence of a foreign body or laryngeal spasm), small airway obstruction (e.g., bronchospasm), and destruction of lung parenchyma (e.g., emphysema). Extrapulmonary causes of hypercarbia include neurologic and muscular problems. Neurologic problems include depression of central respiratory drive due to the pharmacological effects of narcotics or sedatives; depression of respiratory drive as a consequence of stroke, intracranial hemorrhage, or head trauma (i.e., central alveolar hypoventilation); and impaired neuromuscular transmission to phrenic nerve injury or spinal cord injury (C5 or higher), Guillain-Barré syndrome, myasthenia gravis and the multifactorial syndrome, polyneuropathy of critical illness. Muscular weakness or skeletal abnormalities can cause a decrease in tidal volume and minute ventilation. The following are some causes of hypoventilation secondary to musculoskeletal abnormalities: prolonged use of neuromuscular blocking agents, malnutrition, hypomagnesemia, hypokalemia, hypophosphatemia, kyphoscoliosis, rib fractures, and flail chest.

Causes of hypercarbia secondary to increased carbon dioxide production and relative hypoventilation include overfeeding, since fat synthesis increases the ratio of carbon dioxide production relative to oxygen consumption (respiratory quotient), and fever and other hypercatabolic states.

CLINICAL PRESENTATION

Dyspnea is the most common symptom associated with acute respiratory failure. Dyspnea is usually associated with rapid shallow breathing and the use of accessory respiratory muscles.

The investigations to evaluate the causes of respiratory failure depend on the suspected mechanism of acute respiratory failure and the primary disease process. Pulse oximetry is a useful monitoring tool and should be carried out in virtually all cases. Other worthwhile diagnostic studies include the following:

Analysis of arterial blood gases will permit diagnosis of a widened alveolar-arterial P_{O_2} gradient and/or hypercarbia.

Examination of the chest radiograph is useful in almost all cases. If the chest film is clear, then the differential diagnosis should include pulmonary embolism, anatomic right-to-left shunt, pneumothorax, cirrhosis, and COPD. If the chest radiograph shows unilateral infiltrates or effusion, then the differential diagnosis should include pleural effusion, aspiration, lobar pneumonia, atelectasis, and infarction. If bilateral infiltrates are present, then the differential diagnosis should include pulmonary edema (cardiac and noncardiac causes), pneumonia, and pulmonary hemorrhage.[3]

Other more specialized tests, such as computed tomography and cultures, are needed based on the differential diagnosis for the suspected primary disease.

MANAGEMENT

The goal is to maintain adequate oxygenation and ventilation and treat the primary cause of respiratory failure. For hypoxic respiratory failure, the primary goal is to improve arterial oxygenation and maintain PaO_2 of 65 to 70 mm Hg and an arterial blood oxygen saturation (SaO_2) of greater than 93%. Administration of supplemental oxygen improves oxygenation in most clinical situations except for anatomic shunts. Low-flow oxygen can be delivered using a nasal canula or a face mask. The maximum fraction of inspired oxygen (FIO_2) that can be delivered using these approaches is about 0.4. This level of oxygen supplementation is not adequate when the alveolar-arterial (A-a) gradient is very wide. The FIO_2 delivered using a nasal canula or face mask also is dependent on minute ventilation. Accordingly, low-flow methods of providing supplemental oxygen should be used cautiously in patients who are dependent on hypoxic drive or have very high minute ventilation. A higher FIO_2 can be provided if a face mask is combined with a reservoir bag, because admixture of the supplemental oxygen with room air is minimized.

Noninvasive positive pressure ventilation and mechanical ventilation via an endotracheal tube are two approaches for providing supplemental oxygen and, at the same time, providing partial or total support for minute ventilation. In hemodynamically stable patients with mild or moderate respiratory failure, noninvasive positive pressure ventilation may decrease the need for intubation and mechanical ventilation and decrease the patient's length of stay in the ICU.[4,5] Noninvasive positive pressure ventilation should not be used in patients with altered mental status who are unable to protect the airway. Noninvasive positive pressure ventilation should not be used for patients who are unable to clear secretions adequately. For some patients, tolerance for noninvasive positive pressure ventilation can be improved by using a nasal mask and starting at a lower level of inspiratory pressure (5 cm H_2O).

In cases of hypercarbic respiratory failure, the primary goal of treatment is to maintain arterial pH at greater than 7.32 with a $PaCO_2$ appropriate for the pH.[6] Bronchodilators can be delivered as metered dose inhalers or nebulizers. Patients with tachypnea and respiratory distress may not be able to use metered dose inhalers. The bronchodilating effects of β-adrenergic agonists and anticholinergic drugs are synergistic. Long-acting β-adrenergic agonists should not be used to treat acute exacerbations of chronic bronchospasm. Corticosteroids are often used to treat acute exacerbations of diseases associated with airway inflammation and bronchospasm (e.g., asthma and COPD). The reported dosing range is wide. Intravenous methylprednisolone (40 mg i.v. every 12 h to 125 mg i.v. every 6 h) is often employed, if the response is inadequate to initial efforts using bronchodilator treatments with β-adrenergic agonists and anticholinergic agents. Aerosolized steroids may not improve bronchospasm during the acute episode but are useful for maintenance treatment. Although systemic absorption of aerosol steroids is not significant, they may cause adrenal suppression.

Patients who experience changes in the nature of the sputum and signs of infection may benefit from a short course (7-10 days) of antibiotic therapy.

The use of noninvasive positive pressure ventilation in hemodynamically stable patients with mild to moderate ventilatory failure may decrease the need for mechanical ventilatory support and length of stay. The precautions while using noninvasive positive pressure ventilation are the same as listed previously.

INTUBATION AND MECHANICAL VENTILATION

The need for mechanical ventilatory support is a clinical decision based on increased work of breathing (i.e., respiratory

rate >35), inability to clear secretions and maintain an adequate airway. The clinician has only two basic maneuvers for improving PaO_2 using mechanical ventilation. The first is to increase FIO_2. The second is to increase mean airway pressure. The latter goal can be achieved in two main ways: (1) application of positive end-expiratory pressure; or (2) changing the duty cycle so that the duration of inspiration is longer (in the extreme, this maneuver is called inverse ratio ventilation). In patients with acute lung injury, tidal volume should be limited to 6 mL/kg (ideal body weight). Prone positioning, inhaled nitric oxide, and transtracheal gas insufflation are some of the other methods used to improve oxygenation in patients with profound hypoxemia due to acute lung injury, but none of these approaches have been shown to improve survival.

Ventilation should be adjusted to maintain pH and $PaCO_2$ at levels that are appropriate for the patient, particularly in patients with COPD and chronic respiratory acidosis. Hyperventilation and excessive correction of $PaCO_2$ in patients with chronic respiratory acidosis results in secondary metabolic alkalosis and delay in weaning from mechanical ventilation. Alveolar air trapping (so-called auto-positive end-expiratory pressure) and hypotension (due to impaired venous return) may develop in patients with inadequate exhalation time, and caution should be used when increasing minute ventilation by increasing either ventilator-delivered respiratory rate or tidal volume in patients with severe airway obstruction.

PROGNOSIS

Mortality in patients with respiratory failure requiring positive pressure ventilatory support is dependent on the primary cause. The hospital mortality rate is 30% to 40% and the 1-year mortality rate is 50% to 70%. Functional status deteriorates immediately after the illness and improves to baseline by 6 to 12 months in survivors.[7]

Chapter 10
POLYURIA

Ramesh Venkataraman • John A. Kellum

Although polyuria in the critically ill is less common than oliguria, it is an important manifestation of a number of clinical conditions. Unless recognized and appropriately managed, polyuria can rapidly lead to the development of hypovolemia, severe hypernatremia, or both. Generally, urine flow varies, depending on the fluid intake, insensible losses (e.g., perspiration), and renal function. The average person excretes about 600 to 800 mOsm of solutes per day, and the average urine output is about 1.5 to 2.5 L/day.

Polyuria has been defined variably in the literature. The most commonly used definition is based entirely on absolute urine volume and arbitrarily defines polyuria as urine volume of greater than 3 L/day. However, some authors prefer to define polyuria as "inappropriately high urine volume in relation to the prevailing pathophysiologic state," regardless of the actual volume of urine.[1,2]

CLASSIFICATION

Polyuria is broadly classified into water diuresis or solute diuresis, depending on whether water or solute is the primary driving force for the increased urine output. However, some patients have a mixed water and solute diuresis.

WATER DIURESIS

DEFINITION AND PATHOPHYSIOLOGY

If the urine output is greater than 3 L/day and the urine is dilute (urine osmolality <250 mOsm/L), total solute excretion is relatively normal, and the polyuria is due to excessive excretion of water. In general, diuresis is marked, and urine osmolality is often less than 100 mOsm/L. Water diuresis is usually secondary to excess water intake, as in primary polydipsia, or to the inability of the renal tubules to reabsorb free water, as in central or nephrogenic diabetes insipidus. A good understanding of water homeostasis is critical in recognizing and managing water diuresis.

The normal plasma osmolality is 275 to 285 mOsm/L. To maintain this steady state, water intake must equal water excretion. The primary stimulus for water ingestion is thirst, mediated by either an increase in effective osmolality or a decrease in blood pressure or effective circulating volume. Under normal circumstances, water intake generally exceeds physiologic requirements.

Unlike water intake, water excretion is tightly regulated by multiple factors. The most dominant regulating factor affecting water secretion is arginine vasopressin, a polypeptide synthesized in the hypothalamus and secreted by the posterior pituitary gland. Once released, arginine vasopressin binds to vasopressin-2 receptors located on the basolateral membranes of renal epithelial cells lining the collecting ducts. Binding of arginine vasopressin to vasopressin-2 receptors initiates a sequence of cellular events, ultimately resulting in the insertion of water channels into the luminal cell membrane. The presence of these water channels permits passive diffusion of water (and hence its reabsorption) across the collecting duct. Any derangement in this process results in a lack of or inadequate water reabsorption by the collecting duct, resulting in water diuresis. The major stimulus for the release of arginine vasopressin is plasma hypertonicity. Its release is also affected by other nonosmotic factors such as effective circulating volume, hypoglycemia, and drugs. In summary, water diuresis occurs because of either excessive water intake sufficient to overwhelm the renal excretory capacity (primary polydipsia) or impairment of renal water reabsorption (central or nephrogenic diabetes insipidus). Impaired renal water reabsorptive capacity (leading to water diuresis) can occur due to failure of arginine vasopressin release in response to normal physiologic stimuli (central or neurogenic diabetes insipidus) or failure of the kidney to respond to arginine vasopressin (nephrogenic diabetes insipidus). In most patients, the degree of polyuria is determined primarily by the degree of arginine vasopressin lack or resistance.

PRIMARY POLYDIPSIA

Primary polydipsia can be recognized clinically based on the history of the patient. Usually, there is a history of psychiatric illness along with a history of excessive water intake. Many patients with chronic psychiatric illnesses have a moderate to marked increase in water intake (up to 40 L/day).[3,4] It is presumed that a central defect in thirst regulation plays an important role in the pathogenesis of polydipsia. In some cases, the osmotic threshold for thirst is reduced below the threshold for the release of arginine vasopressin. The mechanism responsible for abnormal thirst regulation in this setting is unclear. There is evidence that these patients have other defects in central neurohumoral control as well.[5] The diagnosis of primary polydipsia is usually evident from low urine and plasma osmolalities in the face of polyuria. Hyponatremia, when present, also points to the diagnosis of primary polydipsia. Hypothalamic diseases, such as sarcoidosis; trauma; and certain drugs, such as the phenothiazines, can lead to primary polydipsia (Table 10–1). There is no proven treatment for psychogenic polydipsia. Free water restriction is the mainstay of therapy.

TABLE 10–1. CAUSES OF POLYURIA

- Polyuria secondary to water diuresis
  - Excessive intake of water
    - Psychogenic polydipsia
    - Drugs—anticholinergic drugs, thioridazine
    - Hypothalamic diseases—surgery, sarcoidosis
  - Defective water reabsorption by the kidney
    - Central diabetes insipidus (vasopressin deficiency)
    - Renal tubular resistance to arginine vasopressin
      - Congenital nephrogenic diabetes insipidus
      - Acquired nephrogenic diabetes insipidus
        - Hypercalcemia
        - Hypokalemia
        - Drugs—lithium, demeclocycline
        - Chronic renal diseases—postobstructive diuresis, polyuric phase of acute tubular necrosis
        - Other systemic diseases—amyloidosis, sickle cell anemia
- Polyuria secondary to solute diuresis
  - Electrolyte-induced solute diuresis
    - Iatrogenic—excessive sodium chloride load, loop diuretic use
    - Salt-wasting nephropathy (rarely causes polyuria)
  - Nonelectrolyte-induced solute diuresis
    - Glucosuria—diabetic ketoacidosis, hyperosmolar coma
    - Urea diuresis—high-protein diet, acute tubular necrosis
    - Iatrogenic—mannitol

CENTRAL DIABETES INSIPIDUS

Lack of arginine vasopressin (central diabetes insipidus) can be caused by disorders that act at one or more of the sites involved in its secretion, interfering with the physiologic chain of events that lead to hormone release. The common causes of central diabetes insipidus, accounting for the vast majority of cases, include neurosurgery, head trauma, brain death, primary or secondary tumors of the hypothalamus, and infiltrative diseases (such as Langerhans cell histiocytosis).

NEPHROGENIC DIABETES INSIPIDUS

Nephrogenic diabetes insipidus refers to a decrease in urinary concentrating ability that results from renal resistance to the action of arginine vasopressin. The collecting duct cells may fail to respond to the actions of arginine vasopressin. Other factors that can cause renal resistance to arginine vasopressin involve interference with the countercurrent concentrating mechanism, such as medullary injury or decreased sodium chloride reabsorption in the medullary aspect of the thick ascending limb of the loop of Henle. In children, nephrogenic diabetes insipidus is usually hereditary. Congenital or hereditary nephrogenic diabetes insipidus is an X-linked recessive disorder resulting from mutations in the vasopressin-2 arginine vasopressin receptor gene.[6] The X-linked inheritance pattern means that males tend to have marked polyuria. Female carriers are usually asymptomatic but occasionally have severe polyuria. In addition, different mutations are associated with different degrees of arginine vasopressin resistance. Nephrogenic diabetes insipidus can also be inherited as an autosomal recessive disorder due to mutations in the acquaporin gene that result in absent or defective water channels, thereby causing resistance to the action of arginine vasopressin.[7]

The most common cause of nephrogenic diabetes insipidus in adults is chronic lithium ingestion. Polyuria occurs in about 20% to 30% of patients on chronic lithium therapy. The impairment in the nephron's concentrating ability is thought to be due to decreased density of vasopressin-2 receptors or to decreased expression of aquaporin-2, a water channel protein. Other secondary causes of nephrogenic diabetes insipidus include hypercalcemia, hypokalemia, sicke cell disease, and other drugs (see Table 10–1). A water diuresis also can follow relief of obstructive nephropathy. Hypercalcemia-induced nephrogenic diabetes insipidus occurs when the plasma calcium concentration is persistently above 11 mg/dL (2.75 mmol/L). This defect is generally reversible with correction of the hypercalcemia. The mechanisms responsible for hypercalcemia-induced nephrogenic diabetes insipidus are incompletely understood. Compared with hypercalcemia-induced diabetes insipidus, hypokalemia-induced nephrogenic diabetes insipidus is less severe and often asymptomatic. A rare form of nephrogenic diabetes insipidus can occur during the second half of pregnancy (gestational diabetes insipidus). This condition is thought to be caused by release of a vasopressinase from the placenta, leading to rapid degradation of endogenous or exogenous arginine vasopressin.[8]

DIAGNOSIS OF HYPOTONIC POLYURIA (WATER DIURESIS)

The correct diagnosis is often suggested by the plasma sodium concentration and the history. When the problem is primary polydipsia, the plasma sodium concentration is usually low (dilutional), whereas when the problem is central or nephrogenic diabetes insipidus, the plasma sodium concentration is typically normal or high (related to intravascular volume depletion). The rate of onset of polyuria sometimes provides a clue to the diagnosis; with central diabetes insipidus, the onset of polyuria is generally abrupt, whereas with nephrogenic diabetes insipidus or primary polydipsia, the onset of polyuria tends to be more gradual. Even if the history or plasma sodium concentration is helpful, the diagnosis of central versus nephrogenic diabetes insipidus should be confirmed by determining the urinary response to an acute increase in plasma osmolality induced by either water restriction or, less commonly, the administration of hypertonic saline (Fig. 10–1).

Comparing urine osmolality after dehydration with that after vasopressin administration can help differentiate diabetes insipidus due to vasopressin deficiency from other causes of water diuresis (see Fig. 10–1). In this test, fluids are withheld long enough to result in stable hourly urine osmolalities (<30 mmol/kg rise in urine osmolality for 3 consecutive hours). Plasma osmolality and urine osmolality are measured at this point; then the patient is given 5 units of aqueous vasopressin intravenously. The clinician measures the osmolality of a urine sample collected 30 to 60 minutes after the administration of vasopressin. In subjects with normal pituitary function, urine osmolality does not rise by more than 9% after vasopressin injection; however, in central diabetes insipidus, the increase in urine osmolality after vasopressin administration exceeds 9%. To ensure adequate dehydration, plasma osmolality before vasopressin administration should be greater than 288 mmol/kg. There is little or no increase in urine osmolality with dehydration in patients with nephrogenic diabetes insipidus, and there is no further change after vasopressin injection. In the future, a novel method to confirm the results of the water restriction test will be to measure the urinary excretion of aquaporin-2, the collecting tubule water channel that normally fuses with the

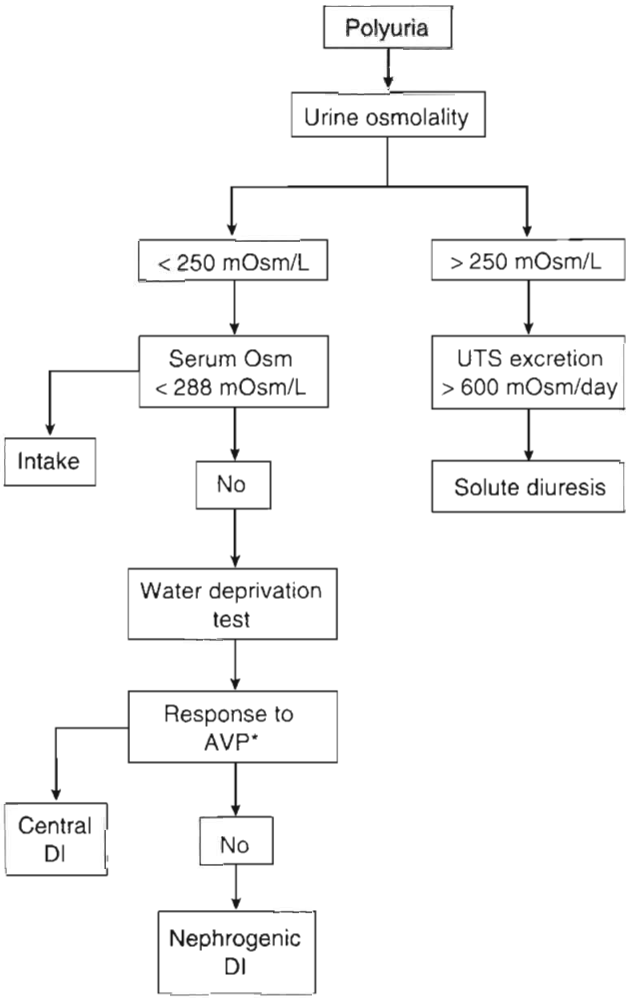

FIGURE 10–1. Approach to polyuria. *Response to arginine vasopressin (AVP) is defined as a greater than 9% increase in urine osmolality 30 to 60 minutes after vasopressin administration (see text for details). DI, diabetes insipidus; UTS, urine total solute concentration.

luminal membrane of the collecting tubule cells under the influence of arginine vasopressin. In one study, urinary aquaporin-2 excretion increased substantially and to a similar extent after the administration of vasopressin in normal subjects and in those with central diabetes insipidus.[9] However, in patients with hereditary nephrogenic diabetes insipidus, urinary aquaporin-2 excretion was unchanged after vasopressin administration.

TREATMENT OF WATER DIURESIS

Central diabetes insipidus can be treated by replacing arginine vasopressin. The agent of choice is desmopressin because it has prolonged antidiuretic activity and a minimal vasopressor effect. It is usually administered intranasally at doses of 10 to 20 μg once or twice per day. Patients with central diabetes insipidus with some residual releasable arginine vasopressin can be treated with drugs such as carbamazepine (100 to 300 mg twice daily), clofibrate (500 mg every 6 hours), or chlorpropamide (125 to 250 mg once or twice per day), which stimulate arginine vasopressin release.

Primary polydipsia can be treated only by eliminating the underlying problem. In patients with schizophrenia and polydipsia, clozapine has been shown to have a beneficial effect.

The mainstay of treatment of nephrogenic diabetes insipidus is solute restriction and diuretics. Thiazide diuretics in combination with a low-salt diet can diminish the degree of polyuria in patients with persistent and symptomatic nephrogenic diabetes insipidus. Thiazide diuretics (hydrochlorothiazide) act by inducing mild volume depletion. Hypovolemia induces an increase in proximal sodium and water reabsorption, thereby diminishing water delivery to the arginine vasopressin–sensitive sites in the collecting tubules and reducing the urine output. The potassium-sparing diuretic amiloride also may be helpful.[10]

SOLUTE DIURESIS

Solute diuresis causing polyuria is due to solute excretion in excess of the usual excretory rate.[11] Total urinary solute excretion varies widely among patients with different ethnicities, cultures, and dietary habits. The average urinary solute excretion in a healthy American adult is between 500 and 1000 mOsm/day. Solute diureses can be severe and can be caused by more than one solute concurrently. Solute diuresis is a relatively common clinical condition with important clinical implications. Unless there is adequate replacement of solute and water, a persistent solute diuresis contracts extracellular volume, leading to severe dehydration and hypernatremia. Although glucosuria is the major cause of an osmotic diuresis in outpatients, other conditions are often responsible when polyuria develops in the hospital. These conditions include administration of a high-protein diet, in which case urea acts as the osmotic agent, and volume expansion due to saline loading or the release of bilateral urinary tract obstruction. Multiplying urine osmolality by the 24-hour urine volume gives an estimate of total urinary solute concentration. If the total urinary solute concentration is abnormally large, a solute diuresis is present.

Solute diuresis can be due to either excessive electrolyte excretion or excessive nonelectrolyte solute excretion. If the total urinary electrolyte excretion exceeds 600 mOsm/day, an electrolyte diuresis is present. The total urinary electrolyte excretion (in mOsm/day) can be estimated as $2 \times (\text{urine } [Na^+] + \text{urine } [K^+]) \times \text{total urine volume}$.[1,12]

An electrolyte diuresis is usually driven by a sodium salt, usually sodium chloride (NaCl).[13] Common causes of NaCl-induced diuresis are iatrogenic administration of excessive normal saline solution, excessive salt ingestion, and repetitive administration of loop diuretics. Most often, NaCl-induced diuresis is accompanied by water diuresis, causing a mixed solute-water diuresis. Also, more than one electrolyte may be responsible for the diuresis.

A clearly excessive value for urine nonelectrolyte excretion (>600 mOsm/day) implies that nonelectrolytes are the predominant solutes contributing to the diuresis. The urinary nonelectrolyte excretion can be calculated by subtracting urine electrolyte excretion from the total urinary solute excretion. The urine osmolality in these disorders is usually above 300 mOsm/kg; the high osmolality contrasts with the dilute urine typically found with a water diuresis. Further, total solute excretion (calculated as the product of urine osmolality and the urine output over a 24-hour urine collection period) is normal with a water diuresis (600 to 900 mOsm/day) but markedly increased with an osmotic diuresis. The most common nonelectrolyte solute causing excessive diuresis is glucose. Conditions associated with glucose-induced diuresis include diabetic ketoacidosis and

hyperosmolar coma.[14] Excessive excretion of urea is another important cause of solute diuresis. This problem can occur with enteral nutrition using a high-protein tube feeding formula, following relief of urinary tract obstruction, or during recovery from acute tubular necrosis.[15] Mannitol administration (e.g., as a therapy for intracranial hypertension) also can lead to significant solute diuresis. This issue is pertinent because mannitol is often administered to patients with head trauma, who are at risk for the development of nephrogenic diabetes insipidus.

The correct diagnosis of solute diuresis depends on a clear systematic approach (see Fig. 10–1). Management usually involves treatment of the underlying disorder and repletion of extracellular volume by hydration. Because solute diuresis is often accompanied by hypernatremia, and because rapid correction of hypernatremia can have disastrous consequences (e.g., cerebral herniation), it is crucial to carefully monitor serum $[Na^+]$. The serum $[Na^+]$ should not be permitted to decrease more than 0.5 to 1 mEq/L per hour.

Chapter 11
OLIGURIA

Sanjay Subramanian • Ramesh Venkataraman • John A. Kellum

Oliguria is a common diagnostic challenge facing the critical care practitioner. This chapter provides a practical, physiology-based approach to diagnosing and treating oliguria.

DEFINITIONS AND EPIDEMIOLOGY

Many definitions for oliguria can be found in the literature. In general, *oliguria* is defined as urine output less than 200 to 500 mL/24 h. To standardize the use of the term across different studies and populations, the Acute Dialysis Quality Initiative (www.ADQI.net) adopted a definition of oliguria as urine output less than 0.3 mL/kg/h for at least 24 hours.

Given the lack of consensus over definitions until now, it is difficult to determine the incidence of oliguria. Some studies estimated that 18% of medical-surgical ICU patients with intact renal function exhibit episodes of oliguria.[1] Of ICU patients who develop acute renal failure, 69% are oliguric.[2] Overall, acute renal failure in the ICU has a poor prognosis; the mortality rates ranges from 30% to 70%. Oliguric acute renal failure compared with nonoliguric acute renal failure carries a higher risk of death. It is essential to understand the physiologic derangements leading to this exceedingly common problem.

PATHOPHYSIOLOGY

Urine output is a function of glomerular filtration rate and tubular secretion and reabsorption. Glomerular filtration rate is directly dependent on renal perfusion. Renal perfusion is a function of arterial pressure and renal vascular resistance. The intrarenal vasculature is capable of preserving glomerular filtration rate in the face of varying systemic pressure through important neurohumoral autoregulating mechanisms that affect tone in the afferent and efferent arterioles. Of these mechanisms, the renin-angiotensin-aldosterone system is perhaps the most important (Fig. 11-1). Oliguria indicates either a marked reduction in glomerular filtration rate or a mechanical obstruction to urine flow.

REDUCTION IN GLOMERULAR FILTRATION RATE

Oliguria secondary to a decrease in glomerular filtration rate usually is related to one of the following conditions:

1. Absolute decrease in intravascular volume. Causes include trauma, hemorrhage, burns, diarrhea, or sequestration of extravascular fluid, as in pancreatitis or after major abdominal surgery.

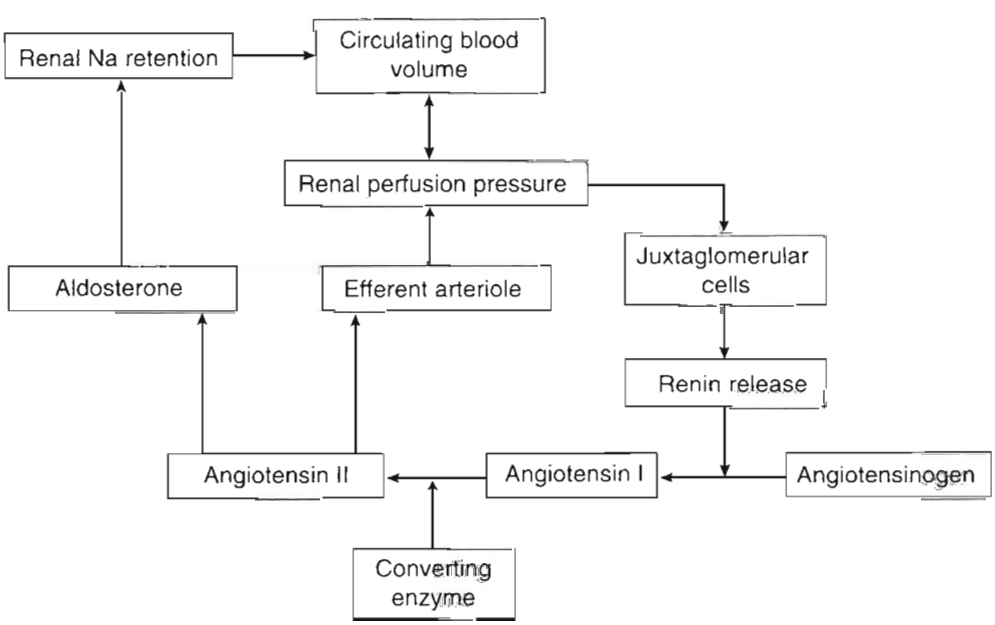

FIGURE 11-1. Network of effects and feedback loop for the renin-angiotensin-aldosterone system. As circulating blood volume or renal perfusion changes, renin secretion changes, resulting in downstream effects that ultimately influence renal resistance and sodium handling by the kidney. Changes in urine output are a direct result of these changes.

2. A relative decrease in blood volume. The primary disturbance is increased capacitance of the vasculature due to vasodilation. This abnormality is encountered commonly in patients with sepsis, hepatic failure, or nephrotic syndrome. Another cause of this abnormality is administration of vasodilating drugs, a category that includes many anesthetic agents.
3. Decreased renal perfusion. Factors that can reduce renal blood flow include structural causes, such as thromboembolism, atherosclerosis, dissection, and inflammation (vasculitis, especially scleroderma) affecting either the intrarenal or the extrarenal circulation. Although renal artery stenosis presents as subacute or chronic renal insufficiency, renal atheroembolic disease can present as acute renal failure with acute oliguria. Renal atheroembolization usually affects older patients with diffuse erosive atherosclerotic disease. Atheromatous embolization is seen most often after manipulation of the aorta or other large arteries during arteriography, angioplasty, or surgery.[3] This condition also may occur spontaneously or after treatment with heparin, warfarin, or thrombolytic agents. Certain drugs, such as cyclosporine, tacrolimus, and angiotensin-converting enzyme inhibitors, cause intrarenal vasoconstriction and reduce renal plasma flow, leading to oliguria. Rarely, decreased renal perfusion can be due to an outflow problem, such as renal vein thrombosis or abdominal compartment syndrome.
4. Acute tubular necrosis. Although acute tubular necrosis is often the result of the above-listed factors, it also can be due to direct nephrotoxic effects of agents such as antibiotics, heavy metals, solvents, contrast agents, or crystals (uric acid or oxalate).

MECHANICAL OBSTRUCTION

Oliguria secondary to mechanical obstruction can be subclassified further according to the anatomic site of the obstruction:

1. Tubular—ureteral obstruction, which can be caused by stones, papillary sloughing, crystals, or pigment.
2. Urethral or bladder neck obstruction—typically due to prostatic hypertrophy or malignancy.
3. A malpositioned or obstructed urinary catheter.

DIAGNOSTIC APPROACH TO OLIGURIA

Oliguria is associated with considerable morbidity and mortality. Merely reversing oliguria, particularly by administering diuretics, does not improve outcome. Rapidly determining the cause of oliguria is essential.

RULE OUT URINARY OBSTRUCTION

The initial step in diagnosis is to rule out urinary obstruction before embarking on a lengthy workup for prerenal or intrarenal causes of renal insufficiency. A prior history of prostatic hypertrophy may provide some clues to the presence of distal obstruction. In the ICU, distal obstruction presenting as oliguria is commonly due to obstruction of the urinary catheter (especially in male patients). In patients with new-onset oliguria, the urinary catheter must be flushed or changed to rule out obstruction. Although uncommon in the acute setting, complete or severe partial bilateral ureteral obstruction also can lead to acute, "acute-on-chronic," or chronic renal failure. Early diagnosis of urinary tract obstruction is important because many causes can be corrected, and a delay in therapy can lead to irreversible renal injury. Renal ultrasonography is usually the test of choice to exclude urinary tract obstruction.[4] It is noninvasive and can be performed at the bedside. Ultrasonography also obviates the potential allergic and toxic complications of radiocontrast media. In almost all cases, ultrasonography successfully diagnoses hydronephrosis and establishes its cause. Ultrasonography also can detect other causes of renal disease, such as polycystic kidney disease. Under some circumstances, however, renal ultrasound may not yield good results. In early obstruction or obstruction associated with severe dehydration, hydronephrosis may not be visualized at the time of the initial ultrasound examination, but may appear on a study done later in the course of the disease. Computed tomography should be performed if the ultrasound results are equivocal, if the kidneys are not well visualized, or if the cause of the obstruction cannot be identified.

LABORATORY INDICES

Some authorities advocate examining the urine sediment, whereas others do not. Although hyaline and fine granular casts are common in prerenal disease, acute tubular necrosis usually is associated with coarse granular casts and tubular epithelial casts. These findings lack discriminating power, however, and are of limited practical value. The main reason to examine the urinary sediment is to detect red blood cell casts, which indicate glomerular disease. The urinary sediment in post–renal failure is often bland, lacking casts or sediments. Occasionally a few red blood cells and white blood cells may be seen. Eosinophilia, eosinophiluria, and hypocomplementemia, if present, suggest that atheroembolization may be the cause of acute oliguria.[5]

Table 11-1 lists laboratory values useful in distinguishing prerenal from intrarenal causes of acute renal failure. A fractional excretion of sodium less than 1 traditionally has been used as evidence for a prerenal cause of oliguria. These indices are unreliable when the patient has received diuretic or natriuretic agents (including dopamine and mannitol)

TABLE 11–1. BIOCHEMICAL INDICES USED TO DISTINGUISH PRERENAL FROM INTRARENAL ACUTE RENAL FAILURE

	Prerenal	Renal
$Osmolality_U$ (mOsm/kg)*	>500	<400
$[Na^+]_U$ (mmol/L or mEq/L)	<20	>40
$[urea]_s/[creatinine]_S$	>0.1	<0.05
$[creatinine]_U/[creatinine]_S$	>40	<20
$Osmolality_U/osmolality_S$	>1.5	>1
FE_{Na} (%)	<1	>2
FE_{urea} (%)	<25	>25

$Osmolality_U$, urine osmolality; $[Na^+]_U$, urinary sodium ion concentration; $[urea]_s/[creatinine]_S$, ratio of serum urea to serum creatinine concentration; $[creatinine]_U/[creatinine]_S$, ratio of urine creatinine concentration to serum creatinine concentration; $osmolality_U/osmolality_S$, ratio of urine osmolality to serum osmolality; FE_{Na}, fractional excretion of filtered sodium; FE_{urea}, fractional excretion of filtered urea. $FE_{Na} = [Na^+]_U \times [creatinine]_S/[Na^+]_S \times [creatinine]_U \times 100$.

and may be confounded by endogenous osmolar substances (e.g., glucose or urea).

CLINICAL PARAMETERS

Traditional indicators of hydration status and tissue perfusion, such as systemic blood pressure, heart rate, body weight, presence or absence of jugular-venous pulsation, and presence or absence of peripheral edema, are of some utility. In the ICU, however, some of these indicators are less useful for a variety of reasons.

Presence or absence of jugular-venous pulsation is not an accurate way to assess right ventricular filling pressure when patients are receiving positive-pressure ventilation and positive end-expiratory pressure. Similarly, peripheral edema is often due to hypoalbuminemia and decreased oncotic pressure in critically ill patients. Patients may have a total body excess of salt and water and yet be intravascularly volume depleted. Blood pressure and heart rate are affected by numerous physiologic and treatment variables in the ICU and are unreliable measures of volume status.

In the ICU, it is common to assume that one can obtain a more accurate assessment of preload by measuring the central venous pressure or pulmonary artery occlusion pressure. These measurements provide unambiguous data, however, only when the pressures are low (<10 mm Hg). If central venous pressure or pulmonary artery occlusion pressure is increased, it does not ensure that filling pressures are adequate. Response to a single fluid challenge or even multiple fluid challenges may not detect hypovolemia depending on the degree of intravascular volume depletion. The presence of a cardiac index greater than 3 L/min/m^2 generally suggests *adequate* preload, but may not reflect *optimal* preload. The mixed venous oxygen saturation can serve as a surrogate for cardiac output, but does not define optimal filling. For patients receiving positive-pressure mechanical ventilation, the absence of arterial pulse-pressure variation provides robust evidence that intravascular volume is adequate. In other cases, echocardiography may provide the only reliable way to assess intravascular volume status.

ABDOMINAL COMPARTMENT SYNDROME

Another important and often overlooked reason for acute oliguria is abdominal compartment syndrome. *Abdominal compartment syndrome* is defined as symptomatic organ dysfunction that results from an increase in intra-abdominal pressure. Although this condition initially was described in trauma patients, abdominal compartment syndrome occurs in a wide variety of medical and surgical patients. Abdominal compartment syndrome is seen sometimes after major abdominal operations that are associated with massive resuscitation or tight abdominal wall closure. Abdominal compartment syndrome leads to acute renal failure and acute oliguria mainly by increasing renal outflow pressure and reducing renal perfusion. Other mechanisms include direct parenchymal compression and decreased venous return to the heart, leading to embarrassment of cardiac output and stimulation of the sympathetic nervous and renin-angiotensin systems on this basis. These factors lead to decreased renal and glomerular perfusion and manifest as acute oliguria. Intra-abdominal pressure greater than 15 mm Hg can lead to oliguria, and intra-abdominal pressure greater than 30 mm Hg can cause anuria.[6]

Abdominal compartment syndrome should be suspected in any patient with a tensely distended abdomen, progressive oliguria, and increased airway pressure (transmitted across the diaphragm). The mainstay of diagnosis is measurement of intra-abdominal pressure. The most common way to assess intra-abdominal pressure is to measure the pressure in the urinary bladder because it is easily performed. Bladder pressure has been shown to correlate well with intra-abdominal pressure over a wide range of pressures. Decompression of the abdomen with laparotomy, sometimes requiring that the abdomen be left open for a time, is the only definitive treatment for oliguria from abdominal compartment syndrome.

TREATMENT OF OLIGURIA

ENSURING ADEQUATE RENAL PERFUSION

The management of oliguria is based on identification and correction of precipitating factors. In addition, nephrotoxic drugs should be avoided, if possible, and doses of all renally excreted drugs should be adjusted appropriately. Efforts should be made to optimize renal perfusion by correcting hypotension and providing appropriate intravascular volume expansion. Correction of hypotension is especially crucial because in cases of acute renal failure secondary to sepsis and ischemia some of the important autoregulating mechanisms that help preserve glomerular filtration rate in the face of fluctuating blood pressure are disrupted. In these patients, renal blood flow is directly related to systemic arterial pressure. Vasoactive drugs may be necessary to increase the mean arterial pressures to more than usual values to maintain adequate renal perfusion urine output.[7] In patients with chronic hypertension and renal vascular disease, renal autoregulation curves (i.e., plots of renal perfusion as a function of blood pressure) are shifted to the right. A higher mean arterial pressure may be required to ensure adequate renal perfusion. Before starting treatment with a vasoactive drug, however, it is imperative to ensure that the patient is adequately volume resuscitated. The blood pressure target must be individualized based on numerous factors, such as the premorbid blood pressure and presence or absence of vascular disease. Hemodynamic monitoring devices may enable a more streamlined, "goal-directed" approach to therapy.

ROLE OF DIURETIC AGENTS

The use of diuretic agents in oliguric renal failure is widespread, despite a paucity of evidence supporting their efficacy. Traditionally, diuretics have been used in the early phases of oliguria to "jump start" the kidney and establish urine flow. Presumably the absence of oliguria makes it easier to regulate volume status, and given that nonoliguric renal failure generally has a better prognosis, clinicians frequently use diuretics in this setting.[8] A study by Anderson and coworkers[9] in 1977 claimed a reduction in mortality from 50% to 26% by using high doses of a loop diuretic to convert oliguric to nonoliguric renal failure. This study excluded patients with shock and perioperative renal failure. These results have not been reproduced in more recent trials. A study in 1997 by Shilliday and colleagues[10] examined the effect of treating acute renal failure patients with loop diuretics. Although administration of loop diuretics increased urine flow, there was no difference in the incidence of renal recovery, dialysis, or death among patients randomized to

diuretic therapy or placebo. Two other randomized controlled trials by Brown and coworkers[11] and Kleinknecht and associates[12] also failed to show any improvement in survival when loop diuretics were used in patients with oliguric renal failure. The PICARD study group reported the results of a large cohort study of critically ill patients with acute renal failure from 1989 through 1995.[13] The study showed that diuretic use was associated with an increased risk of death or nonrecovery of renal function. Accordingly, it is unlikely that the use of diuretics in patients with oliguric acute renal failure affords any benefit to the kidney. The use of diuretics in this setting should be restricted to the treatment of volume overload, and even then caution is advised.

VASOACTIVE AGENTS

Other agents have been used to "treat" oliguria, including dopamine and related compounds. Because urine output often increases with the addition of "low-dose" dopamine, many intensivists assume that it has a beneficial effect. Low-dose dopamine has been advocated since the 1970s as therapy for oliguria on the basis of its action on dopamine-1 receptors in doses less than 5 μg/kg/min. There is abundant evidence, however, that low-dose dopamine does not afford any renal protection in oliguria. Most evidence in favor of low-dose dopamine comes from uncontrolled trials or anecdotal studies. A comprehensive meta-analysis of dopamine in critically ill patients by Kellum and Decker[14] showed that dopamine did not prevent the onset of acute renal failure or decrease mortality or the need for dialysis.

There are important physiologic considerations that argue against a protective role for dopamine or any other dopamine receptor agonists, such as fenoldopam or dopexamine, in the oliguric state. First, the effect of dopamine agonists on urine output may be merely the natriuretic response mediated by inhibition of Na^+,K^+-ATPase in tubular epithelial cells.[15] Dopamine increases urine output because it is a diuretic. Second, treatment with dopaminergic antagonists, such as metoclopramide, has not been shown to affect renal function adversely. Third, the effect of dopamine may be counteracted by increased plasma renin activity in critically ill patients. A significant hysteresis effect has been shown for the action of dopamine on renal blood flow. Finally, although dopamine increases renal blood flow, it does not increase medullary oxygenation,[16] and by increasing solute delivery to the distal tubule, dopamine agonists actually worsen medullary oxygen balance.[17] Despite claims to the contrary, newer dopamine agonists, such as fenoldopam and dopexamine, not only have these limitations, but also can induce hypotension and further increase the risk of renal injury.

CONCLUSION

The presence of oliguria should alert the clinician to undertake a diligent search for any correctable underlying causes. The mainstay of treatment is to ensure adequate renal perfusion by optimizing blood pressure, cardiac output, and intravascular volume status. The use of diuretics and vasoactive agents, although still fairly common, is not supported by the evidence, and emerging data actually suggest harm.

Chapter 12
ACID-BASE DISORDERS

John A. Kellum

Conventional wisdom posits that acid-base disorders are more important for what they tell the clinician about the patient than for any harm that happens to the patient as a direct consequence of abnormal blood (or tissue) pH. This view is reasonable because most acid-base disorders are mild and well tolerated, but they allow the astute clinician to recognize underlying disorders that might be difficult to diagnose or even suspect otherwise. However, there are certain circumstances in which acid-base derangements are themselves dangerous, such as when the disorders are extreme (e.g., pH <7.0 or >7.7), especially when the acid-base derangement develops quickly. Such severe abnormalities can be the direct cause of organ dysfunction and can manifest as cerebral edema, seizures, decreased myocardial contractility, pulmonary vasoconstriction, and systemic vasodilation. Even less extreme derangements can produce harm because of the patient's response to the abnormality. For example, a spontaneously breathing patient with metabolic acidosis will attempt to compensate by increasing minute ventilation. The workload imposed by increasing minute ventilation can lead to respiratory muscle fatigue with respiratory failure or diversion of blood flow from vital organs to the respiratory muscles, resulting in organ injury. Acidemia can promote the development of cardiac dysrhythmias in critically ill patients or increase myocardial oxygen demand in patients with myocardial ischemia. In such cases, one must treat the underlying disorder and also provide treatment for the acid-base disorder itself. Finally, emerging evidence suggests that changes in acid-base status influence immune effector cell function. Thus, avoiding acid-base derangements could influence outcome by modulating systemic inflammation and/or host defenses against infection.

GENERAL PRINCIPLES

Three widely accepted methods are used to analyze and classify acid-base disorders, yielding mutually compatible results. The approaches differ only in assessment of the metabolic component (i.e., all three treat P_{CO_2} as an independent variable): (1) HCO_3^- concentration ($[HCO_3^-]$); (2) standard base-excess; (3) strong ion difference. All three yield virtually identical results when used to quantify the acid-base status of a given blood sample.[1-4] For the most part, the differences among these three approaches are conceptual; in other words, they differ in how they approach the understanding of mechanism.[5-7]

There are three mathematically independent determinants of blood pH:

1. The difference between the sum of the concentrations of strong cations (e.g., Na^+ and K^+) and the sum of the concentrations of strong anions (e.g., Cl^-, lactate); this difference is called the strong ion difference.
2. The total weak acid "buffers" concentration (A_{TOT}), which is mostly composed of the concentrations of albumin and phosphate.
3. P_{CO_2}.

Only these three variables (strong ion difference, A_{TOT}, and P_{CO_2}) can independently affect blood pH. $[H^+]$ and $[HCO_3^-]$ are dependent variables, being functions of strong ion difference, A_{TOT}, and P_{CO_2}. Changes in plasma $[H^+]$ occur as a result of changes in the dissociation of water and A_{TOT} brought about by the electrochemical forces produced by changes in strong ion difference and P_{CO_2}. The standard base-excess is mathematically equivalent to the change in strong ion difference required to restore pH to 7.4 given a P_{CO_2} of 40 mm Hg and the prevailing A_{TOT}. Thus, a standard base-excess of –10 mEq/L means that the strong ion difference is 10 mEq/L less than the strong ion difference that is associated with a pH of 7.4 when P_{CO_2} is 40 mm Hg.

ASSESSING ACID-BASE BALANCE

Acid-base homeostasis is defined by the pH of blood plasma and by the conditions of the acid-base pairs that determine it. Because blood plasma is an aqueous solution containing both volatile (carbon dioxide) and fixed acids, its pH will be determined by the net effects of all these components on the dissociation of water. The determinants of blood pH can be grouped into two broad categories, respiratory and metabolic. Respiratory acid-base disorders are disorders of carbon dioxide (CO_2) tension, and metabolic acid-base disorders comprise all other conditions affecting the pH. This latter category includes disorders of both weak acids (often referred to as "buffers," although the term is imprecise) and strong acids and bases (including both organic and inorganic acids). Acid-base disorders can be recognized by any of the following:

1. An alteration in the pH of the arterial blood (normally 7.35 to 7.45). If the pH is less than 7.35, then acidemia is said to be present; if the pH is greater than 7.45, then alkalemia is said to be present.
2. An arterial partial pressure of CO_2 (P_aCO_2) outside the normal range (35 to 45 mm Hg).
3. A plasma bicarbonate concentration outside the normal range (22-26 mEq/L).
4. An arterial standard base-excess of 3 or –3 mEq/L.

Although these criteria are useful in identifying an acid-base disorder, the absence of all four cannot exclude a mixed

acid-base disorder, alkalosis plus acidosis, which is completely matched. Fortunately, such conditions are quite rare.

METABOLIC ACID-BASE DISORDERS

Metabolic acid-base derangements are associated with a greater number of underlying conditions than are respiratory acid-base disorders and tend to be more difficult to treat. Metabolic acidosis is produced by a decrease in the strong ion difference, which, in turn, generates an electrochemical force that increases $[H^+]$. The strong ion difference decreases when the concentration of organic anions (e.g., lactate or β-hydroxybutyrate) increases. The strong ion difference also decreases when there is a loss of sodium bicarbonate (e.g., due to diarrhea or renal tubular acidosis) or there is a gain of exogenous anions (e.g., iatrogenic acidosis or poisonings). Metabolic alkaloses occur when the strong ion difference is inappropriately wide, although it need not be greater than the "normal" 40 to 42 mEq/L. Widening of the strong ion difference can be brought about by the loss of strong anions in excess of strong cations (e.g., vomiting, diuretics), or, rarely, by administration of strong cations in excess of strong anions (e.g., transfusion of large volumes of banked blood containing sodium citrate).

Similarly, the treatment of metabolic acid-base disorders requires a change in the strong ion difference. Metabolic acidoses are repaired by increasing plasma Na^+ concentration more than plasma Cl^- concentration (e.g., by infusing $NaHCO_3$) and metabolic alkaloses are repaired by replacing Cl^- either as NaCl (large volumes), KCl, or even HCl. Note that so-called "chloride-resistant" metabolic alkaloses are resistant to chloride only because of ongoing renal losses that increase in response to increased Cl^- replacement (e.g., hyperaldosteronism).

Pathophysiology of Metabolic Acid-Base Disorders

Disorders of metabolic acid-base balance occur as a result of

1. Dysfunction of the primary regulating organs.
2. Exogenous administration of drugs or fluids that alter the body's ability to maintain normal acid-base balance.
3. Abnormal metabolism that overwhelms the normal defense mechanisms.

The organs responsible for regulating the strong ion difference in both health and disease are the kidneys and, to a lesser extent, the gastrointestinal tract.

The Kidneys

Plasma flow to the kidneys is approximately 600 mL/min. The glomeruli filter the plasma to yield 120 mL/min of filtrate. Normally, more than 99% of the filtrate is reabsorbed and returned to the plasma. Thus, the kidney can only excrete a very small amount of strong ions into the urine each minute, and several minutes to hours are required to achieve a significant impact on the strong ion difference. The handling of strong ions by the kidney is extremely important, because every Cl^- ion that is filtered but not reabsorbed decreases the strong ion difference. Accordingly, "acid handling" by the kidney is generally mediated through Cl^- balance. The purpose of renal ammoniagenesis is to allow the excretion of Cl^- without Na^+ or K^+. Viewed this way, renal tubular acidosis can be regarded as an abnormality of Cl^- handling rather than of H^+ or HCO_3^- handling.[3]

Renal-Hepatic Interaction

Ammonium ion (NH_4^+) is important to systemic acid-base balance not because it stores H^+ or has a direct action in the plasma (normal plasma NH_4^+ concentration is <0.01 mEq/L). NH_4^+ is important because it is "co-excreted" with Cl^-. Of course, NH_4^+ is not only produced in the kidney. Hepatic ammoniagenesis (and, as we shall see, glutaminogenesis) is also important for systemic acid-base balance and is tightly controlled by mechanisms sensitive to plasma pH.[8] This reinterpretation of the role of NH_4^+ in acid-base balance is supported by the evidence that hepatic glutaminogenesis is stimulated by acidosis.[9] Glutamine is used by the kidney to generate NH_4^+ and thus facilitates the excretion of Cl^-. The production of glutamine therefore can be seen as having an alkalinizing effect on plasma pH because of the way the kidney utilizes it.

The Gastrointestinal Tract

Different parts of the gastrointestinal tract handle strong ions in distinct ways. In the stomach, Cl^- is pumped out of the plasma and into the lumen, thereby reducing the strong ion difference and pH of gastric juice. The pumping action of the gastric parietal cells increases the strong ion difference of the plasma by promoting the loss of Cl^-; this effect produces the so-called "alkaline tide" at the beginning of a meal when gastric acid secretion is maximal.[10] In the duodenum, Cl^- is reabsorbed and the plasma pH is restored. Normally, only slight changes in plasma pH are evident because Cl^- is returned to the circulation almost as soon as it is being removed. However, if gastric secretions are removed from the patient, either through a suction catheter or as a result of vomiting, Cl^- is lost and the strong ion difference increases. It is important to realize that it is the Cl^- loss, not the H^+ loss, that is the cause for widening of the strong ion difference and the development of metabolic alkalosis. Although H^+ is "lost" as HCl, it is also lost with every molecule of water removed from the body.

In contrast to the stomach, the pancreas secretes fluid into the small intestine that has a strong ion difference much greater than that of plasma; the $[Cl^-]$ of pancreatic secretions is quite low. Thus, the strong ion difference in the plasma perfusing the pancreas decreases, a phenomenon that peaks about an hour after a meal and helps counteract the alkaline tide. If large amounts of pancreatic fluid are lost, for example from surgical drainage, acidosis develops as a consequence of the decreased plasma strong ion difference. Fluid in the lumen of the large intestine has a wide strong ion difference because most of the Cl^- has been removed in the small intestine and the remaining electrolytes are mostly Na^+ and K^+ and HCO_3^-. The body normally reabsorbs much of the water and electrolytes from this fluid but when there is severe diarrhea, large amounts of this HCO_3^--rich and Cl^--poor fluid can be lost. If these losses are persistent, the plasma strong ion difference decreases and acidosis results.

In addition, the small intestine may contribute strong ions to the plasma. This effect is most apparent when mesenteric blood flow is compromised and lactate is produced, sometimes in large quantities, by the tissues of the small intestine.

METABOLIC ACIDOSIS

Traditionally, metabolic acidoses are categorized according to the presence or absence of unmeasured anions. The presence of unmeasured anions is routinely inferred by measuring the

TABLE 12–1. CAUSES OF AN INCREASED ANION GAP (AG)

Common Causes
Renal failure
Ketoacidosis
Diabetic
Alcoholic
Starvation
Metabolic errors
Lactic acidosis
Toxins
Methanol
Ethylene glycol
Salicylates
Paraldehyde
Toluene
Rare Causes
Dehydration
Sodium salts
Sodium lactate
Sodium citrate
Sodium acetate
Sodium PCN (>50 m units/day)
Carbenicillin (>30 g/day)
Decreased unmeasured cation
Hypomagnesemia
Hypokalemia
Hypocalcemia
Alkalemia

TABLE 12–2. POTENTIAL CLINICAL EFFECTS OF METABOLIC ACID-BASE DISORDERS

Metabolic Acidosis	Metabolic Alkalosis
Cardiovascular	***Cardiovascular***
Decreased inotropy	Decreased inotropy (Ca^{++} entry)
Conduction defects	Altered coronary blood flow*
Arterial vasodilatation	Digoxin toxicity
Venous vasoconstriction	
Oxygen Delivery	***Neuromuscular***
Decreased oxy-Hb binding	Neuromuscular excitability
Decreased 2,3-DPG (late)	Encephalopathy seizures
Neuromuscular	***Metabolic Effects***
Respiratory depression	Hypokalemia
Decreased sensorium	Hypocalcemia
	Hypophosphatemia
	Impaired enzyme function
Metabolism	***Oxygen Delivery***
Protein wasting	Increased oxy-Hb affinity
Bone demineralization	Increased 2,3-DPG (delayed)
Catecholamine, PTH, and aldosterone stimulation	
Insulin resistance	
Free radical formation	
Gastrointestinal	
Emesis	
Gut barrier dysfunction	
Electrolytes	
Hyperkalemia	
Hypercalcemia	
Hyperuricemia	

*Animal studies have shown both increased and decreased coronary artery blood flow.

concentrations of electrolytes in plasma and calculating the anion gap, as described later. The differential diagnosis for a positive-anion gap acidosis is shown in Table 12-1. Non-anion gap acidoses can be divided into three types: renal, gastrointestinal, and iatrogenic (Fig. 12-1). In the intensive care unit (ICU), the most common types of metabolic acidosis include lactic acidosis, ketoacidosis, iatrogenic acidosis, and acidosis secondary to toxins.

The potential effects of metabolic acidosis and alkalosis on vital organ function are shown in Table 12-2. Metabolic and respiratory acidosis may have different implications with respect to survival, an observation that suggests that the underlying disorder is perhaps more important than the absolute degree of acidemia.[11]

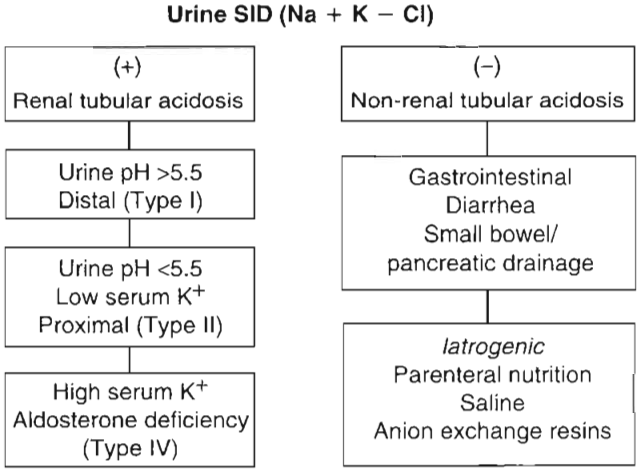

FIGURE 12–1. Differential diagnosis for a hyperchloremic metabolic acidosis. (SID, strong ion difference.)

If metabolic acidemia is to be treated, consideration should be given to the likely duration of the disorder. If it is expected to be short lived (e.g., diabetic ketoacidosis), maximizing respiratory compensation is usually the safest approach. Once the disorder resolves, ventilation can be quickly reduced to normal and there will be no lingering effects of therapy. However, if the disorder is likely to be more chronic (e.g., renal failure), therapy aimed at restoring the strong ion difference is indicated. In all cases, the therapeutic target can be quite accurately determined from the standard base-excess. As discussed, the standard base-excess corresponds to the amount the strong ion difference must change in order to restore the pH to 7.4, assuming a P_{CO_2} of 40 mm Hg. Thus, if the strong ion difference is 30 mEq/L and the standard base-excess is −10 mEq/L, the target strong ion difference would be 40 mEq/L. Accordingly, the plasma Na^+ concentration would have to increase by 10 mEq/L for $NaHCO_3$ administration to completely repair the acidosis. If increasing the plasma Na^+ concentration is inadvisable for other reasons (e.g., hypernatremia), then $NaHCO_3$ administration is also inadvisable. Importantly, $NaHCO_3$ administration has not been shown to improve outcome in patients with lactic acidosis.[12]

In addition, $NaHCO_3$ administration is associated with certain disadvantages. Large (hypertonic) doses given rapidly can lead to hypotension[13] and have the potential to cause a sudden, marked increase in P_{aCO_2}.[14] Accordingly, it is important to assess the patient's ventilatory status before $NaHCO_3$ is administered, particularly in the absence of mechanical ventilation. $NaHCO_3$ infusion also affects circulating $[K^+]$ and $[Ca^{++}]$ concentrations, which need to be monitored closely.

Tromethamine (Tris-buffer or Tham) is an organic buffer that readily penetrates cells.[15] It is a weak base (pK = 7.9) that does not alter the strong ion difference and does not affect plasma [Na^+]. Accordingly, it is often used when administration of $NaHCO_3$ is contraindicated because of hypernatremia. This agent has been available since the 1960s, but limited data are available on its use in humans with acid-base disorders. In small uncontrolled studies, tromethamine appears to be effective in reversing metabolic acidosis secondary to ketoacidosis or renal failure without obvious toxicity.[16] However, adverse reactions have been reported, including hypoglycemia, respiratory depression, and even fatal hepatic necrosis when concentrations exceeding 0.3 *M* are used. In Europe, a mixture of tromethamine, acetate, $NaHCO_3$, and disodium phosphate is available (Tribonate). This mixture seems to have fewer side effects than tromethamine alone, but experience with Tribonate is still quite limited.

The Anion Gap and the Strong Ion Gap

For more than 30 years, the anion gap has been used by clinicians and it has evolved into a major tool to evaluate acid-base disorders.[17] The anion gap is estimated from the differences between the routinely measured concentrations of serum cations (Na^+ and K^+) and anions (Cl^- and HCO_3). Normally, this difference, or "gap," is made up by albumin, and, to a lesser extent, by phosphate. Sulfate and lactate also contribute a small amount, normally less than 2 mEq/L. However, there are also unmeasured cations, such as Ca^{++} and Mg^{++}, and these tend to offset the effects of sulfate and lactate except when the concentration of sulfate or lactate is abnormally increased (Fig. 12-2). Plasma proteins other than albumin can be positively or negatively charged but in the aggregate tend to be neutral, except in rare cases of abnormal paraproteins such as in cases of multiple myeloma.[18] In practice, the anion gap (AG) is calculated as follows:

$$AG = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$$

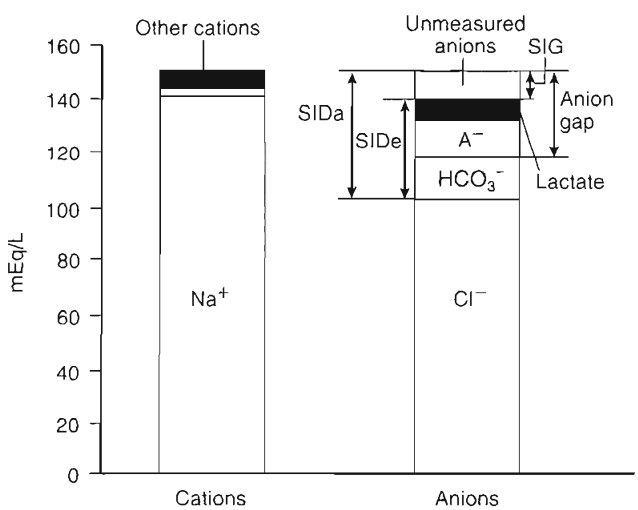

FIGURE 12–2. Charge balance in blood plasma. "Other cations" include Ca^{++} and Mg^{++}. The strong ion difference (SID) is always positive (in plasma) and SID – SIDe (effective) must equal zero. Any difference between SID apparent (SIDa) and SIDe is the strong ion gap (SIG) and must represent unmeasured anions.

Because of its low and narrow extracellular concentration range, K^+ is often omitted from the calculation. The normal value for anion gap is 12 ± 4 (if [K^+] is considered) or 8 ± 4 mEq/L (if [K^+] is not considered). The normal range has decreased in recent years following the introduction of more accurate methods for measuring Cl^- concentration.[19,20] However, the various measurement techniques available mandate that each institution reports its own expected "normal anion gap."

The anion gap is useful because this parameter can limit the differential diagnosis for patients with metabolic acidosis. If the anion gap is increased, the explanation almost invariably will be found among five disorders: ketosis, lactic acidosis, poisoning, renal failure, or sepsis.[21] However, several conditions can alter the accuracy of anion gap estimation, and these conditions are particularly prevalent among patients with critical illness.[22,23] Dehydration can widen the apparent anion gap by increasing the concentration of all the ions used for the calculation. Hypoalbuminemia decreases the anion gap and has been recommended to "correct" the anion gap for changes in albumin concentration, because for every 1 g/dL decrease in serum albumin concentration, the apparent anion gap narrows by 2.5 to 3 mEq/L.[24] Respiratory and metabolic alkaloses are associated with an increase of up to 3 to 10 mEq/L in the apparent anion gap. The basis for this effect is enhanced lactate production (from stimulated phosphofructokinase enzymatic activity), reduction in the concentration of ionized weak acids (A^-), and, possibly, the additional effect of dehydration.

Other factors that can increase the anion gap are low Mg^{++} concentration and administration of the sodium salts of poorly reabsorbable anions (such as beta-lactam antibiotics).[25] Certain parenteral nutrition formulations, such as those containing acetate, may increase the anion gap. Citrate-based anticoagulants rarely can have the same effect after administration of multiple blood transfusions.[26] None of these rare causes, however, increases the anion gap significantly,[27] and they are usually easily identified. In recent years, some additional causes of an increased anion gap have been reported. It is sometimes widened in patients in non-ketotic hyperosmolar states induced by diabetes mellitus; the biochemical basis for this effect remains unexplained.[28] In recent years, unmeasured anions have been reported in the blood of patients with sepsis[29,30] and liver disease[31,32] and in experimental animals injected with endotoxin.[33] These anions may be the source of much of the unexplained acidosis seen in patients with critical illness.[34]

Additional doubt has been cast on the diagnostic value of the anion gap in certain situations, however.[22,30] Salem and Mujais[22] found routine reliance on the anion gap to be "fraught with numerous pitfalls." The primary problem with the anion gap is its reliance on the use of a "normal" range that depends on normal circulating levels of albumin and to a lesser extent phosphate, as discussed earlier. Plasma concentrations of albumin or phosphate are often grossly abnormal in patients with critical illness, leading to change in the "normal" range for the anion gap. Moreover, because these anions are not strong anions, their charge is affected by pH. These considerations have prompted some authors to adjust the "normal range" for the anion gap according to the albumin concentration[24] or phosphate concentration.[6] Each g/dL of albumin has a charge of 2.8 mEq/L at pH 7.4 (2.3 mEq/L at pH 7.0 and 3.0 mEq/L at pH 7.6). Each mg/dL of phosphate has a charge of 0.59 mEq/L at pH 7.4

(0.55 mEq/L at pH 7.0 and 0.61 mEq/L at pH 7.6). Thus, the "normal" anion gap can be estimated using this formula[6]:

$$\text{"normal" anion gap} = 2 \times [\text{albumin}]\ (\text{g/dL}) + 0.5 \times [\text{phosphate}]\ (\text{mg/dL})$$

Or for international units:

$$\text{"normal" anion gap} = 0.2 \times [\text{albumin}]\ (\text{g/L}) + 1.5 \times [\text{phosphate}]\ (\text{mmol/L})$$

These formulas only should be used when the pH is less than 7.35, and even then they are only accurate within 5 mEq/L. When more accuracy is needed, a slightly more complicated method of estimating $[A^-]$ is required.[31,35]

Another alternative to using the traditional anion gap is to use the strong ion difference. By definition, the strong ion difference must be equal and opposite to the negative charges contributed by $[A^-]$ and total CO_2. The sum of the charges from $[A^-]$ and total CO_2 concentration has been termed *strong ion difference effective.*[18] The *apparent strong ion difference* is obtained by measurement of each individual ion. Both the apparent strong ion difference and the strong ion difference effective should equal the true strong ion difference. If the apparent strong ion difference and strong ion difference effective differ, unmeasured ions must exist. If the apparent strong ion difference is greater than strong ion difference effective, these ions are anions and if the apparent strong ion difference is less than strong ion difference effective, the unmeasured ions are cations. This difference has been termed the strong ion gap to distinguish it from the anion gap.[31] Unlike the anion gap, the strong ion gap is normally zero and does not change with changes in pH or albumin concentration.

Positive Anion Gap Acidoses

Lactic Acidosis

In many forms of critical illness, lactate is the most important cause of metabolic acidosis.[36] Blood lactate concentration has been shown to correlate with outcome in patients with hemorrhagic[37] and septic shock.[38] Lactic acid has been viewed as the predominant source of metabolic acidosis due to sepsis.[39] In this view, lactic acid is released primarily from the musculature and the gut as a consequence of tissue hypoxia. Moreover, the amount of lactate produced is believed to correlate with the total oxygen debt, the magnitude of the hypoperfusion, and the severity of shock.[36] In recent years, this view has been challenged by the observation that during sepsis, even with profound shock, resting muscle does not produce lactate. Indeed, studies by various investigators have shown that the musculature actually may consume lactate during endotoxemia.[40-42] Data concerning the gut are less clear. There is little question that underperfused gut can release lactate; however, it does not appear that the gut releases lactate during sepsis if mesenteric perfusion is maintained. Under such conditions, the mesentery circulation can even become a net consumer of lactate.[40,41] Perfusion is likely to be a major determinant of mesenteric lactate metabolism. In a canine model of sepsis, gut lactate production could not be shown when flow was maintained with dopexamine hydrochloride.[42]

Studies in animals as well as humans have shown that the lung may be a prominent source of lactate in the setting of acute lung injury.[40,43-45] While studies such as these do not address the underlying pathophysiologic mechanisms of hyperlactatemia in sepsis, they suggest that using blood lactate concentration as evidence for tissue dysoxia is an oversimplification at best. Indeed, many investigators have begun to offer alternative interpretations of hyperlactatemia in this setting.[44-48] Table 12-3 lists several alternative sources of hyperlactatemia. In particular, pyruvate dehydrogenase, the enzyme responsible for moving pyruvate into the Krebs cycle, is inhibited by endotoxin.[49] However, data from recent studies suggest that increased aerobic metabolism may be more important than metabolic defects or anaerobic metabolism.[50] Finally, administration of epinephrine promotes lactic acidosis, presumably by stimulating cellular metabolism (e.g., increased hepatic glycolysis).

Administration of epinephrine may be a common cause of lactic acidosis in patients with critical illness.[51,52] Interestingly, this phenomenon does not occur when dobutamine or norepinephrine is infused[53] and does not appear to be related to decreased tissue perfusion.

Although controversy exists as to the source and interpretation of lactic acidosis in critically ill patients, there is no question about the ability of lactate accumulation to produce acidemia. Lactate is a strong ion by virtue of the fact that at a pH within the physiologic range, it is almost completely dissociated; for instance, the pKa for lactic acid is 3.9. Thus, at pH 7.4, 3162 lactic acid molecules are dissociated for every one that is not. Because the body can produce and dispose of lactate rapidly, it functions as one of the most dynamic components of the strong ion difference.

Plasma lactate concentration may be increased without an increase in $[H^+]$. There are two possible explanations for this phenomenon. First, if lactate is added to the plasma, not as lactic acid but rather as the salt of a strong acid (e.g., sodium lactate), there will be little change in the strong ion difference. The strong ion difference does not change because a strong cation (Na^+) is being added along with a strong anion. However, only if a very large amount of lactate is infused rapidly will there be an appreciable increase in the plasma lactate concentration. For example, the use of lactate-based hemofiltration fluid can result in hyperlactatemia with an *increased* plasma HCO_3^- concentration and pH.

TABLE 12–3. MECHANISMS ASSOCIATED WITH INCREASED SERUM LACTATE CONCENTRATION

Tissue Hypoxia
Hypodynamic shock
Organ ischemia
Hypermetabolism
Increased aerobic glycolysis
Increased protein catabolism
Hematologic malignancies
Decreased Clearance of Lactate
Liver failure
Shock
Inhibition of Pyruvate Dehydrogenase
Thiamine deficiency
Endotoxin?
Activation of Inflammatory Cells?

A more important mechanism whereby hyperlactatemia exists without acidemia (or with less acidemia than expected) is when the strong ion difference is corrected by the elimination of another strong anion from the plasma.[54] In the setting of sustained lactic acidosis induced by lactic acid infusion, Cl^- moves out of the plasma space, thus normalizing pH. Under these conditions, hyperlactatemia may persist but base-excess may be normalized by compensatory mechanisms to restore the strong ion difference.

Traditionally, lactic acidosis is subdivided into type A, in which the mechanism is tissue hypoxia, and type B, in which there is no hypoxia.[55] However, this distinction may be artificial. Some disorders, such as sepsis, may be associated with lactic acidosis due to a variety of mechanisms (Table 12-3), some of the "A" type and some of the "B" type. A potentially useful method of distinguishing anaerobically produced lactate from other sources is to measure the blood pyruvate concentration. The normal lactate to pyruvate ratio is 10:1.[56] A lactate-to-pyruvate ratio greater than 25:1 is considered to be evidence of anaerobic metabolism.[48] This approach makes biochemical sense, because pyruvate is reduced to lactate during anaerobic metabolism, thereby increasing the lactate-to-pyruvate ratio. Unfortunately, pyruvate is very unstable in solution and therefore is difficult to measure accurately in the clinical setting, greatly reducing the clinical utility of lactate/pyruvate determinations.

Treatment of lactic acidosis remains controversial. The only noncontroversial approach is to treat the underlying cause. The use of sodium bicarbonate ($NaHCO_3$) is equally controversial and remains of unproven value.[12]

Ketoacidosis

Another common cause of a metabolic acidosis with a positive anion gap is ketoacidosis. Ketones are formed by beta-oxidation of fatty acids, a process that is inhibited by insulin. In insulin-deficient states, ketone formation increases substantially. The accumulation of ketone bodies (acetone, β-hydroxybutyrate, and acetoacetate) in the plasma is exacerbated because elevated blood glucose concentrations promote an osmotic diuresis, leading to intravascular volume contraction. This state is associated with elevated circulating cortisol and catecholamine levels, which further stimulates free fatty acid production.[57] In addition, increased glucagon levels, relative to insulin levels, decreases intracellular concentrations of malonyl co-enzyme A and increases the activity of carnitine palmityl acyl transferase, effects that promote ketogenesis.

Both acetoacetate and β-hydroxybutyrate are strong anions (pKa 3.8 and 4.8, respectively).[58] Thus, like lactate, the presence of these ions decreases the strong ion difference and increases the $[H^+]$. Ketoacidosis may result from diabetes (diabetic ketoacidosis) or excessive alcohol consumption (alcoholic ketoacidosis). The diagnosis is established by measuring serum ketone levels. However, it is important to understand that the nitroprusside reaction only measures acetone and acetoacetate, and not β-hydroxybutyrate. Thus, the state of measured ketosis is dependent on the ratio of acetoacetate to β-hydroxybutyrate. This ratio is low when lactic acidosis coexists with ketoacidosis because the reduced redox state of lactic acidosis favors production of β-hydroxybutyrate.[59] In this circumstance, the apparent level of ketosis is small relative to the amount of acidosis and the elevation of the anion gap. There is also a risk of confusion during treatment of ketoacidosis because ketones as measured by the nitroprusside reaction can increase despite resolving acidosis. This effect occurs as a result of rapid clearance of β-hydroxybutyrate, improving acid-base balance without changing the measured level of ketosis. Furthermore, circulating ketone levels can even appear to increase as β-hydroxybutyrate is converted to acetoacetate. Hence, it is better to monitor therapy by measuring blood pH and anion gap than by assaying levels of serum ketones.

Treatment of diabetic ketoacidosis includes infusing insulin and large amounts of fluid; 0.9% saline is usually recommended. Potassium replacement is often required as well. Fluid resuscitation reverses the hormonal stimuli for ketone body formation, as discussed earlier, and insulin promotes metabolism of ketones and glucose. Administration of $NaHCO_3$ may produce a more rapid rise in the pH by increasing the strong ion difference, but there is little evidence that this effect is desirable. Furthermore, because increasing the plasma Na^+ concentration increases the strong ion difference, the strong ion difference will be too high once the ketosis is cleared ("overshoot" alkalosis). In any case, administration of $NaHCO_3$ is rarely necessary and should be avoided except in extreme cases.[60]

A more common problem in the treatment of diabetic ketoacidosis is persistence of acidemia after resolution of ketosis. This hyperchloremic metabolic acidosis occurs as Cl^- replaces ketoacids, thus maintaining decreases in strong ion difference and pH. This effect appears to occur for two reasons. First, exogenous Cl^- is often provided in the form of 0.9% saline, which, if given in large enough quantities, results in a so-called dilutional acidosis (see later). Second, renal Cl^- reabsorption increases as ketones are excreted in the urine. Increases in the tubular Na^+ load produce electrical-chemical forces favoring Cl^- reabsorption.[61]

The acidosis seen in patients with alcoholic ketoacidosis is usually less severe. Treatment consists of intravenous fluid administration and infusion of glucose, instead of insulin, as would be the case with diabetic ketoacidosis.[62] Indeed, insulin is contraindicated, because it may cause precipitous hypoglycemia.[63] Thiamine also must be given to avoid precipitating Wernicke's encephalopathy.

Renal Failure

Renal failure, especially when chronic, leads to accumulation of sulfates and other acids, widening the anion gap, although this increase usually is not large.[64] Similarly, uncomplicated renal failure rarely produces severe acidosis, except when it is accompanied by a high rate of acid generation, such as occurs during hypermetabolism.[65] In all cases, the strong ion difference is decreased and remains so unless some therapy is provided. Hemodialysis removes sulfate and other ions and allows normal Na^+ and Cl^- balance to be restored, thus returning the strong ion difference to normal (or near normal). However, patients not yet requiring dialysis and those who are between treatments often require some other therapy to increase the strong ion difference. $NaHCO_3$ is used as long as the plasma Na^+ concentration is not already elevated.

Toxins

Metabolic acidosis with an increased anion gap is a major feature of various types of drug and substance intoxications (see Table 12-1).

Other and Unknown Causes

In the nonketotic hyperosmolar state associated with poorly controlled diabetes, the anion gap widens for unexplained

reasons.[28] Even when very careful methods are applied, using the strong ion gap or similar strategies, unmeasured anions have been detected in the blood of patients with sepsis[29,30] and liver disease[31] and in experimental animals given endotoxin.[32] Furthermore, unknown cations also appear in the blood of some critically ill patients.[30] The significance of these findings remains to be determined.

Non-Anion Gap (Hyperchloremic) Acidoses

Hyperchloremic metabolic acidosis occurs as a result of either the increase in $[Cl^-]$ relative to strong cations, especially Na^+, or the loss of cations with retention of Cl^-. As seen in Figure 12-1, these disorders can be separated by history and by measurement of urinary Cl^- concentration. When acidosis occurs, the normal response by the kidney is to increase Cl^- excretion. Failure to do so identifies the kidney as the problem. Extrarenal causes of hyperchloremic acidosis are exogenous Cl^- loads (iatrogenic acidosis) or loss of cations from the lower gastrointestinal tract without proportional losses of Cl^-.

Renal Tubular Acidosis

Examination of the urine and plasma electrolytes and pH and calculation of the urine apparent strong ion difference allow one to correctly diagnose most cases of renal tubular acidosis (see Fig. 12-1).[66] However, caution must be exercised when the plasma pH is greater than 7.35, because urinary Cl^- excretion is normally decreased when pH is this high. In such circumstances, it may be necessary to infuse sodium sulfate or furosemide. These agents stimulate Cl^- and K^+ excretion and can be used to unmask the defect and probe K^+ secretory capacity.

The defect in all types of renal tubular acidosis is an inability to excrete Cl^- in proportion to Na^+, although the reasons vary by type. Treatment largely depends on whether the kidney responds to mineralocorticoid replacement or whether there are losses of Na^+ that can be replaced as $NaHCO_3$.

Classic distal (type I) renal tubular acidosis responds to $NaHCO_3$ replacement; typically, only 50 to 100 mEq/day are required. Defects in K^+ reabsorption are also common in this type of renal tubular acidosis and K^+ replacement is also required. A variant of the classic distal renal tubular acidosis is a hyperkalemic form that actually is more common than the classic type. The central defect here appears to be impaired Na^+ transport in the cortical collecting duct. These patients also respond to $NaHCO_3$ replacement. Proximal (type II) renal tubular acidosis is characterized by both Na^+ and K^+ reabsorption defects. The disorder is uncommon and usually appears as a component of Fanconi's syndrome, which also is characterized by defects in the reabsorption of glucose, phosphate, urate, and amino acids.

Treatment of this disorder with $NaHCO_3$ is ineffective because increased ion delivery merely results in increased excretion. Thiazide diuretics have been used to treat this disorder, with varying success.

Type IV renal tubular acidosis is caused by aldosterone deficiency or resistance. These disorders are diagnosed by the presence of high serum $[K^+]$ concentration and low urine pH (<5.5). Treatment is usually most effective if the cause can be removed; most commonly, drugs, such as nonsteroidal anti-inflammatory agents, heparin, or potassium-sparing diuretics, are responsible. Occasionally, mineralocorticoid replacement is required.

Gastrointestinal Acidosis

Fluid secreted into the gut lumen contains higher amounts of Na^+ than Cl^-. Large losses of these fluids, particularly if volume is replaced with fluids containing equal amounts of Na^+ and Cl^-, results in a decrease in the plasma Na^+ concentration relative to the Cl^- concentration and a decrease in strong ion difference. Such a scenario can be avoided if formulations such as lactated Ringer's solution are used instead of normal saline to replace gastrointestinal losses.

Iatrogenic Acidosis

Two of the most common causes of a hyperchloremic metabolic acidosis are iatrogenic and both are due to administration of Cl^-. Modern parenteral nutrition formulas contain weak anions, such as acetate, in addition to Cl^-. The proportions of each anion can be adjusted depending on the acid-base status of the patient. If an insufficient amount of weak anions is provided, the plasma Cl^- concentration increases, decreasing the strong ion difference and resulting in acidosis. A similar condition can arise when normal saline is used for fluid resuscitation, resulting in the development of "dilutional acidosis." Dilutional acidosis was first described more than 40 years ago,[67,68] although some authors have argued that this problem is rarely clinically significant.[69] This view pertains because large doses of NaCl produce only minor degrees of hyperchloremic acidosis in healthy animals.[70] This line of reasoning cannot be applied to critically ill patients, who often require infusion of a very large volume of resuscitation fluid. Furthermore, acid-base balance is often already deranged in critically ill patients, and these patients may not be able to compensate normally by increasing ventilation or may have abnormal buffer capacity due to hypoalbuminemia. In intensive care unit and surgical patients[71-73] as well as in animals with experimental sepsis,[74] saline-induced acidosis clearly occurs.

Administration of normal saline causes acidosis because this solution contains equal amounts of Na^+ and Cl^-, whereas the normal Na^+ concentration in plasma is 35 to 45 mEq/L greater than the normal Cl^- concentration. Administration of 0.9% saline increases the Cl^- concentration relatively more than the Na^+ concentration. Many critically ill patients have a significantly lower strong ion difference than do healthy individuals, even when there is no evidence of a metabolic acid-base derangement.[75] The lower strong ion difference in critical illness is not surprising given that the positive charge of the strong ion difference is balanced by the negative charges of A^- and total CO_2. Since many critically ill patients are hypoalbuminemic, A^- tends to be reduced. Because the body defends P_{CO_2} for other reasons, a reduction in A^- leads to a reduction in strong ion difference to maintain normal pH. Thus, a typical intensive care unit patient might have a strong ion difference of 30 mEq/L rather than 40 to 42 mEq/L. If this same patient then develops a metabolic acidosis (e.g., lactic acidosis), the strong ion difference decreases further. If the patient is resuscitated with a large volume of 0.9% saline, metabolic acidosis is exacerbated. This relationship is illustrated in Figure 12-3, which shows that a patient with a lower baseline strong ion difference is more susceptible to a subsequent acid load.

One alternative to using normal saline to resuscitate patients is to use Ringer's lactate solution. This fluid contains a more physiologic difference between $[Na^+]$ and $[Cl^-]$ and thus its strong ion difference is closer to normal (28 mEq/L as compared to 0 mEq/L for normal saline). Morgan and

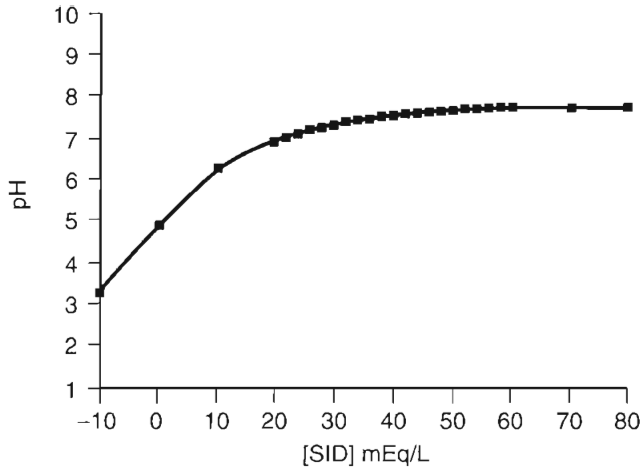

FIGURE 12–3. Plot of pH versus strong ion difference (SID). For this plot, A_{TOT} and Pco_2 were held constant at 18 mEq/L and 40 mm Hg, respectively. This plot assumes a water dissociation constant for blood of 4.4×10^{-14} (Eq/L). Note how steep the pH curve becomes at SID < 20 mEq/L.

colleagues recently showed that a solution with a strong ion difference of approximately 24 mEq/L results in a neutral effect on the pH as blood is progressively diluted.[76]

Unexplained Hyperchloremic Acidosis

Critically ill patients sometimes manifest hyperchloremic metabolic acidosis for unclear reasons. Often these patients have other coexisting types of metabolic acidosis, making the precise diagnosis difficult. Patients with sepsis and acidosis frequently have normal circulating lactate levels.[77] Often, unexplained anions are the cause,[29-31] but hyperchloremic acidosis also can be a contributing factor.

METABOLIC ALKALOSIS

Metabolic alkalosis occurs as a result of an increase in strong ion difference or a decrease in A_{TOT}. These changes can occur secondary to the loss of anions (e.g., Cl^- from the stomach, albumin from the plasma) or the retention of cations (rare). Sometimes the loss of Cl^- is temporary and can be treated effectively by replacing the anion; metabolic alkalosis in this category is said to be "chloride responsive." In other cases, hormonal mechanisms produce ongoing losses of Cl^-. Thus, at best, the Cl^- deficit can be offset only temporarily by Cl^- administration; this form of metabolic alkalosis is said to be "chloride resistant" (Table 12-4). Similar to hyperchloremic acidosis, these disorders can be distinguished by measurement of the urine Cl^- concentration.

Chloride-Responsive Disorders

The chloride-responsive disorders usually occur as a result of Cl^- losses from the stomach, such as from vomiting or gastric drainage. The treatment is to replace the Cl^-, which can be achieved slowly with NaCl or more rapidly with KCl or even HCl. Saline plus KCl is the treatment of choice because volume depletion and K^+ usually coexist with the acid-base disturbance in patients with chloride-responsive metabolic alkalosis. Dehydration in turn stimulates aldosterone secretion, leading to increased tubular Na^+ reabsorption and increased urinary losses of K^+. Administration of normal saline is effective because the administration of equal amounts of Na^+ and Cl^- result in larger relative increases in Cl^- concentration compared to Na^+ concentration. In rare circumstances, when neither K^+ nor intravascular volume depletion is a problem, it may be desirable to give back Cl^- as HCl.

Diuretics and other forms of volume contraction produce metabolic alkalosis predominantly by stimulating aldosterone secretion, as discussed earlier. However, diuretics also induce K^+ and Cl^- excretion directly, further complicating the problem and inducing metabolic alkalosis more rapidly.

TABLE 12–4. DIFFERENTIAL DIAGNOSIS OF A METABOLIC ALKALOSIS (INCREASED STRONG ION DIFFERENCE)

Chloride Loss < Sodium
Chloride-responsive (urine Cl^- concentration <10 mmol/L)
Gastrointestinal losses
Vomiting
Gastric drainage
Chloride wasting diarrhea (villous adenoma)
Post-diuretic use
Post-hypercapnea
Chloride-unresponsive (urine Cl^- concentration >20 mmol/L)
Mineralocorticoid excess
Primary hyperaldosteronism (Conn's syndrome)
Secondary hyperaldosteronism
Cushing's syndrome
Liddle's syndrome
Bartter's syndrome
Exogenous corticoids
Excessive licorice intake
Ongoing diuretic use
Exogenous Sodium Load (>Chloride)
Sodium salt administration (acetate, citrate)
Massive blood transfusions
Parenteral nutrition
Plasma volume expanders
Sodium lactate (Ringer's solution)
Other
Severe deficiency of intracellular cations
Magnesium, potassium

Chloride-Resistant Disorders

The chloride-resistant disorders (see Table 12-4) are characterized by an increased urine Cl^- concentration (>20 mEq/L) and are said to be "chloride resistant" because of ongoing Cl^- losses. Most commonly, excessive chloride occurs as a result of excessive mineralocorticoid activity. Treatment requires that the underlying disorder be addressed (Table 12-5).

Other Causes of Metabolic Alkalosis

Rarely, an increased strong ion difference and therefore metabolic alkalosis occurs secondary to cation administration rather than anion depletion. Examples of these disorders include milk-alkali syndrome and intravenous administration of strong cations without strong anions. The latter occurs with massive blood transfusion because Na^+ is given with citrate (a weak anion) instead of Cl^-. Similar results occur when parenteral nutrition formulations contain too much acetate and not enough Cl^- to balance the Na^+ load.

RESPIRATORY ACID-BASE DISORDERS

Respiratory disorders are far easier to diagnose and treat than metabolic disorders because the mechanism is always the same, although the underlying disease process may vary.

TABLE 12–5. TREATMENT OF METABOLIC ALKALOSIS

Condition	Treatment
Primary aldosteronism	Spironolactone or other agents that block distal tubular sodium reabsorption improve alkalosis, hyokalemia, and hypertension. Large doses may be necessary. Restriction of sodium intake and potassium supplementation may be necessary. When an adenoma can be identified, surgery is curative. When the cause is bilateral adrenal cortical hyperplasia, therapy is medical. Dexamethasone is effective in long-term therapy of familial dexamethasone-responsive aldosteronism.
Secondary aldosteronism	Angiotensin-converting enzyme inhibitors are usually effective. Repair of the underlying lesion, if feasible, may be required.
Cushing's syndrome	Due to pituitary oversecretion of ACTH: surgery or radiation Due to adrenal adenoma or carcinoma: adrenalectomy Due to secondary or ectopic ACTH production: address the underlying malignancy
Liddle's syndrome	Triamterene may be effective.
Bartter's syndrome	Treatment often unsatisfactory long-term. Potassium-sparing diuretics, potassium and magnesium supplementation, angiotensin-converting enzyme inhibitors, cyclooxygenase inhibitors are partially effective.
Exogenous corticoids	Discontinuation of the offending agent(s) and vigorous initial potassium replacement.
Severe K or Mg depletion	Replacement of these electrolytes (may require very large amounts).

From Spital and Garella[23] with permission.

CO_2 is produced by cellular metabolism or by the titration of HCO_3^- by metabolic acids. Normally, alveolar ventilation is adjusted to maintain the arterial $Paco_2$ between 35 and 45 mm Hg. When alveolar ventilation is increased or decreased out of proportion to $Paco_2$ production, a respiratory acid-base disorder exists.

Pathophysiology of Respiratory Acid-Base Disorders

Normal CO_2 production by the body (about 220 mL/min) is equivalent to 15,000 mM/day of carbonic acid.[78] This amount compares to less than 500 mM/day for all nonrespiratory acids that are handled by the kidney and gut. Pulmonary ventilation is adjusted by the respiratory center in response to changes in $Paco_2$, blood pH, and Pao_2 as well as other factors (e.g., exercise, anxiety, wakefulness). Normal $Paco_2$ (40 mm Hg) is maintained by precise matching of alveolar minute ventilation to metabolic CO_2 production. $Paco_2$ changes in compensation for alterations in arterial pH produced by metabolic acidosis or alkalosis in predictable ways (Table 12-6).

Respiratory Acidosis

When CO_2 elimination is inadequate relative to the rate of tissue production, $Paco_2$ increases to a new steady state determined by the new relationship between alveolar ventilation and CO_2 production. Acutely, the increase in $Paco_2$ increases both the $[H^+]$ and the $[HCO_3^-]$ in blood according to the carbonic acid equilibrium equation. Thus, the change in $[HCO_3^-]$ is mediated simply by the dissociation of H_2CO_3 into H^+ and HCO_3^-, not by an active physiologic adaptation response. Similarly, the increase in $[HCO_3^-]$ does not "buffer" the increase in $[H^+]$. There is no change in the strong ion difference and hence no change in standard base-excess. Cellular acidosis always occurs in respiratory acidosis, since CO_2 builds up in the tissues. If the $Paco_2$ remains increased, active compensatory mechanisms are activated and the strong ion difference increases to restore $[H^+]$ toward normal.

Primarily, compensation is accomplished by removal of Cl^- from the plasma space. Since movement of Cl^- into the tissues or red blood cells results in intracellular acidosis, Cl^- must be removed from the body to achieve a lasting effect on the strong ion difference. The kidney is the primary organ for Cl^- removal, although the adaptive capacity of the gastrointestinal tract for Cl^- elimination has not been fully explored. Accordingly, patients with renal disease have a difficult time adapting to chronic respiratory acidosis. When renal function is intact, Cl^- is eliminated in the urine and, after a few days, the strong ion difference increases to the level necessary to return blood pH to about 7.35. It is unclear whether this amount of time is required by the physiologic constraints of the system or to avoid being overly sensitive to transient changes in alveolar ventilation. In any case, this adaptation results in an increased pH for any degree of hypercarbia. According to the Henderson-Hasselbalch equation, the increased pH will result in an increased $[HCO_3^-]$

TABLE 12–6. OBSERVATIONAL ACID-BASE PATTERNS

Disorder	HCO_3^- (mEq/L)	Pco_2 (mm Hg)	SBE (mEq/L)
Metabolic acidosis	<22	$= (1.5 \times HCO_3^-) + 8$ $= 40 + SBE$	< −5
Metabolic alkalosis	>26	$= (0.7 \times HCO_3^-) + 21$ $= 40 + (0.6 \times SBE)$	> +5
Acute respiratory acidosis	$= [(Pco_2 - 40)/10] + 24$	>45	= 0
Chronic respiratory acidosis	$= [(Pco_2 - 40)/3] + 24$	>45	$= 0.4 \times (Pco_2 - 40)$
Acute respiratory alkalosis	$= [(40 - Pco_2)/5] + 24$	<35	= 0
Chronic respiratory alkalosis	$= [(40 - Pco_2)/2] + 24$	<35	$= 0.4 \times (Pco_2 - 40)$

From Kellum,[6] with permission.

for a given P_{CO_2}. Thus, the "adaptive" increase in $[HCO_3^-]$ *results from* the increase in pH and is not the *cause for* the increase in pH.

Although the change in HCO_3^- concentration is a convenient and reliable marker for the metabolic compensation, it is not the mechanism. This point is more than semantic because only changes in the independent variables of acid base balance (P_{CO_2}, A_{TOT}, strong ion difference) can affect the plasma $[H^+]$, and $[HCO_3^-]$ is not an independent variable.

Diseases of Ventilatory Impairment

As for virtually all acid-base disorders, treatment begins with addressing the underlying disorder. Acute respiratory acidosis can be caused by central nervous system suppression, neuromuscular disease or impairment (e.g., myasthenia gravis, hypophosphatemia, hypokalemia), or airway and parenchymal lung disease (e.g., asthma, acute respiratory distress syndrome). This last category of conditions also produces primary hypoxia, not just alveolar hypoventilation. The two can be distinguished by the alveolar gas equation:

$$P_{AO_2} = P_{IO_2} - Pa_{CO_2}/R$$

where R is the respiratory exchange coefficient (generally assumed to be 0.8) and P_{IO_2} is the inspired oxygen tension (room air is approximately 150). Thus, as Pa_{CO_2} increases, the P_{AO_2} will decrease in a predictable fashion. If the P_{AO_2} is reduced further, there is a defect in gas exchange.

Chronic respiratory acidosis is most often caused by chronic lung disease (e.g., chronic obstructive lung disease) or chest wall disease (e.g., kyphoscoliosis). Rarely, its cause is central hypoventilation or chronic neuromuscular disease.

When and How to Treat

The primary threat to life in cases of respiratory acidosis comes not from acidosis but from hypoxemia. If the patient is breathing room air, Pa_{CO_2} cannot exceed 80 mm Hg before life-threatening hypoxemia results. Accordingly, supplemental oxygen is always required, although, unfortunately, oxygen administration alone is almost never sufficient treatment, and the defect in ventilation must be addressed directly. When the underlying cause can be addressed quickly (e.g., reversal of narcotics with naloxone), it may be possible to avoid endotracheal intubation. More often, however, mechanical ventilation must be initiated. Mechanical support is indicated when the patient is unstable or at risk for instability or when central nervous system function deteriorates. Furthermore, in patients who are exhibiting signs of respiratory muscle fatigue, mechanical ventilation should be instituted before overt respiratory failure occurs. Thus, it is not the absolute Pa_{CO_2} value that is important but rather the clinical condition of the patient.

Chronic hypercapnia requires treatment when there is an acute deterioration. In this setting, it is important to recognize that the goal of therapy is not a normal value for Pa_{CO_2} (35-45 mm Hg) but rather restoration of the patient's baseline Pa_{CO_2} (if known). If the baseline Pa_{CO_2} is not known, a target Pa_{CO_2} of 60 mm Hg is reasonable. Overventilation has two undesirable consequences. First, life-threatening alkalemia can occur if the Pa_{CO_2} is rapidly normalized in a patient with chronic respiratory acidosis and an appropriately large strong ion difference. Second, even if the Pa_{CO_2} is corrected slowly, the patient will reduce the plasma strong ion difference over time, making it impossible to wean the patient from mechanical ventilation.

Noninvasive ventilation is another treatment option that is useful in selected patients, particularly those with normal sensorium.[79] Rapid infusion of $NaHCO_3$ in patients with respiratory acidosis can induce acute respiratory failure if alveolar ventilation is not increased to adjust for the increased CO_2 load. Thus, if $NaHCO_3$ is used, it must be administered slowly and alveolar ventilation adjusted appropriately. Furthermore, as discussed previously, $NaHCO_3$ works by increasing the plasma $[Na^+]$. If this is not possible or not desirable, $NaHCO_3$ should be avoided.

Occasionally, it is useful to reduce CO_2 production, which can be achieved by reducing the carbohydrate load in the nutritional support regimen, lowering the temperature in febrile patients, and providing adequate sedation for anxious or combative patients. Treatment of shivering in the postoperative period can reduce CO_2 production. However, it is unusual to control hypercarbia with these techniques alone.

Permissive Hypercapnia

In recent years, there has been increased recognition of ventilator-associated lung injury. Accordingly, a strategy designed to reduce minute ventilation and hence increase Pa_{CO_2}, so-called permissive hypercapnia or controlled hypoventilation, has been increasingly employed.[11] However, permissive hypercapnia is not without risks. Sedation is mandatory and the use of neuromuscular blocking agents is frequently required. Hypercapnia is associated with increased intracranial pressure and pulmonary hypertension, making this technique unusable in patients with brain injury or right ventricular dysfunction. Controversy exists as to how low to allow the pH to go. While some authors have reported good results with pH values less than 7.0,[11] most authors advocate more modest pH reductions (>7.25).

Respiratory Alkalosis

Respiratory alkalosis may be the most frequently encountered acid-base disorder. It occurs in a number of pathologic conditions, including salicylate intoxication, early sepsis, hepatic failure, and hypoxic respiratory disorders. Respiratory alkalosis also occurs with pregnancy and with pain or anxiety. Hypocapnia appears to be a particularly bad prognostic indicator in patients with critical illness.[80] As in acute respiratory acidosis, acute respiratory alkalosis results in a small change in $[HCO_3^-]$ as dictated by the Henderson-Hasselbalch equation. If hypocapnia persists, the strong ion difference will begin to decrease as a result of renal Cl^- reabsorption. After 2 to 3 days, the strong ion difference assumes a new, lower, steady state.[81] Severe alkalemia is unusual in patients with respiratory alkalosis, and management is therefore directed to the underlying cause. Typically, these mild acid-base changes are clinically more important for what they can alert the clinician to, in terms of underlying disease, than for any threat they pose to the patient. In rare cases, respiratory depression with narcotics is necessary.

Pseudorespiratory Alkalosis

The presence of arterial hypocapnia in patients with profound circulatory shock has been termed *pseudorespiratory alkalosis*.[82] This condition can be seen when alveolar ventilation is supported but the circulation is grossly inadequate. In such conditions, the mixed venous P_{CO_2} is significantly elevated but the arterial P_{CO_2} is normal or even decreased secondary to decreased CO_2 delivery to the lungs and increased pulmonary transit time. Overall CO_2 clearance is markedly decreased and there is marked tissue acidosis, usually involving both

metabolic and respiratory components. The metabolic component comes from tissue hypoperfusion and hyperlactatemia. Arterial oxygen saturation also may appear to be adequate despite tissue hypoxemia. This condition is rapidly fatal unless cardiac output is rapidly corrected.

UNIFIED APPROACH TO THE PATIENT WITH ACID-BASE IMBALANCE

CHARACTERIZING THE DISORDER

The first step in the approach to a patient with an acid-base imbalance is to characterize the disorder. Acid-base imbalances are usually recognized by abnormalities in the venous plasma electrolyte concentrations, so it is useful to start there. Measurement of venous $[HCO_3^-]$ is the easiest way to screen for acid-base disorders. However, a normal $[HCO_3^-]$ does not exclude the possibility of an acid-base derangement, even a serious one. Therefore, if the history and physical examination findings lead one to suspect a disease process that results in an acid-base imbalance, more investigation is required. The normal $[HCO_3^-]$ is 22 to 26 mEq/L. Increases in $[HCO_3^-]$ occur with primary and compensatory metabolic alkaloses and decreases occur with primary or compensatory metabolic acidoses. Unfortunately, in mixed disorders, $[HCO_3^-]$ may be misleading and the presence of any abnormality in $[HCO_3^-]$ requires further investigation. In addition to examining the $[HCO_3^-]$, venous blood can be used to calculate the anion gap: $([Na^+] + [K^+]) - ([Cl^-] - [HCO_3^-])$. If $[HCO_3^-]$ or the anion gap are abnormal or if there is clinical suspicion for a mixed disorder, arterial blood should be sampled for blood gas analysis. This test will provide information on the pH, $Paco_2$, and standard base-excess. Although simple disorders will conform to the equations presented in Table 12-6, "mixed" disorders are quite common.

In patients with acidemia, the next step is to examine the anion gap. The anion gap should also be examined when there is suspicion of an occult metabolic acidosis even in a patient with alkalemia. However, severe alkalemia will increase the anion gap by 2 to 4 mEq/L and hence wider "tolerance limits" should be used. If the anion gap is calculated from an alkalemic blood sample, only significant abnormalities (>8-10 mEq/L above normal) should be considered important. More often, however, it is not excessive sensitivity but rather insensitivity that plagues the anion gap calculation. The accuracy of the anion gap can be improved easily by using a patient-specific normal range, rather than a standard one. If unmeasured anions are detected, it is a good idea to compare their amounts to the abnormality in standard base-excess. For example, if the calculated anion gap is 5 mEq/L greater than expected and the standard base-excess is −15 mEq/L, a mixed metabolic acidosis is present. The unmeasured anions (e.g., ketones) are accounting for a standard base-excess of −5 mEq/L while some other process is responsible for another 10 mEq/L. This sort of abnormality can occur if very large amounts of 0.9% saline are used to treat a patient with diabetic ketoacidosis. As the ketosis resolves, the acidosis persists because the strong ion difference has been decreased due to excessive Cl^- administration.

DETERMINING THE CAUSE

Once the disorder has been characterized, the clinician must integrate the information obtained from the history and physical examination to arrive at an accurate diagnosis. Mixed disorders continue to be problematic, as any acid-base disorder that fails to fit into the classification scheme shown in Table 12-5 can be considered a mixed disorder, but some mixed disorders appear to be simple disorders when first encountered. For example, a patient with chronic respiratory acidosis and a $Paco_2$ of 60 mm Hg would be expected to have a standard base-excess of +8 mEq/L (see Table 12-6). If this patient develops a metabolic acidosis, the standard base-excess will decrease and may be 0 mEq/L. At this point, it may appear that the patient has a pure, acute respiratory acidosis rather that a mixed disorder. If the metabolic acidosis causes an increase in the anion gap, this abnormality may provide a clue. Another useful method is to obtain at least two blood gas analyses to examine for trends. In general, however, it is only by careful attention to history and physical examination that the true diagnosis can be made.

Chapter 13

HYPERNATREMIA AND HYPONATREMIA

John K. McIlwaine • Howard L. Corwin

Disorders of plasma sodium concentration—hyponatremia and hypernatremia—are among the most common clinical problems observed in the critically ill. These disorders are often asymptomatic; however, in some patients, they may result in symptoms ranging from minor to life threatening. The approach to treating these disorders in individual patients involves balancing the risk of treatment versus the risk of the disorder itself.

HYPERNATREMIA

Hypernatremia is a common clinical problem, being observed in up to 2% of the general hospital population and 15% of patients admitted to the intensive care unit.[1–4] In the outpatient setting, hypernatremia is most prevalent in the geriatric patient population; however, hypernatremia in hospitalized patients is observed in all age groups.[1,5] Mortality rates in patients with hypernatremia can range as high as 70%.[1–6] Although this high mortality rate no doubt reflects the severity of underlying disease in these patients, there is significant morbidity related to hypernatremia itself. Neurologic sequelae from hypernatremia are common, particularly in the pediatric population.[6]

The maintenance of a normal serum sodium concentration (135 to 145 mEq/L) is dependent on the balance between water intake and water excretion. Hypernatremia results from a deficit of free water that leads to an increase in serum tonicity. The usual mechanism underlying the development of hypernatremia is inadequate water intake and increased free water loss. However, hypernatremia also can result from the intake of hypertonic sodium solutions. Hypernatremia may be associated with volume depletion, euvolemia, or hypervolemia, depending on the balance of salt and water loss and intake. Sodium content is low, normal, or high, respectively, in each of these circumstances. Relative sodium and volume status has important implications for the treatment of patients with hypernatremia.

The brain is particularly susceptible to the effects of hypernatremia. The acute increase in extracellular tonicity as a result of the hypernatremia results in intracellular dehydration as water moves across the cell membrane to maintain osmotic equilibrium. The net result is a loss of brain volume, which in turn places mechanical stress on cerebral vessels. This mechanical stress can result in bleeding. With chronic hypernatremia, cellular adaptation occurs. So-called idiogenic osmoles accumulate in brain cells, which minimizes cellular dehydration. However, the presence of these idiogenic osmoles presents a risk for the development of cerebral edema during the treatment of hypernatremia.

The symptoms of hypernatremia are nonspecific and often difficult to separate from those of the underlying illness in hospitalized patients. Central nervous system abnormalities are most common. These symptoms can include confusion, weakness, and lethargy in the early stages and progress to seizures, coma, and death in the later stages. The symptoms result from the movement of water out of the brain cells rather than the hypernatremia per se. Neurologic deterioration can be seen during treatment as a result of the development of cerebral edema. Signs of volume depletion or volume overload may be present, depending on the cause of the hypernatremia.

The treatment of hypernatremia is water repletion (Table 13–1). The water deficit may be estimated as follows: Water deficit = [0.6 × Total body weight] × [(Serum sodium concentration/140) − 1]. Total body water is assumed to be 60% of body weight. However, the percentage of water relative to total body weight is closer to 50% in women and in the elderly of both genders. Treatment should be instituted at a rate that balances the risk of hypernatremia with the risk of too rapid correction, particularly in cases of chronic hypernatremia. Half the calculated deficit should be replaced within the first 12 to 24 hours at a rate of sodium concentration correction no greater than 2 mEq/L per hour. The remainder of the water deficit can be replaced over the next 48 hours. The rapidity of replacement should be determined by the acuteness of onset and the severity of symptoms. Neurologic status needs to be closely monitored during replacement for evidence of the development of cerebral edema. Ongoing fluid and electrolyte losses also need to be replaced during treatment. In patients with hypernatremia associated with volume depletion and hemodynamic instability, volume replacement with isotonic saline is indicated initially. Once hemodynamic stability is achieved, water replacement can be initiated. Hypotonic saline (e.g., 0.45 saline) may be preferable to water as the replacement fluid

TABLE 13–1. TREATMENT OF HYPERNATREMIA

Calculate water deficit
Replace half the deficit over 12–24 h
Do not correct more rapidly than 2 mEq/L/h
Replace the remaining deficit over 48 h
If hemodynamic instability is present, give isotonic saline until stable before replacing water deficit with hypotonic saline
If volume overload is present, treat with diuretic and 5% dextrose
Dialysis may be indicated if renal failure is present
Ongoing fluid and electrolyte losses should be replaced
Neurologic status should be closely monitored

for these patients. If hypernatremia is associated with hypervolemia (e.g., intake of hypertonic saline or sodium bicarbonate), treatment should be directed toward reducing sodium intake and inducing its loss. In these patients, diuretics can be used along with free water (5% dextrose) infusion. However, if renal failure is present, dialysis may be necessary.

HYPONATREMIA

Hyponatremia is one of the most common electrolyte abnormalities seen in hospitalized patients. It occurs in 2% to 4% of hospitalized patients and up to 30% of patients in intensive care units.[7–10] Mortality for patients with acute hyponatremia is reportedly as high as 50%, whereas mortality for those with chronic hyponatremia is 10% to 20%.[7–11]

Hyponatremia is a water problem, not a sodium problem; there is always an excess of water relative to sodium when hyponatremia is present. In hyponatremia, water excretion by the kidney is impaired. Patients who are hyponatremic may be volume depleted, or hypovolemic (water deficit and sodium deficit), euvolemic (water excess and normal sodium content), or hypervolemic (water excess and sodium excess). As with hypernatremia, the patient's volume status has implications for the treatment of hyponatremia.

In the presence of hyponatremia, there is a decrease in extracellular tonicity relative to the intracellular space. The osmolar gap causes movement of water from the extracellular space into the intracellular space and results in cell swelling. In the central nervous system, cellular swelling manifests as cerebral edema and results in the symptoms associated with hyponatremia. The degree of cerebral cell swelling correlates with the severity of symptoms observed. The central nervous system adapts to hyponatremia in two ways. First, cerebral edema causes an increase in interstitial hydrostatic pressure and results in the movement of fluid from the interstitial space into the cerebrospinal fluid, leading to some amelioration of cerebral edema. Second, solutes are lost from cells, resulting in a decrease in intracellular osmolarity and thus water movement out of cells. The solutes lost are initially sodium and potassium, followed by organic solutes over the next several days. Because of cerebral adaptation, the severity of neurologic symptoms is related to the acuteness and magnitude of the hyponatremia. If hyponatremia develops gradually, brain cells can compensate by decreasing intracellular osmolarity through the loss of osmolytes, thereby limiting the degree of cerebral edema and resultant neurologic dysfunction. However, with the correction of chronic hyponatremia, the regeneration of these osmolytes lags behind, and cerebral dehydration can occur with rapid correction.

In acute hyponatremia, nausea, vomiting, lethargy, and confusion can progress to coma, seizures, and eventual herniation and death.[11,12] The elderly and the young are more likely to be symptomatic from hyponatremia.[9] Menstruating women also tend to be more symptomatic and are at greater risk for neurologic complications from acute hyponatremia.[11] Early in the development of hyponatremia, the symptoms are difficult to separate from those related to the underlying disease process.

Treatment of hyponatremia is dependent on the acuteness of the hyponatremia and the presence and severity of symptoms (Table 13–2). Acute (<48 hours) or chronic (>48 hours) symptomatic hyponatremia (e.g., seizures) requires immediate therapy. However, the optimal approach for the treatment of these patients is controversial.[12–14] The controversy results from reports of the occurrence of a central demyelination syndrome associated with the correction of hyponatremia in some patients.[15–22] This syndrome appears to be more common with chronic hyponatremia (>48 hours), overcorrection of hyponatremia, large corrections (>12 to 25 mEq/L per 24 hours), and rapid correction (>1 to 2 mEq/L per hour).[19–22]

TABLE 13–2. TREATMENT OF HYPONATREMIA

Acute Symptomatic Hyponatremia
3% hypertonic saline with loop diuretic
Correct no more than 2 mEq/L/h
Correct no more than 12–15 mEq/L/h over first 24 h
Chronic Symptomatic Hyponatremia (>48 h, or unknown duration)
3% hypertonic saline with loop diuretic
Correct no more than 1.5 mEq/L/h initially
Correct to resolution of symptoms or 10% correction of serum sodium
Correct no more than 12 mEq/L/24 h
Close monitoring of electrolytes and neurologic status
Asymptomatic Hyponatremia
Euvolemia
Treat underlying cause
Water restriction
Occasionally loop diuretic or demeclocycline to lower urine osmolarity
Hypertonic saline rarely indicated
Hypovolemia
Treat underlying cause of fluid loss
Normal saline
Hypervolemia
Treat underlying cause of decreased effective circulating volume
Salt and water restriction
Loop diuretics for some patients

The approach to the treatment of acute symptomatic hyponatremia is infusion of hypertonic saline (3%). Therapy is targeted toward resolution of symptoms or a 10% to 15% increase in serum sodium concentration. In patients with a high urine osmolarity, the addition of a loop diuretic facilitates correction of the hyponatremia by decreasing urine osmolarity. The rate of correction should be less than 2 mEq/L per hour and less than 15 mEq/L total over 24 hours. The amount of hypertonic saline necessary to correct the serum sodium concentration to a safe level (e.g., 120 mEq/L) can be estimated by calculating the sodium deficit:

$$\text{Sodium deficit} = 0.5 \times \text{Lean body weight} \times (120 - \text{Observed serum sodium concentration})$$

The amount of hypertonic saline required to replace the deficit is then infused at a rate that permits correction within the parameters noted earlier. Frequent checking of electrolytes is necessary to ensure that correction is not too rapid.

In treating patients with chronic (>48 hours, or of unknown duration) symptomatic hyponatremia, the higher risk of neurologic complications related to therapy mandates a more cautious approach. As with acute hyponatemia, neurologic symptoms predominate in the clinical presentation of these patients. Initial treatment with 3% sodium chloride should be directed toward the resolution of symptoms or a 10% increase in serum sodium concentration. The increase in serum sodium concentration should be at a rate less than

1.5 mEq/L per hour initially, and the total correction should not exceed 12 mEq/L per 24 hours. Close monitoring of serum electrolytes and neurologic status is mandatory. The resolution of symptoms allows for a decrease in the rate of correction. Calculation of sodium deficit can be used to estimate the volume of hypertonic saline necessary for correction, as noted earlier.

Most patients with hyponatremia are asymptomatic. Aggressive correction of serum sodium in these patients is not indicated. Treatment in asymptomatic patients is based on the underlying cause of the hyponatremia and the patient's volume status: euvolemic, hypovolemic, or hypervolemic (edema).

The majority of hyponatremic patients are euvolemic. In this group, the syndrome of inappropriate antidiuretic hormone is the most common diagnosis. The inappropriate (nonosmotic) presence of antidiuretic hormone impairs free water excretion by the kidney; impaired water excretion coupled with water intake results in hyponatremia. Water restriction is the mainstay of therapy for these patients. The amount of water restriction must be sufficient to achieve negative water balance (i.e., the difference between the total intake and excretion of water), or correction of hyponatremia will not occur. Therefore, all water losses (insensible losses, urinary losses, and gastrointestinal losses) must be considered when deciding on the degree of water restriction. If urine osmolarity is high, it may be necessary to decrease it to achieve a negative water balance. This can be achieved by adding a loop diuretic; however, salt intake must be increased to correct for losses resulting from the increased natriuresis with diuresis. Less commonly, demeclocycline (300 to 600 mg twice a day), which interferes with the action of antidiuretic hormone, is used to decrease urine osmolarity. In patients with more pronounced hyponatremia, the combination of normal saline and a loop diuretic can be used to correct hyponatremia. The use of hypertonic saline is rarely, if ever, indicated in these asymptomatic patients.

Hyponatremia associated with volume depletion is a result of the loss of both sodium and water, combined with the simultaneous intake of water or hypotonic fluids. The release of antidiuretic hormone stimulated by hypovolemia inhibits the kidney's ability to excrete water. The net result is positive water balance and hyponatremia. The treatment of hyponatremia in this setting is infusion of normal saline to correct the volume depletion. As volume status is corrected, antidiuretic hormone excretion is switched off, and the kidney excretes the excess water, correcting the serum sodium concentration. The cause of the initial sodium and water loss should also be identified and treated.

Hyponatremia associated with hypervolemia is very common. Clinical conditions associated with hyponatremia and hypervolemia include heart failure, cirrhosis, and nephrotic syndrome. The hallmark of these conditions is the presence of edema. The mechanism for the development of hyponatremia in these settings is diminished effective circulating volume leading to sodium and water retention. The water retention is a result of nonosmotic antidiuretic hormone release impairing the kidney's ability to excrete water. In this respect, the mechanism is similar to that responsible for hyponatremia associated with volume depletion. Therapy is directed toward correcting the primary disease process responsible for the decrease in effective circulating volume. Specific treatment of the hyponatremia consists of sodium and water restriction. The use of loop diuretics may facilitate free water excretion and correction of the hyponatremia; however, thiazide diuretics may exacerbate hyponatremia and should be avoided.

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Karp BI, Laureno R: Pontine and extrapontine myelinolysis: A neurologic disorder following rapid correction of hyponatremia. Medicine 1993;72:359–373.

In this retrospective study of patients who developed neurologic dysfunction after correction of hyponatremia, there appeared to be a correlation between the rate of sodium correction and neurologic dysfunction.

Palevsky PM, Bhagrath R, Greenberg A: Hypernatremia in hospitalized patients. Ann Intern Med 1996;124:197–203.

This well-done prospective cohort study identifying the epidemiology and causes of hypernatremia in a hospitalized patient population found that hospitalized patients of any age may develop hypernatremia.

Snyder NA, Feigal DW, Arieff AI: Hypernatremia in elderly patients: A heterogeneous, morbid, and iatrogenic entity. Ann Intern Med 1987;107:309–319.

These investigators followed a prospective cohort of hospitalized elderly patients (older than 60 years) and determined that hospitalized patients often develop hypernatremia secondary to inappropriate fluid management. These patients had a longer length of stay and slightly increased mortality, although there was no control for severity of illness.

Sterns RH, Cappuccio JD, Silver SM, et al: Neurologic sequelae after treatment of severe hyponatremia: A multicenter perspective. J Am Soc Nephrol 1994;4:1522–1530.

This multicenter retrospective study evaluated the effect of correction rates of severe hyponatremia (<106 mEq/L) on outcome. Patients who were chronically hyponatremic and corrected to a normal serum sodium concentration at a rate of less than 12 mEq/day or 0.55 mEq/h did not develop postcorrection neurologic sequelae.

Chapter 14
HYPERKALEMIA AND HYPOKALEMIA

Sergio Zanotti-Cavazzoni • R. Phillip Dellinger

Hyperkalemia and hypokalemia are the most common electrolyte abnormalities found in hospitalized patients.[1] Data regarding their precise prevalence in intensive care unit (ICU) patients are not available. However, the high incidence of abnormalities in serum potassium concentration undoubtedly reflects both physiologic abnormalities that are common in ICU patients and the effects of therapeutic interventions that are commonly used in the care of critically ill patients. Because of comorbid conditions, critically ill patients are also at a higher risk of developing complications from altered serum potassium levels. Timely recognition and intervention are essential for minimizing morbidity and mortality due to abnormal serum potassium levels.

HYPERKALEMIA

Hyperkalemia is defined as a serum potassium concentration (serum $[K^+]$) greater than 5.0 mEq/L. Hyperkalemia is less frequent than hypokalemia but is more likely to cause serious complications in critically ill patients. Severe hyperkalemia requires rapid correction to prevent serious cardiovascular complications. The measured value for serum $[K^+]$ can be elevated as a result of in vitro phenomena, usually the release of K^+ from cells during the clotting process. Pseudohyperkalemia should be recognized and considered in patients with marked elevations of white blood cells or platelets.[2] Simultaneous measurements of plasma (unclotted) and serum (clotted) $[K^+]$ should identify this problem. A serum $[K^+]$ that is 0.2 to 0.3 mEq/L greater than plasma $[K^+]$ is indicative of pseudohyperkalemia. Pseudohyperkalemia may also result from hemolysis of a blood specimen after collection; this event is usually identified in the laboratory and reported.

True hyperkalemia occurs by two mechanisms: (1) impaired K^+ excretion, and (2) shifts in intracellular and extracellular K^+ (Table 14–1). Renal insufficiency is the most common cause of altered K^+ excretion. With acute oliguric renal failure, elevated potassium levels, if not treated, are life threatening. In most patients with nonoliguric chronic renal failure, mild hyperkalemia is evident.[3] With some causes of chronic renal failure, such as diabetes mellitus and tubulointerstitial diseases, hyperkalemia is more pronounced and is probably related to low circulating renin and aldosterone levels.[4] Decreased aldosterone production promotes the development of hyperkalemia. Patients with acquired adrenal insufficiency develop hyperkalemia despite normal renal function. Various drugs used in the ICU can produce hyperkalemia by impairing K^+ excretion. Patients with abnormal renal function are more susceptible to drug-induced hyperkalemia, and potassium supplements are the most common cause.[5] Potassium-sparing diuretics (spironolactone, amiloride, and triamterene) inhibit K^+ excretion and can produce severe hyperkalemia.[6,7] Spironolactone is the most dangerous of these drugs with respect to impaired K^+ excretion, and it has prolonged effects even after discontinuation. Its use has increased significantly after reports of improved mortality in patients with congestive heart failure.[8] Angiotensin-converting enzyme inhibitors reduce circulating aldosterone levels and are associated with hyperkalemia in patients with renal insufficiency.[9] Angiotensin receptor blockers have less impact on circulating aldosterone levels and are less likely to produce hyperkalemia.[9] Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors block prostaglandin synthesis, causing indirect suppression of renin release and aldosterone secretion. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors also reduce renal blood flow and glomerular filtration rate, particularly in patients with prerenal azotemia (due to decreased intravascular volume or heart failure). These compounds may produce hyperkalemia by these mechanisms in patients with or without renal dysfunction.[10,11] Heparin inhibits aldosterone synthesis and can cause significant hyperkalemia in patients with altered renal function.[12–14] Other drugs that may cause hyperkalemia by decreasing glomerular filtration rate and aldosterone secretion include cyclosporine and tacrolimus.[15] Trimethoprim and pentamidine inhibit renal K^+ excretion and can cause hyperkalemia in patients with renal insufficiency.[15] Patients undergoing ureterojejunostomy may develop hyperkalemia in the immediate postoperative period, presumably from increased jejunal absorption of urinary K^+.[16]

TABLE 14–1. CAUSES OF HYPERKALEMIA

Impaired K^+ Excretion
Renal failure
Mineralocorticoid deficiency
Addison's disease
Renal tubular acidosis (type 4)
Heparin-induced inhibition of aldosterone synthesis
Hereditary enzyme deficiencies
Pseudohypoaldosteronism
Drugs: potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, trimethaphan, cyclosporine, tacrolimus, pentamidine
Shifts of K^+ out of Cells
Hypertonicity
Tissue breakdown: rhabdomyolysis, burns, trauma
Drugs: beta blockers, digoxin, succinylcholine, arginine, lysine
Familial hyperkalemic periodic paralysis
Insulin deficiency or resistance

Alterations in the relationship between intracellular and extracellular [K^+] may lead to severe hyperkalemia in critically ill patients, either by increased release of intracellular K^+ or by inhibition of extracellular-to-intracellular K^+ movement. The effects of acidosis on serum [K^+] are complicated and are not fully understood. The traditional teaching that acidosis produces a shift of K^+ from the intracellular to the extracellular space, thus causing hyperkalemia, was based on observations of hyperkalemia in patients with diabetic ketoacidosis and renal failure.[17] Based on these data, an inverse relationship with serum pH and serum [K^+] was described. This relationship has since been disproved, and changes in serum [K^+] in relation to acid-base disorders are more complex than initially thought. Most forms of acute acidosis do not present with hyperkalemia. The most common forms of acute metabolic acidosis in critically ill patients, diabetic ketoacidosis and lactic acidosis, are not associated with K^+ shifts out of cells.[18] Hyperkalemia seen with diabetic ketoacidosis is most likely caused by increased release of intracellular K^+ due to the breakdown of muscle cells.[16] Hypertonicity of the extracellular fluid causes water to exit cells, and K^+ follows. Unless renal function is adequate to eliminate the excess K^+, hyperkalemia develops. This situation may occur in patients with uncontrolled diabetes and can lead to severe hyperkalemia in the presence of renal failure and hypoaldosteronism.[19] Massive tissue breakdown can occur with trauma, burns, and rhabdomyolysis, leading to release of K^+ into the extracellular space. If renal mechanisms for K^+ excretion are impaired, severe hyperkalemia may develop. Drugs can affect the transmembrane balance of K^+. Beta-adrenergic blockers inhibit the entry of K^+ into cells and, in combination with renal failure, can promote the development of hyperkalemia.[20] Succinylcholine blocks normal reentry of K^+ into cells after depolarization and causes a transitory increase in serum [K^+]. In patients with severe burns or extensive trauma, the transient hyperkalemia induced by succinylcholine can be more prolonged and severe.[21,22] Digoxin impairs K^+ entry into cells by inhibiting the cell membrane Na^+, K^+-ATPase. It does not produce hyperkalemia in therapeutic doses but may cause hyperkalemia with toxic levels.[23,24] Familial hyperkalemic periodic paralysis is a rare congenital disease that causes a mutation in cell membrane Na^+ channels, producing transient episodes of severe hyperkalemia secondary to paroxysmal shifts in K^+ from cells to the extracellular compartment.[25]

CLINICAL EFFECTS

Most of the clinical consequences of potassium abnormalities are related to the effect on the transmembrane resting cell potential. Cardiac and neuromuscular cells are particularly sensitive to changes in serum [K^+]. Most often, hyperkalemia is asymptomatic. However, it affects the cardiac conduction system, as evidenced by characteristic changes in the electrocardiogram (ECG) that serve as indicators of potential life-threatening arrhythmias (Table 14–2). The first sign of increased serum [K^+] is tenting of the T wave. Changes associated with progressive increases in serum [K^+] include widening of the QRS complex, the progressive development of atrioventricular conduction blocks, a slow idioventricular rhythm, an ECG tracing that looks like a sine wave, ventricular fibrillation, and finally asystole.[26] There is no absolute level of serum [K^+] associated with a particular ECG abnormality, but rapid rises seem to be more dangerous, particularly in patients without a history of chronic renal insufficiency.[27,28] Hyperkalemia can cause paresthesias and weakness in the arms and legs, followed by a symmetrical flaccid paralysis of the extremities that ascends toward the trunk, finally involving the respiratory muscles. The cranial nerves are usually not affected by hyperkalemia.

TABLE 14–2. ELECTROCARDIOGRAM CHANGES CAUSED BY ABNORMAL [K^+]

Hyperkalemia	Hypokalemia
Peaked T waves	Broad, flat T waves
Loss of P waves	ST depression
Widening QRS complexes	U wave
Sine wave	QT interval prolongation
Ventricular arrhythmias	Ventricular arrhythmias
Asystole	

TREATMENT

The primary goal of treating hyperkalemia is to prevent adverse cardiac complications. Treatment modalities are aimed at one of three mechanisms to prevent or decrease these complications: (1) direct antagonism of hyperkalemic effect on the cell membrane polarization, (2) movement of extracellular K^+ into the intracellular compartment, and (3) removal of K^+ from the body. Patients with a serum [K^+] greater than 6.5 mEq/L or ECG signs suggestive of hyperkalemia should be treated emergently.

Direct Antagonism of Hyperkalemic Effect on Cell Membrane Polarization. The intravenous infusion of calcium gluconate antagonizes the effects of hyperkalemia on the heart. This effect occurs within minutes and lasts 30 to 60 minutes. If a salutary effect is noted, repeat doses may be used. The recommended dose is 10 mL of 10% calcium gluconate or chloride. Extreme caution must be used in patients with hyperkalemia and digitalis toxicity, because the administration of ionized calcium may potentiate the effects of digoxin on the conduction system.[15,29] Calcium should be avoided in the setting of digoxin toxicity.

Movement of Extracellular K^+ into the Intracellular Compartment. Administration of insulin shifts K^+ into cells; this effect occurs in 15 to 30 minutes and lasts approximately 2 to 4 hours.[30] The recommended dose is 10 units of regular insulin intravenously; dextrose (50 g) should be added to avoid hypoglycemia. This dose will decrease serum [K^+] by 0.5 to 1.5 mEq/L. Patients without intravenous access can be treated with inhaled $beta_2$-adrenergic agonists such as albuterol. Albuterol drives K^+ into cells by increasing Na^+, K^+-ATPase activity. Albuterol (10 to 20 mg in 4 mL of saline by nasal inhalation over 10 minutes) can lower the serum [K^+] by 0.5 to 1.5 mEq/L.[31] Sodium bicarbonate is much less effective than either insulin or albuterol but may produce shifting of [K^+] into cells.[32] The use of sodium bicarbonate should be limited to situations in which it is indicated for the treatment of concurrent acidosis.

Removal of K^+ from the Body. Finally, removal of K^+ is necessary to prevent a recurrence of hyperkalemia once the effects of the preceding measures have waned. Loop diuretics can be helpful in patients with sufficient renal function (dosing depends on medication and renal function); however,

TABLE 14–3. TREATMENT OF HYPERKALEMIA

Treatment	Mechanism	Dosage/Comment	Onset	Duration
Calcium	Cardiac cell stabilizer	10 mL of 10% solution (calcium gluconate or calcium chloride)	Seconds	30–60 min
Insulin (regular)	Shifts K^+ into cells	10 U i.v. + glucose (50 g)	15–30 min	2–4 h
Albuterol	Shifts K^+ into cells	10–20 mg by inhaler over 10 min	20–30 min	2–3 h
Sodium bicarbonate	Shifts K^+ into cells	In cases of acidosis	Delayed	—
Kayexalate with sorbitol	Removes K^+ from body	Oral: 15–30 g	4–6 h	—
		Retention enema: 30–50 g	1 h	—
Loop diuretics	Removes K^+ from body	Intravenous, varies by drug and renal function	1 h	—
Hemodialysis	Removes K^+ from body	Preferred over peritoneal dialysis in acute cases	15–30 min	—

most often, other measures are needed. Sodium polystyrene sulfonate (Kayexalate) binds to K^+ secreted in the colon. Each gram of resin removes 0.5 to 1 mEq of K^+. The usual dose of Kayexalate is 15 to 30 g orally. Because the resin causes constipation, sorbitol (15 mL of a 70% solution) should be administered to induce osmotic diarrhea. If oral administration is not feasible, Kayexalate can be given as a retention enema, consisting of 30 to 50 g of the resin in 70% sorbitol solution. It is important, however, that the enema be retained for at least 30 to 60 minutes to obtain the desired therapeutic effect. The effects of Kayexalate on serum $[K^+]$ occur in 4 to 6 hours when the agent is given orally and in 1 to 2 hours when it is given as an enema. Serious side effects of Kayexalate and sorbitol include bowel necrosis and perforation. These complications seem to be more likely in severely immunocompromised patients or shortly after operation; accordingly, Kayexalate should be avoided in these circumstances.[33–35] Both peritoneal dialysis and hemodialysis are very effective in removing K^+ from the body. In acute cases when serum $[K^+]$ needs to be corrected rapidly, hemodialysis is preferred. Hemodialysis can quickly remove 50 to 125 mEq of K^+ and should be used as definitive treatment when other treatments fail. Peritoneal dialysis is also effective in removing K^+ from the body, but its effects are slower than those achieved with hemodialysis or cation exchange resins. In addition to the implementation of rapid treatment, the causes of hyperkalemia should be sought and corrected, and offending drugs should be discontinued when possible. See Table 14–3 for a summary of the treatment for hyperkalemia.

HYPOKALEMIA

Hypokalemia is more common than hyperkalemia and is defined as serum $[K^+]$ less than 3.6 mEq/L. Severe hypokalemia can lead to significant complications; more important, understanding its causes and how to treat it may reduce complications from the treatment itself. Low serum $[K^+]$ reflects a disbalance of normal K^+ homeostasis, with one rare exception. In patients with leukemia and markedly elevated white cell counts, K^+ can be taken up by the abnormal cells in the test tube and produce pseudohypokalemia.[36] However, as noted earlier, in vitro changes in $[K^+]$ more commonly produce pseudohyperkalemia. Hypokalemia usually occurs as a consequence of K^+ depletion due to either increased excretion or inadequate intake. Shifts in extracellular and intracellular $[K^+]$ also can cause hypokalemia (Table 14–4).

In critically ill patients, increased losses are more commonly responsible for K^+ depletion than is inadequate ingestion. The use of diuretics is the most common cause of hypokalemia in hospitalized patients. Both loop and thiazide diuretics cause increased delivery of Na^+ and Cl^- to the collecting duct, promoting the secretion of K^+ and causing hypokalemia. Diuretics are often used in high doses or administered by continuous infusion in critically ill patients, increasing the risk of hypokalemia. K^+ losses can also occur from increased stool output. Because K^+ is secreted into the colon, patients with high outputs from ileal or jejunal ostomies do not develop hypokalemia. Upper gastrointestinal losses such as vomiting or nasogastric suctioning contain small amounts of K^+. However, these losses are associated with hypochloremia and metabolic alkalosis, both of which may cause increased renal K^+ excretion, exacerbating the resultant hypokalemia. Large doses of laxatives or repeated enemas lead to excessive K^+ losses and hypokalemia. Magnesium depletion and some forms of renal tubular acidosis (type 1 and some forms of type 2) can cause renal K^+ wasting. Other drugs also can lead to hypokalemia. For example, fludrocortisone and hydrocortisone increase K^+ excretion. Aminoglycosides, amphotericin B, cisplatin, and foscarnet

TABLE 14–4. CAUSES OF HYPOKALEMIA

Increased Excretion

- Diarrhea, laxative or enema abuse
- Renal losses
  - Diuretics (loop and thiazides)
  - Metabolic alkalosis
  - Osmotic diuresis (uncontrolled hyperglycemia)
  - Nonreabsorbable anions
  - Mineralocorticoid excess
    - Primary hyperaldosteronism
    - Congenital adrenal hyperplasia
    - Glucocorticoid-responsive aldosteronism
  - Other causes
    - Liddle's disease
    - Enzyme deficiencies
    - Bartter's syndrome
  - Magnesium depletion
  - High-dose glucocorticoids

Shifts of K^+ into Cells

- Drugs
  - Beta-adrenergic agonists
  - Insulin
  - Theophylline
  - Caffeine
- Delirium tremens
- Hyperthyroidism
- Familial hypokalemic periodic paralysis
- Barium poisoning

cause magnesium depletion and increased K^+ renal losses.[37] Penicillin and its synthetic derivatives, when given intravenously, cause increased Na^+ delivery to the distal nephron, promoting K^+ secretion and potentially causing hypokalemia.[37]

Alkalosis can cause movement of K^+ into cells. This effect is seen with both metabolic and respiratory alkalosis and occurs as a consequence of hydrogen ions leaving the cell to minimize changes in extracellular pH, and K^+ moving into the cells to maintain electroneutrality. The direct effects of alkalosis on serum [K^+] are small, and the hypokalemia seen with metabolic alkalosis is more often caused by chloride losses producing increased delivery of Na^+ to the distal nephron, which stimulates K^+ losses. A number of $beta_2$-adrenergic agonist drugs, including bronchodilators, decongestants, and tocolytics, can cause K^+ shifts into cells and transient hypokalemia.[37] Theophylline stimulates cell membrane Na^+, K^+-ATPase and promotes K^+ entry into cells; hypokalemia is commonly seen with theophylline toxicity.[38] Barium can block the exit of K^+ from cells and cause hypokalemia.[39] Thyroid hormone can stimulate Na^+, K^+-ATPase, and hypokalemia is sometimes seen with hyperthyroidism. Increased endogenous beta-adrenergic stimulation occurs with delirium tremens, producing intracellular movement of K^+ and hypokalemia.[40] Familial hypokalemic periodic paralysis, a rare hereditary disease, is associated with a mutation in cell membrane calcium channels and causes episodes of severe hypokalemia triggered by high sodium intake or exercise.[41] These patients can present with severe muscle weakness and respiratory failure from hypoventilation.

CLINICAL EFFECTS

It is estimated that approximately 20% of hospitalized patients have a serum [K^+] less than 3.6 mEq/L; most are asymptomatic. As discussed earlier, the consequences of changes in serum [K^+] occur as a result of alterations in the resting membrane potential, making cardiac and neuromuscular cells the most susceptible targets. The most serious and potentially fatal effects of hypokalemia are related to disturbances in cardiac electrical activity that can lead to cardiac arrest. However, cardiac arrest caused by hypokalemia occurs almost exclusively in patients with underlying cardiac disease or patients taking digitalis.[42] Hypokalemia is also associated with characteristic ECG changes (see Table 14–2). Progressive decreases in serum [K^+] produce broad, flat T waves; ST depression; and the appearance of U waves, QT interval prolongation, and finally ventricular arrhythmias, leading to cardiac arrest.[26] When serum [K^+] is less than 3.0 mEq/L, generalized weakness can develop. When serum [K^+] decreases to less than 2.5 mEq/L, muscle necrosis and rhabdomyolysis can occur. With progression of hypokalemia, an ascending muscle paralysis develops, leading to respiratory failure and arrest.

TREATMENT

The immediate goal of treatment in hypokalemia is to prevent or correct cardiac electrical disturbances and serious neuromuscular weakness. The long-term goal of treatment is to achieve repletion of total body potassium to normal levels. Supplementation of [K^+] is the principal treatment for hypokalemia and is achieved with the administration of potassium chloride or potassium phosphate. In general, plasma [K^+] decreases by approximately 0.3 mEq/L for each 100 mEq decrease in total body K^+. This relationship is more difficult to estimate when serum [K^+] is less than 2 mEq/L.[37] K^+ replacement should be given orally except when severe hypokalemia is associated with respiratory or cardiac instability, in which case the intravenous route is recommended. Intravenous administration of K^+ should not exceed 20 mEq/h, to minimize possible iatrogenic hyperkalemia. For infusion of K^+, an infusion pump and continuous cardiac monitoring are mandatory.[15] In the case of life-threatening arrhythmias due to severe hypokalemia, more rapid infusion into a central vein may be appropriate. In these rare circumstances, KCl should be diluted to 10 mEq per 100 mL of infusion fluid. In most cases, oral supplementation of K^+ is preferred, because this route is safer and produces a more gradual increase in serum [K^+]. Because supplementation of K^+ is usually not an emergency, it is best accomplished using moderate doses of KCl (20 to 40 mEq once or twice a day) over several days. Potassium phosphate is used when hypophosphatemia is also present (as in diabetic ketoacidosis); occasionally, potassium bicarbonate is used in the setting of metabolic acidosis and hypokalemia. However, for most cases of hypokalemia, KCl is the salt of choice for replacement of K^+. Serum [K^+] should be followed closely, especially when using intravenous or higher doses, to prevent the development of hyperkalemia. If magnesium levels are low, they should be corrected, because hypomagnesemia promotes renal loss of K^+, making correction of hypokalemia more difficult. Finally, prevention of further episodes should be addressed with proper K^+ intake and supplementation in patients with a continuous cause for hypokalemia. The use of potassium-sparing diuretics may be helpful in certain clinical situations, but caution must be exercised, because the development of hyperkalemia can have severe consequences.

Chapter 15
HYPOPHOSPHATEMIA AND HYPERPHOSPHATEMIA

Stephen Trzeciak • R. Phillip Dellinger

PHOSPHATE HOMEOSTASIS

Derangements in the metabolism of phosphate are common in the intensive care unit and can be clinically significant. One of the keys to understanding phosphate homeostasis is an appreciation of the fact that serum phosphate measurements may not reflect total body phosphorus stores because (1) the vast majority of total body phosphorus is found in the bones (in the form of hydroxyapatite); (2) the majority of phosphate is intracellular, and extracellular phosphate accounts for only a small fraction of total body phosphorus stores; and (3) shifts between the intracellular and extracellular compartments occur. There is no common laboratory test to accurately measure total body phosphate stores. Low serum phosphate concentration is referred to as *hypophosphatemia*, whereas a state of low total body phosphorus stores is referred to as *phosphate depletion*.

Phosphate serves a number of crucial functions. It is an essential component of the main energy "currency" of the cell: adenosine triphosphate. Phosphate is also a component of phospholipids in cell membranes and of hydroxyapatite, the structural matrix of bone. Phosphate also serves as a buffer against acid-base derangements.

Phosphate homeostasis is a function of bone metabolism, intestinal absorption, and kidney resorption. Bone metabolism is linked to calcium homeostasis. In the setting of hypocalcemia, increased parathyroid hormone levels cause phosphate and calcium to be released from the bone. Intestinal absorption of phosphate occurs in the small bowel, mostly in the jejunum. Vitamin D, produced by the kidney in increased amounts when serum phosphate levels are low, increases the intestinal absorption of both calcium and phosphate. Phosphate is excreted from the kidneys, but most of the excreted phosphate load undergoes resorption in the proximal tubule. Parathyroid hormone increases phosphate excretion by inhibiting phosphate resorption in the kidney. Resorption increases in the setting of phosphate deficiency.

HYPOPHOSPHATEMIA

Hypophosphatemia is typically classified as mild (serum phosphate concentration 2.5 to 3 mg/dL), moderate (1 to 2.5 mg/dL), or severe (<1 mg/dL). Although mild to moderate hypophosphatemia may be subclinical, severe hypophosphatemia may be associated with significant morbidity. The all-cause mortality rate in patients with serum phosphate concentrations less than 1 mg/dL has been reported to be as high as 30%.[1]

Common causes of hypophosphatemia are summarized in Table 15–1. Respiratory alkalosis (of any cause) may induce a transcellular shift of phosphate and cause hypophosphatemia. Other causes of hypophosphatemia include renal phosphate losses, inadequate intestinal absorption of phosphate, and extreme catabolic states. Renal losses of phosphate occur with osmotic diuresis or excessive diuretic therapy. Hyperparathyroidism (either primary or secondary) causes hypophosphatemia by decreasing urinary resorption of phosphate. Proximal renal tubular disorders also impair phosphate resorption and cause hypophosphatemia. Total body phosphate depletion also occurs in extreme catabolic states, such as burns or sepsis.

Hypophosphatemia should be anticipated when nutritional support is initiated in a chronically malnourished patient. When a carbohydrate load is administered in the setting of chronic malnutrition, there is a spike in insulin release that increases cellular phosphate uptake and can induce a precipitous decrease in serum phosphate concentration. This phenomenon has been termed the *refeeding syndrome*. A common example is the initiation of enteral or parenteral nutrition in an alcoholic patient who suffers from chronic hypophosphatemia due to malnutrition.[2] Profound hypophosphatemia in the refeeding syndrome can produce severe clinical manifestations, and death has been reported.[3] Concurrent hypokalemia and hypomagnesemia are common. In chronically malnourished patients, the refeeding syndrome can be avoided with a cautious introduction of nutritional

TABLE 15–1. COMMON CAUSES OF HYPOPHOSPHATEMIA

- Transcellular shift
  - Refeeding syndrome
  - Respiratory alkalosis
  - Insulin administration
- Renal losses
  - Diuretic therapy
  - Osmotic diuresis
  - Hyperparathyroidism (primary or secondary)
  - Proximal renal tubular dysfunction
    - Fanconi's syndrome
- Insufficient intestinal absorption
  - Malnutrition
  - Phosphate-binding antacids
  - Vitamin D deficiency
  - Chronic diarrhea
  - Nasogastric suctioning
  - Malabsorption syndromes
- Extreme catabolic states
  - Burns
  - Trauma
  - Sepsis

support (especially carbohydrates), careful monitoring of serum phosphorus levels, and appropriate phosphate supplementation when indicated.[3]

Patients with diabetic ketoacidosis typically have phosphate depletion because hyperglycemia induces increased urinary losses of phosphate via an osmotic diuresis. However, the serum phosphate concentration may be normal in the initial phase of therapy, because severe acidosis causes a shift of phosphate into the extracellular space from the intracellular compartment. As the acidosis is corrected, however, phosphate shifts back to the intracellular compartment, leading to a precipitous decrease in serum phosphate levels.[4] Although common, the clinical significance of moderate hypophosphatemia in diabetic ketoacidosis is unclear. Therapy for hypophosphatemia in diabetic ketoacidosis is typically warranted only if the serum phosphate level is less than 1.0 mg/dL or if hypophosphatemia is associated with severe clinical manifestations, such as central nervous system or left ventricular dysfunction.[5]

Clinical manifestations due to hypophosphatemia are rare unless the serum phosphate concentration is less than 1 mg/dL. The clinical findings are summarized in Table 15–2. Diffuse skeletal muscle weakness may be profound.[6] Respiratory failure secondary to diaphragmatic weakness may occur.[7,8] Respiratory failure may be primary, or it may manifest as an inability to wean from mechanical ventilation. Central nervous system dysfunction may include confusion, lethargy, and gait disturbance. Hematologic manifestations, including acute hemolytic anemia and leukocyte dysfunction (impaired phagocytosis and chemotaxis), have been reported. Cardiovascular manifestations may include acute left ventricular dysfunction and a reversible dilated cardiomyopathy that typically responds only to phosphate repletion. Rhabdomyolysis also may occur.[9]

Hypophosphatemia also may cause disorders of oxygen transport. Profound hypophosphatemia can impair oxygen delivery to the tissues because of decreased production of 2,3-diphosphoglycerate, a key molecule in erythrocytes that facilitates the release of oxygen from hemoglobin. Decreased intracellular levels of 2,3-diphosphoglycerate cause a leftward shift of the oxyhemoglobin dissociation curve.

Because phosphate serves as a buffer in acid-base derangements, hypophosphatemia may be clinically significant in the interpretation of acid-base status. Phosphate and proteins (albumin) are measured anions. Unmeasured anions are accounted for in acid-base interpretation by calculation of the anion gap. Although there is no true "normal" value for the anion gap, the value is typically lower for a patient with low measurable anions (i.e., either hypophosphatemia or hypoalbuminemia, or both). Therefore, a "normal" value for the calculated anion gap in the setting of profound hypophosphatemia may actually represent the presence of unmeasured anions. As a rule, the expected anion gap (in mEq/L) equals twice the serum albumin concentration (in g/dL) plus one half of the serum phosphate concentration (in mM/L). Thus, a patient with hypophosphatemia and hypoalbuminemia may have an elevated anion gap even if the measured anion gap is less than the commonly used threshold of 10 to 12.

Severe hypophosphatemia (phosphate concentration <1 mg/dL) mandates intravenous phosphate replacement. Phosphate should not be administered by the intravenous route to patients with renal failure; it should also be avoided in patients with hypercalcemia, because metastatic calcification can occur. For moderate hypophosphatemia (phosphate concentration 1 to 2.5 mg/dL), oral supplementation may be adequate for a patient who is able to take medications by mouth or nasogastric tube. The degree of true phosphate depletion is difficult to assess because most phosphate is intracellular; therefore, it is impossible to accurately predict the exact amount of phosphate supplementation required to replenish phosphate stores.

TABLE 15–2. CLINICAL MANIFESTATIONS OF SEVERE HYPOPHOSPHATEMIA

Respiratory
Acute respiratory failure
Ventilator dependence
Musculoskeletal
Muscle weakness
Rhabdomyolysis
Bone demineralization
Hematologic
Hemolysis
Disorders of leukocyte phagocytosis or chemotaxis
Neurologic
Altered mental status
Gait disturbance
Paresthesias
Cardiovascular
Cardiomyopathy
Decreased inotropy

HYPERPHOSPHATEMIA

Hyperphosphatemia is defined as a serum phosphate level greater than 4.5 mg/dL; it may be clinically significant at levels greater than 5 mg/dL. The most common cause of hyperphosphatemia is renal failure. Renal insufficiency causes hyperphosphatemia because phosphate excretion by the kidneys is impaired. The serum phosphate level is usually normal until the creatinine clearance falls below 30 mL/min. Other causes of hyperphosphatemia include rhabdomyolysis, hemolysis, and tumor lysis syndrome[10]; any insult causing extensive cell damage releases phosphorus into the extracellular space. Hyperphosphatemia has also been reported in patients using bisphosphonate medications (decreased renal phosphate clearance) and patients abusing phosphate-containing laxatives. Causes of hyperphosphatemia are summarized in Table 15–3.

The most frequent clinical findings in acute hyperphosphatemia are signs and symptoms of hypocalcemia.

TABLE 15–3. COMMON CAUSES OF HYPERPHOSPHATEMIA

Renal
Acute or chronic renal failure
Increased renal resorption
Hypoparathyroidism
Thyrotoxicosis
Cellular injury
Rhabdomyolysis
Tumor lysis syndrome
Hemolysis
Medication related
Abuse of phosphate-containing laxatives
Excessive (iatrogenic) phosphate administration
Bisphosphonate therapy

Hyperphosphatemia produces hypocalcemia by three mechanisms: (1) precipitating calcium (formation of calcium-phosphorus complexes), (2) interfering with parathyroid hormone–mediated resorption of bone, and (3) decreasing vitamin D levels.[11] Clinical signs and symptoms of hypocalcemia, such as muscle cramping, tetany, hyperreflexia, and seizures, as well as cardiovascular manifestations, may be evident.

Management of acute hyperphosphatemia includes limiting phosphate intake and enhancing urinary phosphate excretion. In the absence of end-stage renal disease, phosphate excretion can be optimized with saline infusion (volume diuresis) and diuretic administration. Diuretics that work on the proximal tubule, such as acetazolamide, are especially effective for enhancing phosphate excretion. Any patient with life-threatening hyperphosphatemia should be considered for dialysis.

Oral phosphate binders decrease the absorption of phosphate in the gut and are a mainstay for preventing and treating hyperphosphatemia in patients with chronic renal failure. Calcium and aluminum salts are widely used. However, calcium salts can produce hypercalcemia and metastatic calcification from a high calcium-phosphorus ($Ca \times PO_4$) product, and aluminum salts may be toxic. In dialysis patients, chronic management of hyperphosphatemia with calcium-free phosphate binders, such as sevelamer hydrochloride (Renagel), may reduce long-term mortality by preventing cardiovascular complications associated with a high calcium-phosphorus product.[12] Sevelamer is highly effective in increasing fecal elimination of phosphate without producing hypercalcemia or aluminum toxicity.[13] In the acute management of patients with hyperphosphatemia accompanied by hypocalcemia, the likelihood (and clinical significance) of metastatic calcification with acute calcium administration is unclear.

Chapter 16
HYPOMAGNESEMIA

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Magnesium (Mg^{++}) is an important ion that participates in more than 300 enzymatic reactions, especially those involving adenosine triphosphate (ATP) as a cofactor. Although the relationship between hypomagnesemia and intracellular magnesium deficiency remains unclear, hypomagnesemia is common in critically ill patients and is associated with increased mortality.[1,2]

CELLULAR PHYSIOLOGY AND METABOLISM OF MAGNESIUM

Magnesium is a divalent cation that is localized predominantly to the intracellular compartment. It is the second most abundant intracellular cation after potassium and plays an important role in cellular metabolism and homeostasis. At the cellular level, magnesium influences membrane function by regulating ion transport. Magnesium is required for Na^+, K^+-ATPase activity, which maintains transmembrane gradients for sodium (Na^+) and potassium (K^+).[3,4] Magnesium also regulates intracellular calcium (Ca^{++}) flux by competing for Ca^{++} binding sites and influencing intracellular Ca^{++} transport.[3,4] Magnesium is an essential cofactor for most processes that require ATP. It acts by neutralizing the negative charge on the phosphate anion of ATP to facilitate enzyme binding and hydrolysis of the phosphate moiety. Intracellular Mg^{++} is required for numerous critical biochemical processes, including DNA synthesis, activation of gene transcription, initiation of protein synthesis, and regulation of energy metabolism via glycolysis and the tricarboxylic acid cycle.[3–6]

Total body magnesium (21 to 28 g) is distributed in bone (53%), muscle (27%), soft tissue (19%), and blood (0.8%).[3] The normal concentration of total magnesium in serum is 1.5 to 2.3 mg/dL. Approximately 19% of circulating magnesium is bound to protein (predominantly albumin), whereas 14% is complexed to serum anions (citrate, phosphate, and bicarbonate). The majority of magnesium in serum exists as an ionized species (67%), which represents the physiologically active form.[3,7] Consequently, measurements of total serum Mg^{++} may not accurately reflect the relative abundance of circulating Mg^{++}.[1–3]

Magnesium homeostasis is maintained by the small intestine, kidney, and bone.[3,8] The average dietary intake of magnesium is approximately 300 mg/day. Normally, only one third of dietary Mg^{++} is absorbed.[8,9] However, intestinal Mg^{++} uptake increases to compensate for dietary or total body Mg^{++} deficiency.[3,8,9] Unlike calcium, there are no hormonal mechanisms for regulating Mg^{++}. Consequently, normal renal filtration and reabsorption of Mg^{++} are important regulatory mechanisms for Mg^{++} homeostasis.[3,8] Non–protein-bound Mg^{++} is filtered by the glomerulus. Under normal conditions, up to 95% of filtered Mg^{++} is reabsorbed in either the proximal tubule (35%) or the thick ascending loop of Henle (60%).[3,8] Magnesium reabsorption in the loop of Henle is linked to sodium chloride transport and is inversely related to flow. Consequently, diuretic use and other conditions associated with increased tubular flow result in decreased Mg^{++} reabsorption.[3,8] Under conditions of persistent Mg^{++} deficiency, mobilization of Mg^{++} from bone also represents a potential homeostatic mechanism.[3]

PREVALENCE AND CAUSE OF HYPOMAGNESEMIA

The reported prevalence of hypomagnesemia in adult patients admitted to the intensive care unit ranges from 15% to 60%, depending on whether total or ionized magnesium is measured.[1,2,10,11] A recent study found that severe ionized hypomagnesemia is most common after liver transplantation and in patients with severe sepsis.[2] Magnesium deficiency in critically ill patients may be caused by inadequate Mg^{++} intake, increased renal or gastrointestinal losses, acute intracellular shifts of Mg^{++}, and other medical conditions (e.g., burn injury, massive blood transfusion, cardiopulmonary bypass). Increased renal losses of Mg^{++} are associated with alcohol abuse, diabetes, acute tubular necrosis, diuretics, aminoglycosides, amphotericin, cyclosporine, cisplatin, digoxin, and other medications.[2,3,8,10,12] Vomiting, diarrhea, nasogastric tube losses, and pancreatitis are associated with increased gastrointestinal losses of Mg^{++}.[2,3,8,10,12] Acute extracellular-to-intracellular shifts of magnesium caused by refeeding with glucose or amino acids, insulin, catecholamines, or metabolic acidosis may also result in hypomagnesemia.[2,3,8,10,12] Hypoalbuminemia is associated with a reduction in total Mg^{++} in plasma, but the ionized fraction may remain normal. Critically ill patients are at increased risk for hypomagnesemia, and the development of hypomagnesemia is associated with an increased risk of mortality.[1,2]

CLINICAL SIGNS AND SYMPTOMS OF HYPOMAGNESEMIA

Hypomagnesemia is frequently asymptomatic in critically ill patients and is commonly identified through routine blood work or when hypomagnesemia is suspected clinically.[8,10–12] However, the relationship between systemic and cytoplasmic hypomagnesemia is unclear, and it has not been established whether changes in enzymatic function caused by cytoplasmic

TABLE 16–1. CLINICAL SIGNS AND SYMPTOMS OF MAGNESIUM DEFICIENCY

Cardiovascular
Atrial fibrillation, flutter
Ventricular tachycardia, especially torsades de pointes
Supraventricular tachycardia
Electrocardiogram changes (↑ PR, wide QRS, ↑ QT)
Hypertension
Risk of digitalis toxicity
Metabolic
Hypokalemia
Hypocalcemia
Hypophosphatemia
Insulin resistance
Neurologic
Seizures
Nystagmus
Delirium
Coma
Athetoid movements
Neuromuscular
Chvostek's sign
Muscle cramps
Carpopedal spasm
Muscle weakness
Muscle fasciculations

Mg^{++} depletion can lead to clinically significant problems. Hypomagnesemia is most commonly seen in conjunction with hypokalemia, hypocalcemia, and other electrolyte abnormalities. Consequently, it is difficult to assess the clinical consequences of isolated hypomagnesemia. In most instances, symptoms are attributed to Mg^{++} deficiency only after other electrolyte abnormalities are corrected.[3,8,10–12] As summarized in Table 16–1, the clinical sequelae of magnesium deficiency most commonly affect the cardiovascular, metabolic, and neuromuscular systems.

CLINICAL USES OF MAGNESIUM

Hypomagnesemia is associated with electrocardiographic changes that are similar to those found in hypokalemia; these include flattened T waves, U waves, and prolonged QT interval. Magnesium is a cofactor for Na^+, K^+-ATPase in cardiac tissue.[3,8,11,12] Reductions in intracellular K^+ result in cell depolarization and can lower the threshold for generation of an action potential, as well as decrease the time for repolarization. Consequently, hypomagnesemia is associated with atrial (premature atrial contractions, atrial fibrillation, multifocal atrial tachycardia), digoxin-related, and ventricular (ventricular tachycardia, torsades de pointes) dysryhthmias.[8,11,12] Magnesium is currently recommended as the initial therapy for torsades de pointes and as an adjunct for refractory ventricular dysrhythmias.[3,8,11,12] Magnesium administration during acute myocardial infarction was associated with reduced mortality in the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2)[13] but not the fourth International Study of Infarct Survival (ISIS-4).[14] However, in the ISIS trial, magnesium replacement was performed following coronary reperfusion. So at present, there are no conclusive data to support routine magnesium administration in patients with acute myocardial infarction. However, based on the LIMIT-2 study, there is some evidence that magnesium may be beneficial if given before coronary reperfusion.[15]

Hypomagnesemia is commonly associated with both hypokalemia and hypocalcemia.[8] This association is related in part to the fact that medications and homeostatic changes that affect magnesium often affect potassium as well. In addition, renal losses of potassium are increased in hypomagnesemia and are refractory to supplementation unless the magnesium deficiency is corrected first.[3,8] A somewhat similar condition exists for hypocalcemia, in that hypomagnesemia suppresses parathyroid hormone release and activity.[16] Consequently, hypocalcemia is refractory to Ca^{++} replacement unless the magnesium deficiency is corrected as well.[3,8]

Magnesium can have a depressant effect on the nervous system due to its ability to cause presynaptic inhibition.[3,8,12] It depresses the seizure threshold by competitively inhibiting *N*-methyl-D-asparate receptors.[3,8,11,12] The neurologic and neuromuscular manifestations of hypomagnesemia include coma, seizures, weakness, and signs of muscular irritability.[3,8,11,12] Hypomagnesemic patients may have a positive Chvostek's sign even with normal ionized calcium and may develop nystagmus, tetany, or seizures followed by rhabdomyolysis.[3,8,11,12] Consequently, Mg^{++} replacement is indicated in this setting and is also commonly used in patients with preeclampsia (blood pressure >140/90 with proteinuria) or eclampsia (associated seizures) during late pregnancy.[11,12]

Magnesium replacement has been used to treat bronchospasm in patients with asthma.[11,12] The proposed mechanism of action for the therapeutic benefit of Mg^{++} in bronchospasm involves its relaxant effects on smooth muscle.[11,12] Several studies have shown improved FEV_1 following intravenous magnesium or improved peak flow rates with nebulized magnesium, while others have not.[11,12] Consequently, additional studies are needed to adequately define the role of magnesium in patients with asthma.

TREATMENT OF HYPOMAGNESEMIA

The initial step in managing hypomagnesemia is to identify and eliminate factors contributing to the development of magnesium deficiency. This may involve interventions to minimize gastrointestinal losses or reevaluating the need for medications that cause renal magnesium wasting (e.g., aminoglycosides, diuretics). The severity of hypomagnesemia, urgency of clinical symptoms (dysrhythmias, muscle cramps.), associated electrolyte abnormalities (K^+ and Ca^{++}), and renal function should be assessed before initiating Mg^{++} therapy.

In general, intravenous administration of Mg^{++} is preferred in symptomatic critically ill patients. However, caution must be used with Mg^{++} replacement when renal dysfunction is present, because severe hypermagnesemia may result. Current recommendations for magnesium replacement therapies are of limited value, owing to the lack of controlled studies examining time-matched controls and the use of total serum versus ionized magnesium concentration for monitoring. Magnesium can be administered intravenously as magnesium sulfate ($MgSO_4$; 1 g = 4 mmol) or magnesium chloride ($MgCl_2$; 1 g = 4.5 mmol) and orally as magnesium gluconate (500 mg = 1.2 mmol) or magnesium oxide (400 mg = 6 mmol). When intravenous magnesium replacement is used, a bolus followed by continuous infusion or infusion

alone is preferred, because renal filtration and excretion may limit Mg^{++} retention. For torsades de pointes, 1 to 2 g of intravenous $MgSO_4$ over 5 minutes is recommended. For urgent hypomagnesemia, an intravenous bolus of 8 to 12 mmol of Mg^{++} (2 to 3 g $MgSO_4$), followed by an infusion of 40 mmol Mg^{++} (10 g $MgSO_4$) over the next 5 hours, should be considered. For routine treatment of hypomagnesemia, an infusion of 40 mmol Mg^{++} should be given over a 24-hour period. For outpatients on diuretics with chronic magnesium losses, oral magnesium therapy with 2 to 3 g (12 to 24 mmol) per day is recommended. Orally, magnesium oxide is more easily absorbed than other formulations.

Chapter 17
HYPOCALCEMIA AND HYPERCALCEMIA

Richard J. King • Robert N. Cooney

Abnormal serum calcium is a common finding in critically ill patients. The prevalence of hypocalcemia in intensive care unit (ICU) patients ranges from 70% to 90% when total serum calcium is measured and from 15% to 50% when ionized calcium is measured.[1] Hypercalcemia occurs less frequently; the reported incidence is less than 15% in critically ill patients.[2] Hypocalcemia is associated with injury severity and mortality in critically ill patients.[1,3–6] However, it is not known whether a low serum calcium concentration is protective, harmful, or simply prognostic in critical illness. Therefore, in most instances, the management of hypocalcemia involves treating the underlying medical condition, except when patients are symptomatic or hemodynamically unstable. This chapter provides a brief overview of calcium physiology, the regulation of serum calcium concentration, potential causes and symptoms of hypocalcemia, conditions associated with hypocalcemia, and guidelines for treating hypo- and hypercalcemia in critically ill patients.

CALCIUM PHYSIOLOGY AND METABOLISM

Calcium is a divalent ion (Ca^{++}) involved in critical biologic processes such as muscle contraction, blood coagulation, neuronal conduction, hormone secretion, and the activity of various enzymes.[3,7] Therefore, it is not surprising that intra- and extracellular calcium concentrations are tightly regulated. A normal adult has approximately 1 to 2 kg of total body calcium, localized primarily in bone (99%) as hydroxyapatite.[1,3,4] Skeletal stores of calcium represent a virtually unlimited reservoir. Release of calcium from this reservoir is regulated predominantly by extracellular Ca^{++} concentration, parathyroid hormone (PTH), and calcitonin. Extracellular concentrations of Ca^{++} are typically 10,000 times greater than cytoplasmic Ca^{++} levels.[1,3] Similarly, the majority of intracellular calcium (>90%) is found in subcellular organelles (mitochondria, microsomes, endoplasmic or sarcoplasmic reticulum) as opposed to the cytoplasmic compartment. Ca^{++}-mediated cell signaling involves rapid changes in cytoplasmic Ca^{++} concentration secondary to movement of the ion from both internal and external stores.[8,9] Cytoplasmic Ca^{++} influx occurs through cell membranes by receptor-activated, G protein–linked channels. The release of internal Ca^{++} from endoplasmic or sarcoplasmic reticulum is stimulated by second messengers.[8] The efflux of cytoplasmic Ca^{++} involves transport of Ca^{++} across the cell membrane and into the endoplasmic or sarcoplasmic reticulum by specific transporters.[8–10] Alterations in Ca^{++}-dependent signaling have been identified in muscle, hepatocytes, neutrophils, and T lymphocytes during sepsis and may contribute to the development of organ dysfunction during catabolic illness (for review see reference 9).

Extracellular calcium homeostasis is maintained by the coordinated actions of the gastrointestinal tract, kidneys, and bone.[1,3] Levels of extracellular Ca^{++} are detected by calcium-sensing receptors on parathyroid cells.[10] In response to low serum Ca^{++} concentrations, the parathyroid glands secrete PTH. This hormone reduces renal reabsorption of phosphate, increases renal calcium reabsorption, and stimulates renal hydroxylation of vitamin D.[1,3] PTH and 1,25-dihydroxy-vitamin D (calcitriol) promote the release of calcium from bone by activating osteoclasts.[1,3] Calcitriol also stimulates intestinal absorption of dietary calcium and regulates PTH secretion by inhibiting PTH gene transcription. PTH secretion is also influenced by serum phosphate concentration. Increases in circulating phosphate concentration stimulate PTH secretion by lowering the extracellular Ca^{++} concentration. Magnesium is required for the release of PTH from parathyroid cells, which may explain why hypocalcemia is common in patients with magnesium deficiency. Calcitonin is a calcium-regulating hormone secreted by the parafollicular C cells of the parathyroid glands during hypercalcemia. Although calcitonin inhibits bone resorption and stimulates urinary excretion of calcium, its does not appear to play a major role in calcium homeostasis in humans.[1,3]

The normal concentration of Ca^{++} in the extracellular space (plasma and interstitium) is 1.2 mmol/L and represents 50% of the total extracellular calcium; of the remaining 50%, 40% is bound to plasma proteins and 10% is combined with citrate, phosphate, or other anions. Total serum calcium normally ranges from 9.4 to 10.0 mg/dL (2.4 mmol). The distribution of ionized and bound calcium may be altered in critically ill patients. Chelating substances such as citrate and phosphate can influence the abundance of ionized Ca^{++}. An increased free fatty acid concentration caused by lipolysis or parenteral nutrition results in increased binding of calcium to albumin.[11] Protein-bound calcium is also increased during alkalosis and reduced during acidosis.[1,3] Correcting total serum calcium for albumin and pH does not accurately estimate ionized Ca^{++}.[12,13] Therefore, most ICU laboratories measure ionized calcium. Hypocalcemia is defined as an ionized Ca^{++} level less than 1.0 mmol/L or a total level less than 8.5 mg/dL.[13]

HYPOCALCEMIA IN CRITICALLY ILL PATIENTS

Ionized hypocalcemia is frequently seen in critically ill patients with sepsis, pancreatitis, or severe traumatic injuries or following major surgery. The incidence ranges from 15% to 50%.[3] The degree of hypocalcemia correlates with illness severity as measured by the Acute Physiology and Chronic

TABLE 17–1. CAUSES OF HYPOCALCEMIA

Impaired parathyroid hormone secretion or action
Primary hypoparathyroidism
Secondary hypoparathyroidism
Impaired vitamin D synthesis or action
Poor intake
Malabsorption
Liver disease
Renal disease
Hypomagnesemia
Sepsis
Calcium chelation or precipitation
Hyperphosphatemia
Citrate
Pancreatitis
Rhabdomyolysis
Ethylene glycol
Decreased bone turnover
Hypothyroidism
Calcitonin
Cis-platinum
Diphosphonates
Mithramycin
Phosphates

From Zaloga GP: Hypocalcemia in critically ill patients. Crit Care Med 1992;20:251-261.

Health Evaluation (APACHE) II score and is associated with increased mortality in critically ill patients.[6] In particular, the degree of systemic inflammation as assessed by circulating cytokine or procalcitonin levels appears to correlate with hypocalcemia in ICU patients.[14] Potential causes for the hypocalcemia of critical illness include impaired PTH secretion or action, vitamin D deficiency or resistance, calcium sequestration or chelation, or impaired mobilization of Ca^{++} from bone (Table 17–1).

Hypocalcemia in the ICU is rarely caused by primary hypoparathyroidism. However, sepsis and systemic inflammatory response syndrome are commonly associated with hypocalcemia, which is caused in part by impaired secretion and action of PTH and failure to synthesize calcitriol.[1,3,14] Hypomagnesemia can contribute to hypocalcemia during critical illness by inhibiting PTH secretion and target organ responsiveness.[1,3,7] However, hypomagnesemia correlates with hypocalcemia in ICU patients only weakly.[6] In many instances, the cause of hypocalcemia of critical illness is multifactorial. Elderly patients are at increased risk for vitamin D deficiency owing to malnutrition, poor absorption, and hepatic or renal dysfunction.[3] Renal failure can precipitate hypocalcemia by impairing the formation of calcitrol and promoting hyperphosphatemia; phosphate chelates ionized calcium.[1,3] Other potential causes of ionized hypocalcemia in critically ill patients include alkalosis (increased binding of Ca^{++} to albumin), medications (anticonvulsants, antibiotics, diphosphonates, radiocontrast agents), massive blood transfusion, sepsis, and pancreatitis.[1,3,6,7]

Patients receiving blood transfusions can develop hypocalcemia as a consequence of Ca^{++} chelation by citrate, which is used as an anticoagulant in banked blood.[15–17] The incidence of transfusion-related hypocalcemia is related to both the rate and the volume of blood transfusion.[15,16] When blood transfusions are administered at a rate of 30 mL/kg per hour (2 L/h in a 70-kg patient) and hemodynamic stability is maintained, ionized Ca^{++} levels are preserved by physiologic compensatory mechanisms.[17] Transient hypocalcemia can be observed during rapid transfusion and can be prolonged or exacerbated by hypothermia or renal or hepatic failure.[15–17] Consequently, ionized calcium should be monitored and calcium replaced when clinically indicated during massive transfusion.

HYPOCALCEMIA IN SEPSIS AND PANCREATITIS

Hypocalcemia is especially common in critically ill patients with systemic infection and pancreatitis.[1,3,6,9,14] Animal models of sepsis demonstrate reductions in serum calcium concentration following endotoxin infusion.[9,14,18,19] When septic patients with hypocalcemia were compared with nonseptic controls, increased tumor necrosis factor and interleukin-6 levels were inversely correlated with ionized Ca^{++}.[20] Septic patients with hypocalcemia can have increased or decreased PTH levels; however, urinary excretion of calcium and bone resorption are preserved when compared with controls.[14,20] Procalcitonin levels appear to be increased during sepsis-induced hypocalcemia, but mature calcitonin exerts only a weak and transient effect on calcium levels.[20,21] The collective results from studies of animal models and patients suggest that the cause of hypocalcemia during severe infection is multifactorial, but the effects of inflammatory cytokines, impaired activation of vitamin D, and elevated procalcitonin levels are all contributory.

It is unclear whether sepsis-induced hypocalcemia is pathologic or protective. Calcium administration in experimental sepsis has been shown to increase or have no effect on mortality.[18,19] Similarly, investigations of the effects of Ca^{++} channel blockade on septic mortality demonstrate conflicting results.[22,23] Therefore, although sepsis-induced hypocalcemia is common in critically ill patients, neither routine replacement of calcium nor the use of calcium channel blockers is supported by the existing literature. As with most situations, sepsis-induced hypocalcemia should be treated if patients are symptomatic.

Pancreatitis represents another inflammatory condition that is associated with hypocalcemia in critically ill patients.[1,3,23–25] Saponification of retroperitoneal fat contributes to the development of hypocalcemia in patients with pancreatitis.[3,23–25] In experimental pancreatitis, injection of free fatty acids into the peritoneum induces hypocalcemia in rats.[23] However, the amount of calcium chelated is relatively small compared with the amount available for exchange from calcium stores in the bone reservoir. Interestingly, elevated levels of PTH seen in pancreatitis, as in sepsis, do not result in normalized ionized calcium levels.[25] Although resistance of bone and kidney to PTH may be a factor, it is likely that inflammatory pathways identical to those in sepsis are responsible. In pancreatitis, as in sepsis, hypocalcemia is an indicator of disease severity. As with most clinical conditions, calcium replacement during pancreatitis should be reserved for symptomatic or hemodynamically unstable patients.

SIGNS AND SYMPTOMS OF HYPOCALCEMIA

Hypocalcemia is frequently asymptomatic, and attributable signs or symptoms may be difficult to elucidate in critically

ill patients. In general, the signs and symptoms of hypocalcemia correlate with both the magnitude of the condition and the rapidity of its onset. Neurologic (paresthesias, seizures, dementia) and cardiovascular (hypotension, impaired cardiac contractility, dysrhythmias) signs can be seen with ionized hypocalcemia when Ca^{++} is less than 1.0 mmol/L.[3,7] Neuromuscular symptoms of hypocalcemia include muscle spasms and tetany, when severe. Psychiatric disturbances (dementia, psychosis, depression) also may be attributable to hypocalcemia.[3,7]

Classic signs of hypocalcemia include Chvostek's and Trousseau's signs, which test for latent tetany. Chvostek's sign is an involuntary twitching of facial muscles in response to light tapping of the facial nerve. It is nonspecific and is present in 10% to 25% of normal adults, and it may be completely absent in chronic hypocalcemia. Trousseau's sign is carpopedal spasm induced by reduced blood flow to the hand when a blood pressure cuff is inflated to 20 mm Hg for 3 minutes. Trousseau's sign is also nonspecific and may be absent in a third of patients with hypocalcemia.

Cardiac dysrhythmias such as ventricular tachycardia, prolonged QT interval, and heart block are more serious complications of hypocalcemia.[3,7] In addition, decreased cardiac output and hypotension, especially when refractory to vasopressors and volume infusion, should prompt calcium replacement when hypocalcemia is present.[3,7]

TREATMENT OF HYPOCALCEMIA

Critical thresholds for calcium replacement vary, but severe ionized hypocalcemia (<0.8 mmol/L) and symptomatic hypocalcemia should be replaced in critically ill patients.[1,3,7,26] Calcium treatment of asymptomatic ionized hypocalcemia (>0.8 mmol/L) is usually unnecessary and may be potentially harmful in conditions such as sepsis and cellular hypoxia.[1,3,7,26]

Treatment of hypocalcemia requires intravenous calcium replacement. The two solutions most commonly used are 10% calcium chloride and 10% calcium gluconate. Each solution contains 100 mg/mL of calcium salt and is available in 10-mL ampules. Ten percent calcium chloride contains 27 mg/mL (1.36 mEq) of elemental calcium; 10% calcium gluconate contains 9 mg/mL (0.46 mEq). Typically, 10 mL of 10% calcium gluconate solution is infused over 10 minutes. A total of 200 mg of elemental calcium may be necessary to raise the total serum calcium by 1 mg/dL. Because the effect of calcium infusion is usually brief, a continuous infusion may be necessary. Calcium chloride should not be infused peripherally if calcium gluconate is available; the former can produce tissue necrosis and thrombophlebitis if extravasation occurs.

Hemodynamically unstable patients in the ICU who are hypocalcemic may show a transient increase in blood pressure or cardiac output with calcium administration. This is probably due to increased cardiac performance.[26] However, in the presence of tissue hypoxia, calcium administration may aggravate the cellular injury.[9,13,22] Nonetheless, calcium administration is probably warranted in hypocalcemic, hemodynamically unstable patients, especially those requiring adrenergic support.

HYPERCALCEMIA

Hypercalcemia is rare in critically ill patients, estimated to occur in 1% to 15% of ICU patients.[2] Defined as an increase in serum calcium above 10.4 mg/dL (2.60 mmol/L), hypercalcemia is usually caused by excessive bone resorption. Hyperparathyroidism and humoral hypercalcemia of malignancy are the most common causes of hypercalcemia in hospitalized patients.[2,7,27] Less common causes of hypercalcemia include sarcoidosis, prolonged immobilization, and medications such as thiazide diuretics.

Mild hypercalcemia is usually asymptomatic. However, patients with circulating Ca^{++} concentrations above 12 mg/dL may manifest symptoms of confusion, delirium, psychosis, and coma.[2,7,27] Patients with hypercalcemia may also experience nausea, vomiting, constipation, abdominal pain, and ileus. Cardiovascular effects of hypercalcemia include hypotension, hypovolemia, and shortened QT interval. Profound skeletal muscle weakness may result. Seizures, however, are rare.

Treatment of hypercalcemia should be directed at the underlying medical condition. Saline infusion and diuresis are indicated in symptomatic patients and when the serum calcium level rises above 14 mg/dL (3.5 mmol/L). For patients with underlying malignancy, treatment with salmon calcitonin, pamidronate, or plicamycin may be necessary. These agents act to inhibit bone resorption. Salmon calcitonin should be started at 4 IU/kg every 12 hours via subcutaneous or intramuscular injection. If the response is inadequate after 2 days, the dose may be increased to 8 IU/kg every 12 hours to a maximum of 8 IU/kg every 6 hours. Hydrocortisone can also be used in combination with calcitonin to treat hypercalcemia associated with multiple myeloma. Dosing of pamidronate depends on the severity of hypercalcemia. For a corrected serum calcium level of 12 to 13.5 mg/dL, pamidronate should be given as a single intravenous dose of 60 to 90 mg over 4 to 24 hours. For higher calcium levels, a single 90-mg dose should be given over 24 hours. Longer infusion times (i.e., >4 hours) may reduce renal toxicity. If necessary, retreatment should be initiated only after 7 days have elapsed, to allow time for a complete response to the initial dose. The dose and manner of treatment are the same as for initial therapy. The recommended dose of plicamycin for hypercalcemia is 25 μg/kg daily for 3 to 4 days. Additional treatments may be given at 1-week intervals. Usual maintenance regimens are two to three doses per week.

Chapter 18
HYPOGLYCEMIA

Greet Van den Berghe

DEFINITION AND DIAGNOSIS

Hypoglycemia is the most common endocrine emergency, the most frequent complication of insulin-requiring diabetes, and the principal factor limiting optimization of glycemic control. When unrecognized and not treated appropriately, significant morbidity, including permanent neurologic deficits and death, may ensue. Hypoglycemia is generally defined arbitrarily as a blood glucose concentration less than 50 mg/dL (2.8 mmol/L) with neuroglycopenic symptoms or less than 40 mg/dL (2.2 mmol/L) in the absence of symptoms. Clinically significant hypoglycemia is characterized by Whipple's triad: (1) symptoms of neuroglycopenia, (2) simultaneous blood glucose concentration less than 40 mg/dL (2.2 mmol/L), and (3) relief of symptoms with the administration of glucose. This blood glucose concentration cutoff corresponds to a plasma glucose concentration of 45 mg/dL (2.5 mmol/L). All three criteria should be met to establish a diagnosis of hypoglycemia, at least outside the intensive care unit (ICU), because a precipitous fall from hyperglycemia to euglycemia in a patient with diabetes can produce hypoglycemic symptoms,[1] and because asymptomatic hypoglycemia with glucose levels as low as 30 mg/dL (1.7 mmol/L) can occur during fasting in normal women and during pregnancy.[2] In the ICU, however, sedation can mask symptoms of neuroglycopenia and counterregulatory responses may be impaired, which complicates the diagnosis of hypoglycemia in this setting. Further, asymptomatic patients can have artifactual hypoglycemia due to in vitro consumption of glucose by blood cells (especially when the blood leukocyte count is very high).

A hypoglycemic disorder should be suspected whenever the blood glucose reading is low. However, most reflectance glucometers in home and hospital use have poor precision at low levels of blood glucose.[3] Caution should be exercised with alternative-site capillary blood glucose testing, which has been demonstrated to have a 30-minute lag time compared with finger-stick testing for the detection of hypoglycemia.[4] The recently developed continuous interstitial glucose monitoring system[5] and the noninvasive Glucowatch Biographer[6] are less effective at detecting low blood glucose levels and can have a delayed response to low blood glucose concentrations. Therefore, the laboratory measurement of a low plasma glucose concentration, in the presence of appropriate symptoms, remains the most reliable way to diagnose severe hypoglycemia. In the ICU, the measurement of arterial blood glucose concentration using modern blood gas analyzers approaches the accuracy of conventional laboratory methods.[7]

INCIDENCE OF SEVERE HYPOGLYCEMIA

Although the frequency of severe hypoglycemia in diabetes is well documented, there is little information on the incidence of serious hypoglycemia in nondiabetic subjects or in the general population. A retrospective study of adults requiring hospitalization indicated that 0.4% of acute medical admissions per year are hypoglycemia related.[8] In a prospective study of 130 hospital admissions due to adverse drug reactions, hypoglycemia was the fourth most common disorder.[9] A review of 54,850 autopsies in a large medical center revealed 123 deaths (0.2%) due to hypoglycemic coma.[10] Because of the difficulty of postmortem diagnosis and frequent associated comorbidities, severe hypoglycemia is often unrecognized, particularly in nondiabetic individuals.

Severe hypoglycemia occurs commonly in patients with diabetes, even if the stringent definition of the Diabetes Control and Complications Trial is employed (i.e., symptoms severe enough to require assistance for treatment). Hypoglycemia occurs at least once a year in up to 30% of patients with type 1 diabetes.[11] In type 2 diabetes, even with intensive therapy, the risk is probably 100-fold less. Over 6 years of observation in the United Kingdom Prospective Diabetes Study, severe hypoglycemia was reported in 2.4% of patients treated with metformin, 3.3% of those treated with a sulfonylurea, and 11.2% of those treated with insulin.[12] However, when matched for duration of insulin therapy and circulating levels of HbA_{1c}, the frequency of severe hypoglycemia was similar in type 1 and type 2 diabetes.[13] As insulin usage among patients with type 2 diabetes increases, it is inevitable that severe hypoglycemia will become more common in daily practice.

With the introduction of tight blood glucose control in the surgical ICU, the incidence of blood glucose values below 40 mg/dL (2.2 mmol/L) has been reported to range from 0.8% to 5.2% of patients, depending on the targeted level of blood glucose control.[7] With the use of algorithms advising frequent blood glucose measurements (i.e., every 1 to 4 hours), brief episodes of such low blood glucose levels do not impose a major risk of sequelae.

PATHOPHYSIOLOGY

The central nervous system relies primarily on glucose for the generation of cellular energy. Cells in the central nervous system have endogenous glucose reserves that are sufficient for only minutes if the supply of glucose from the bloodstream is inadequate. In addition, neurons are unable to synthesize glucose. Finally, the brain cannot use fuels other

than glucose during acute hypoglycemia.[14] Hence, when the brain is acutely deprived of glucose, serious neurologic dysfunction occurs. Therefore, the body has several mechanisms to maintain the plasma glucose concentration within the narrow range of 60 to 140 mg/dL (3.3 to 7.7 mmol/L) in both the fed and fasting states. When glucose use exceeds glucose production, the brain senses decreasing glucose levels and activates counterregulatory pathways. The glucose threshold for activation of these mechanisms is approximately 67 mg/dL (3.6 mmol/L), but this setpoint can be altered by recent hyperglycemia or antecedent hypoglycemia. The important components of the endocrine defense against hypoglycemia were identified in the 1980s.[15] As glucose levels decline, the first counterregulatory mechanism is the suppression of endogenous insulin secretion. Next in the hierarchy of responses is the release of two hormones, glucagon and epinephrine, that antagonize the action of insulin. These hormones activate glycogenolysis and gluconeogenesis and stimulate fatty acid oxidation and protein breakdown to provide substrates for gluconeogenesis. With more severe or prolonged hypoglycemia (>3 hours), increases in growth hormone and cortisol release raise the blood glucose level.

The physiologic responses to hypoglycemia and the glucose threshold at which they occur can be modulated in normal and diabetic humans. In type 1 diabetes, the glucagon response to hypoglycemia is lost within 3 years after diagnosis, rendering patients dependent on epinephrine-mediated counterregulation and making them more vulnerable to prolonged episodes of severe hypoglycemia. Exposure to antecedent hypoglycemia diminishes the counterregulatory response to a subsequent episode. The brain adapts to antecedent hypoglycemia by increasing glucose uptake so that a more profound hypoglycemic stimulus is required to trigger sympathoadrenal activation and autonomic symptoms.[16] Also, the level of glycemic control affects counterregulatory thresholds. With strict glycemic control, epinephrine release is not triggered until a lower glucose level is reached.[17,18] Conversely, diabetic patients with poor glycemic control can experience hypoglycemic symptoms when the blood glucose concentration decreases to lower values within the normal or even hyperglycemic range.[19]

There are four pathophysiologic mechanisms capable of exceeding the body's counterregulatory capacity and causing severe hypoglycemia: (1) excessive insulin effect, (2) diffuse hepatic dysfunction, (3) limited substrate for gluconeogenesis, and, rarely, (4) excessive glucose consumption. More than one mechanism can be operative in critically ill patients.

DIFFERENTIAL DIAGNOSIS

Hypoglycemia is commonly classified as (1) drug or toxin induced, (2) fasting induced, or (3) postprandial. An alternative clinical classification of hypoglycemic disorders separates patients who appear healthy (with or without coexistent disease) from those who appear ill (including those with a predisposing illness and those who are hospitalized). For otherwise healthy patients, the most important causes of fasting hypoglycemia are accidental or factitious drug ingestion and insulinoma. The differential diagnosis in ill or hospitalized patients includes predisposing illness, drug interactions, and other iatrogenic factors (Table 18–1).[20]

Insulin treatment of diabetes is the most common cause of hypoglycemia in adults. Risk factors for frequent severe hypoglycemia in type 1 diabetes include lower HbA_{1C} levels, higher daily insulin dose, longer duration of diabetes, absence of residual C peptide, and a prior history of severe hypoglycemia.[11] Hypoglycemia unawareness is the loss of autonomic warning symptoms of developing hypoglycemia. It affects approximately 25% of subjects with type 1 diabetes and is an important predictor of severe hypoglycemia. Insulin-treated type 2 diabetics are also vulnerable to severe hypoglycemia, especially if their disease is well controlled and they have been on insulin for many years.[13] Whether intensive insulin therapy increases the incidence of severe hypoglycemia is controversial.[21-23] Switching from animal to human insulin does not result in an increased incidence of severe hypoglycemia,[24] and newer insulin analogs, such as glargine and lispro, as well as continuous delivery systems, may lessen the risk of fasting or postprandial severe hypoglycemia.[25-27]

Sulfonylureas are a common cause of severe hypoglycemia.[28] The incidence is higher in the elderly and with the use of long-acting agents, such as chlorpropamide and glyburide (glibenclamide),[29] although the latter remains controversial.[19] Liver dysfunction prolongs the hypoglycemic

TABLE 18–1. DIFFERENTIAL DIAGNOSIS OF HYPOGLYCEMIA

	Increased Insulin Effect	Hepatic Dysfunction	Decreased Substrate	Increased Glucose Consumption
Drug/toxin	Insulin overdose Sulfonylureas Rodenticide Vacor Pentamidine Quinine Angiotensin-converting enzyme inhibitors	Ethanol Nonselective beta blockers	Chronic renal insufficiency	Exercise
Fasting	Insulinoma Autoimmune disease Insulin-like growth factor-II–secreting tumor	Congestive heart failure Septic shock Combined endocrine deficiencies	Uremia Severe wasting	Large tumors Prolonged exercise
Postprandial	Upper gastrointestinal surgery (e.g., Bilroth II) Ethanol Noninsulinoma Pancreatogenous hypoglycemia	Unripe akee fruit (*Blighia sapida*) (hypoglycin)		

activity of tolbutamide, acetohexamide, glyburide, and glipizide. Renal insufficiency especially prolongs the activity of chlorpropamide and glyburide. A crude rate of serious hypoglycemia of 1.23 per 100 person-years has been reported in elderly users of sulfonylureas.[30] Sulfonylurea-induced hypoglycemia can be prolonged (up to 27 days), with recurrences after initial normalization of glucose levels.[31] Discovery of inadvertent or factitious sulfonylurea overdose may avoid an exhaustive search for insulinoma in patients presenting with hyperinsulinemic hypoglycemia.[32]

The metabolism of ethanol depletes hepatocellular levels of nicotinamide-adenine dinucleotide, which is a cofactor critical for the entry of substrates into gluconeogenesis pathways.[33] Ethanol also inhibits cortisol and growth hormone responses and delays the epinephrine response to hypoglycemia.[34] However, ethanol does not inhibit glycogenolysis. Therefore, ethanol-induced hypoglycemia does not occur until hepatic glycogen stores have been depleted (after 8 to 12 hours of fasting).[35] There is no correlation between blood ethanol levels (although alcohol is usually detected) and the degree of hypoglycemia, and severe hypoglycemia can occur with ethanol levels as low as 45 mg/dL. The incidence of alcohol-induced hypoglycemia is generally less than 1% in adults, but hypoglycemic coma is commonly related to ethanol ingestion.[36]

In the absence of a drug or toxic cause, adults with severe fasting hypoglycemia should be evaluated for insulinoma, insulin-secreting tumor of the islets of Langerhans,[37] or unusual causes, such as excessive production of insulin-like growth factor II or rapid glucose consumption by tumors, diffuse hepatic dysfunction, septic shock, panhypopituitarism, polyglandular endocrine deficiency syndromes, and autoimmune hypoglycemia. The diagnosis of postprandial (reactive) hypoglycemia remains controversial.[38]

CLINICAL PRESENTATION

The symptoms of hypoglycemia can be divided into autonomic and neuroglycopenic. Autonomic symptoms such as sweating, palpitations, tremor, and hunger are due to the effects of increased activation of the sympathetic nervous system in response to blood glucose levels of approximately 55 mg/dL (3.7 mmol/L). Elderly patients report fewer autonomic symptoms.[39] Neuroglycopenic symptoms are due to impairment of cerebral functioning and include confusion, odd behavior, drowsiness, difficulty with speech, blurred vision, hemiplegia (Todd's palsy), seizure, and coma. Neuroglycopenic symptoms occur at blood glucose levels of approximately 45 mg/dL (2.5 mmol/L). Symptoms of hypoglycemia appear to be similar in type 1 and type 2 diabetes[13] and whether they are induced by sulfonylureas, insulin, or its analogs.[24,40,41]

Patients with hypoglycemia unawareness have a sevenfold increased risk of severe hypoglycemia, and episodes of hypoglycemia in these patients can be recurrent and unpredictable.[42] Likely pathogenic mechanisms for hypoglycemia unawareness include recurrent exposure to hypoglycemia, with subsequent increases in brain glucose uptake and possibly reduced beta-adrenergic sensitivity.[43,44] Fortunately, scrupulous avoidance of hypoglycemia for a period of weeks to months restores hypoglycemia awareness.[45,46] Surgical removal of an insulinoma also restores autonomic symptoms of hypoglycemia.[47]

EVALUATION

The first step in the evaluation of a patient with suspected hypoglycemia is documentation of low plasma glucose concentration in the presence of neuroglycopenic symptoms (Fig. 18–1). Unless there is an obvious medication-related cause for severe hypoglycemia, blood should be drawn for the measurement of glucose, insulin, and C peptide before the administration of glucose and, when indicated, for the diagnosis of thyroid hormone and cortisol deficiency or uremia. In cases of fasting hypoglycemia, intentional, accidental, or surreptitious ingestion of glucose-lowering medications should be investigated to avoid the lengthy workup for insulinoma.[37] Sulfonylurea ingestion causes elevated insulin and C peptide levels, which mimics the findings associated with an insulinoma. Confirmation of the diagnosis of sulfonylurea ingestion can be made using high-pressure liquid chromatography or radioimmunoassay to detect sulfonylureas in blood or urine. The results of these tests are extremely important for further management.

MANAGEMENT

In all cases of suspected severe hypoglycemia, a patent airway and hemodynamic stability should be secured while a rapid bedside estimation of blood glucose is performed. In cases of suspected overdose, emesis should not be induced in a hypoglycemic patient. When alcohol abuse is suspected, thiamine (100 mg i.v. or i.m. per day until the patient is consuming a complete diet) should be given to avoid acute Wernicke's encephalopathy. Administration of glucose is the fundamental remedy. In an awake patient with a protected airway, an initial dose of 20 g of glucose orally works. Examples of oral carbohydrates suitable for the correction of hypoglycemia are flavored glucose tablets and juices and sodas high in sugar content. A response should occur within 10 to 15 minutes and typically lasts 1 to 2 hours. Hence, a snack is advisable to avoid recurrent hypoglycemia.

When patients are unwilling or unable to take oral carbohydrates, intravenous dextrose (glucose) should be given. The recommended initial dose of 50 mL of 50% dextrose provides 25 g dextrose and, within 5 minutes, produces a mean rise in blood glucose to 220 mg/dL (12.5 mmol/L) from nadir values as low as 20 mg/dL (1.1 mmol/L).[48] In ICU patients receiving insulin by continuous intravenous infusion and also receiving a baseline enteral or intravenous glucose load, an additional 10-g glucose bolus is usually sufficient to correct hypoglycemia, and the smaller glucose load avoids the need to greatly modify the insulin dosing regimen.[7,49] For prolonged hypoglycemia (e.g., caused by sulfonylurea overdose), prolonged dextrose infusion plus octreotide may be required.[50]

Parenteral glucagon directly stimulates hepatic glycogenolysis. Glucagon is effective in restoring consciousness if given soon after the onset of hypoglycemic coma. Glucagon is particularly effective in pancreatectomized patients but is much less useful in type 2 diabetes because it stimulates insulin secretion as well as glycogenolysis. Patients with depleted glycogen stores, such as those with alcohol-induced hypoglycemia, may not respond to glucagon. Adverse reactions to glucagon administration include nausea and vomiting, delaying carbohydrate ingestion.

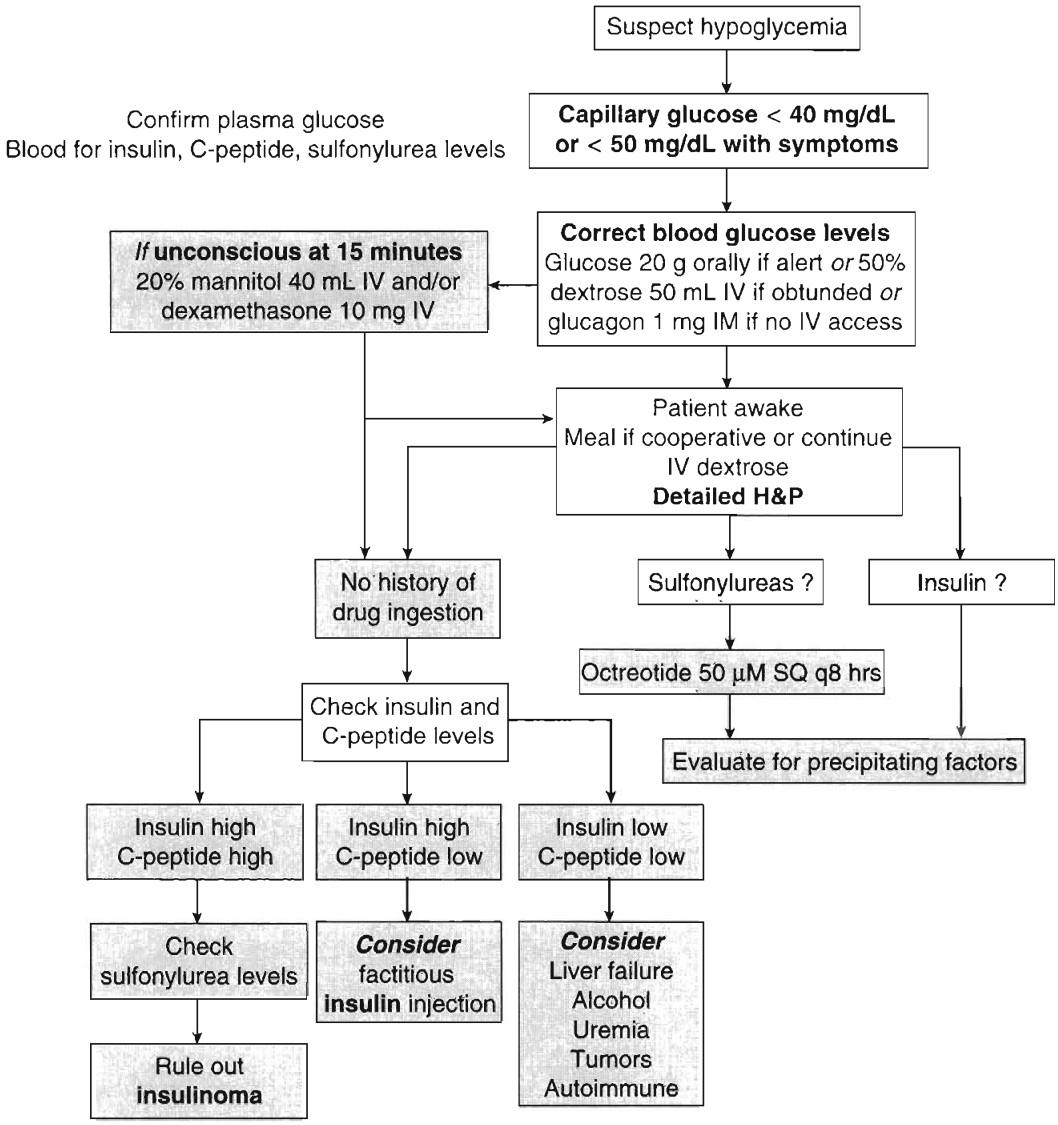

FIGURE 18–1. Approach to severe hypoglycemia in adults. H & P, history and physical examination

In cases of sulfonylurea overdose, octreotide is more effective than diazoxide for reversing hyperinsulinemia, reducing dextrose requirements, and preventing recurrent hypoglycemia.[50] The recommended dose of octreotide as an antidote for sulfonylurea overdose is 50 µg subcutaneously, repeated every 8 hours if necessary. Activated charcoal binds sulfonylureas and can be administered in cases of suspected overdose.

Cerebral edema can complicate severe hypoglycemia and should be suspected when unconsciousness lasts more than 30 minutes following normalization of blood glucose. Treatment with intravenous mannitol (40 mL of a 20% solution) and glucocorticoids (10 mg of dexamethasone) in addition to intravenous dextrose is advised.

SEQUELAE

Although severe hypoglycemia induces marked cognitive dysfunction,[51] most patients recover rapidly and completely.[52] The effect of repeated severe hypoglycemia on cognitive function in adults is controversial.[53,54] Although focal neurologic symptoms secondary to severe hypoglycemia occur occasionally, severe and permanent cognitive impairment is usually the result of protracted hypoglycemia, often in association with excess alcohol consumption.

The overall mortality from severe hypoglycemia is unknown. The mortality rate from alcohol-induced hypoglycemia may be as high as 10% in adults.[36] An estimated 2% to 4% of deaths in patients with type 1 diabetes have been attributed to hypoglycemia. Severe hypoglycemia is the cause of unexpected overnight death in young diabetic patients,[55] which is explained by the impairment of hormonal responses to hypoglycemia during sleep in normal and diabetic patients.[47,56]

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the counterregulatory hormonal responses; this, in turn, evokes unawareness of hypoglycemia.

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This paper reports on the incidence of hypoglycemia in a multicenter, randomized, controlled clinical trial (N = 1441) of intensive versus conventional diabetes therapy, with an average follow-up of 6.5 years.

Jones TW, Porter P, Sherwin RS, et al: Decreased epinephrine responses to hypoglycemia during sleep. N Engl J Med 1998;338:1657-1662.

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Marks V, Teale JD: Drug-induced hypoglycemia. Endocrinol Metab Clin North Am 1999;28:555-577.

Therapeutically administered antidiabetic drugs—notably, insulin and sulfonylureas—are the most common causes of hypoglycemia in clinical practice. Nevertheless, an impressive list of other drugs can produce hypoglycemia, as discussed in this review paper.

Wang PH, Lau J, Chalmers TC: Meta-analysis of effects of intensive blood-glucose control on late complications of type 1 diabetes. Lancet 1993;341:1306-1309.

This paper reports the results of a meta-analysis of 16 randomized trials of intensive therapy to estimate its impact on the progression of diabetic retinopathy and nephropathy and the risk of severe hypoglycemia.

Chapter 19
ANEMIA OF CRITICAL ILLNESS

Ali Hallal • Carl Schulman • Stephen Cohn

Anemia is a common clinical problem in the ICU. In the United States, 12.4 million units of blood were transfused into 4.5 million patients in 1999, with about 25% given to the critically ill.[1] Approximately 85% of patients spending more than 1 week in the ICU receive 1 or more units of packed red blood cells (RBCs) in their first week and continue to require 2 to 3 units of blood per week thereafter.[2] A recent multicenter European study showed that 37% of patients in the ICU are transfused.[3] Similarly, a multicenter observational study in the United States evaluated 4992 patients from 284 different ICUs and found that 44% of patients received at least one transfusion during their ICU stay.[4]

Blood is an increasingly scarce resource. The National Blood Data Resource Center suggests that the need for blood transfusion in the United States will exceed its availability in the near future. Patients have historically been transfused at a hemoglobin (Hb) threshold of 10 g/dL. Over the last decade, several studies have shown that packed RBC transfusion is independently associated with worse clinical outcomes, independent of the degree of anemia or the severity of illness. The scarcity of blood and the considerable economic impact of blood transfusion (about $500 per unit) have prompted new approaches for the management of anemia in the ICU.

There are three major classes of anemia: (1) hypoproliferative anemia secondary to marrow production defects, (2) ineffective erythropoiesis caused by red cell maturation defects, and (3) decreased survival of red cells secondary to blood loss, hemolysis, or both (Fig. 19-1). The majority of anemia cases (75%) are hypoproliferative. The pathogenesis of this type of anemia is explained by a form of marrow dysfunction characterized by inadequate erythropoiesis in response to the degree of anemia. Most cases of anemia encountered in critically ill patients are of the hypoproliferative type, although other causes may play a role.

BASIC LABORATORY PARAMETERS

The complete laboratory evaluation of anemia is beyond the scope of this chapter; only the pertinent iron studies that aid in understanding the pathogenesis of anemia of the critically ill are discussed. Of these, the most important laboratory tests are measurements of serum iron concentration, serum transferrin and transferrin receptor protein concentrations, total iron binding capacity, and serum ferritin concentration.

Iron absorbed from food or released from stores circulates in plasma bound to transferrin, the iron transport protein. The iron-transferrin complex interacts with a specific transferrin receptor protein on the surface of early erythroid cells. Subsequently, the complex is internalized, and iron is released intracellularly. Within erythroid cells, iron in excess of the amount needed for hemoglobin synthesis binds to the storage protein apoferritin, forming ferritin. Iron in the ferritin pool can be released and reused in the iron metabolism pathway. The serum ferritin level correlates with the total body iron stores and, therefore, is the most suitable laboratory estimate of iron stores.[5] During the maturation of reticulocytes to erythrocytes, the cells lose all activities of the components of the hemoglobin-synthesizing system, including transferrin receptor proteins, which are released into the circulation.[6] The level of transferrin receptor protein in the circulation provides a quantitative measure of total erythropoiesis and can be used to measure the expansion of the erythroid marrow in response to recombinant erythropoietin therapy. The serum iron level represents the amount of circulating iron bound to transferrin. The total iron binding capacity is an indirect measure of the circulating transferrin. Once the iron binding capacity of transferrin is exceeded, the expression of transferrin receptor protein decreases, limiting further access of iron into the cells. The normal range for serum iron is 50 to 150 μg/dL; the normal range for total iron binding capacity is 300 to 360 μg/dL, and transferrin saturation is normally 25% to 50%. Iron deficiency states are associated with a transferrin saturation of less than 18%. The normal values of ferritin vary with age and gender. Adult men have ferritin levels averaging approximately 100 μg/dL, whereas adult women have levels around 30 μg/dL. Normal values for transferrin receptor protein concentration are 4 to 9 μg/L.[5] Because the anemia of critical illness is caused by impaired iron release and a blunted response to erythropoietin, the laboratory findings in this syndrome are characterized by a low serum iron concentration, low total iron binding capacity and transferrin saturation, normal transferrin receptor protein level, and normal to high ferritin level.

CAUSE AND PATHOGENESIS

Anemia in critically ill patients is the result of multiple factors, including (1) blood loss secondary to phlebotomy, gastrointestinal bleeding, coagulation disorders, or surgical procedures; (2) bone marrow depression secondary to renal failure or chronic diseases; (3) nutritional deficiencies; and (4) immunologically mediated iron deficiency in combination with a blunted response to erythropoietin.

Blood loss due to phlebotomy is an often unrecognized yet significant cause of anemia in the ICU. A recent study

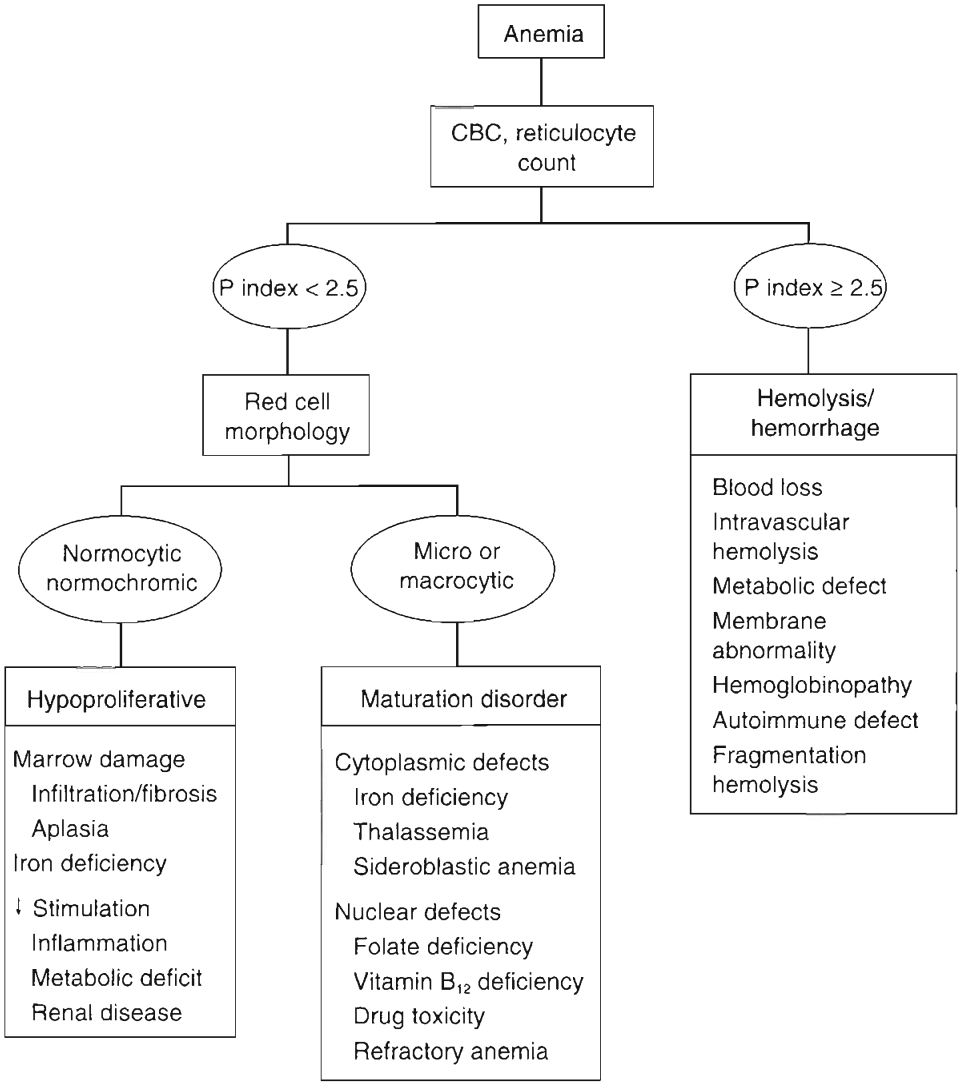

FIGURE 19–1. Physiologic classification of anemia. The reticulocyte production index (P index) is a correction of the reticulocyte count based on the level of anemia and the circulatory life span of a prematurely released reticulocyte. CBC, complete blood count. (From Adams JW, Longo DL: Anemia and polycythemia. In Braunwald E, Fauci AS, Kasper DL, et al: Harrison's Principles of Internal Medicine, 15th ed. New York, McGraw-Hill, 2001, p 352.)

showed that patients admitted to the ICU are phlebotomized an average of 4.6 times a day, for an average total volume of 41.1 mL.[3] Patients with arterial catheters have blood drawn four times a day, for a mean of 944 mL over the course of an ICU stay.[7] Approximately half of patients are transfused as a direct result of excessive phlebotomy.[2]

Although rare since the advent of effective gastrointestinal prophylaxis, gastrointestinal bleeding can be a serious problem in the ICU. The overwhelming majority of critically ill patients demonstrate evidence of mucosal damage within the first 24 hours of their admission to the ICU. Overt anemia occurs in 5% of patients with stress-related gastrointestinal bleeding. Clinically important bleeding necessitating transfusion is observed in only 1% to 4% of critically ill patients.[8] Stress gastritis occurs predominantly in critically ill patients on mechanical ventilation and those with coagulopathy.[9]

Anemia of critical illness is a distinct multifactorial entity, although it is similar in many respects to the anemia of chronic disease. Inflammation appears to be a major factor, causing an alteration in the metabolism of intracellular iron. In addition, these patients have a blunted response to erythropoietin, which leads to a decrease in RBC production.[10,11] In anemia related to critical illness, there is also a decrease in iron availability, secondary to a decrease in both iron reutilization and iron absorption.[12,13]

When iron availability is reduced, critically ill patients who are anemic fail to respond with an appropriate increase in circulating erythropoietin levels. In addition, their reticulocytes are unable to respond suitably to endogenous erythropoietin.[10] Erythropoietin is a glycoprotein with a molecular weight of approximately 34,000 daltons; it is produced mainly in the kidney and, to a lesser extent, in the liver. The primary role of erythropoietin is to regulate RBC production. It also is required for the survival and differentiation of erythroid progenitors in the bone marrow, but it is not responsible for the commitment of stem cells to the erythroid lineage.[14] Erythropoietin production is regulated by hypoxia, which leads to an increase in its gene transcription; it then exerts its action in the bone marrow by stimulating the expression of erythroid colony-forming units that become mature erythrocytes. As tissue oxygenation improves, receptors in the kidney act to down-regulate the production of erythropoietin through a negative feedback mechanism.

The erythropoietin response observed in critically ill patients appears to result from inhibition of the erythropoietin gene by inflammatory mediators. Interleukin-1 beta and

tumor necrosis factor are known to suppress gene expression and erythropoietin production in isolated, perfused rat kidneys and in human hepatoma cell cultures.[15] Interleukin-6 is also an inhibitor of erythropoietin production in the kidney.[15]

The clinical data demonstrate that critically ill patients fail to produce the appropriate amount of endogenous erythropoietin in response to anemia and also have a markedly blunted response to exogenously administered erythropoietin. Rogiers and coworkers compared erythropoietin concentrations in critically ill patients and in those with iron deficiency anemia.[16] Serum erythropoietin concentrations were serially determined by enzyme-linked immunosorbent assay in 36 critically ill, nonhypoxemic patients who stayed more than 7 days in the ICU. Eighteen ambulatory patients with iron deficiency anemia served as the control group. Although erythropoietin concentrations in the critically ill patients were somewhat greater than those in adults without anemia, they were significantly lower than those measured in the control group at similar hematocrits. Whether the critically ill patient is a trauma victim[17] or a surgical, medical,[18] or pediatric patient,[19] the anemia encountered in the ICU appears to be the result of both a blunted response to erythropoietin and abnormalities in iron metabolism (Fig. 19-2). The cascade of events contributing to anemia in the critically ill is summarized in Figure 19-3.

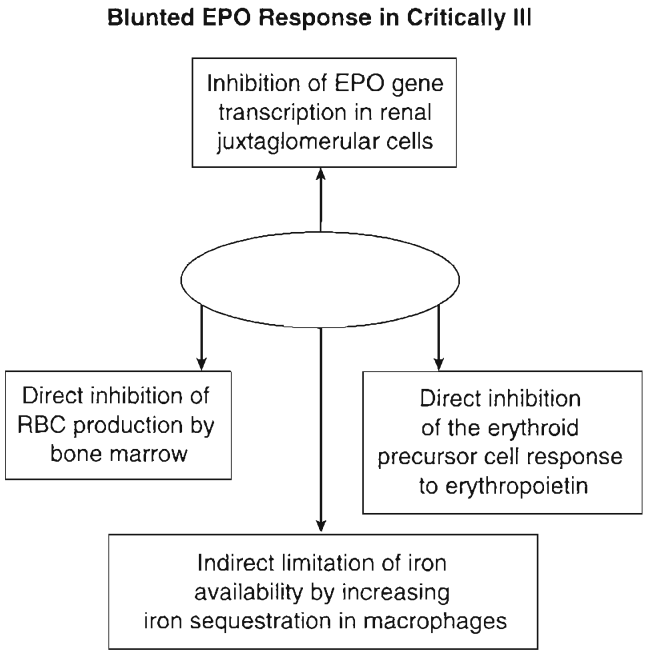

FIGURE 19–2. The inflammatory response that occurs early in injury is related to the release of proinflammatory mediators. This leads to the inhibition of erythropoietin (EPO) gene transcription in the renal juxtaglomerular cells. The inflammatory response has a direct inhibitory effect on red blood cell (RBC) production in the bone marrow and also inhibits the erythroid precursor cell response to erythropoietin. The availability of iron is limited due to decreased iron absorption and increased iron sequestration. IFN, interferon; IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor. (Adapted from Advancement in Critical Care Education (ACCE): Managing Anemia in the Surgical Patient. Princeton, NJ, DesignWrite, 2003, p 28, fig 1.)

MANAGEMENT

BLOOD TRANSFUSION

Blood transfusion is the standard management of anemia in the critically ill. Among the issues being reevaluated are the identification of patients who might benefit from conservative treatment of anemia and the threshold for transfusion at which the benefits outweigh the risks. These risks include infectious disease transmission, immune-mediated reactions (acute or delayed hemolytic reactions, febrile allergic reactions, anaphylaxis, and graft-versus-host disease), and non–immune-related complications (fluid overload, hypothermia, electrolyte toxicity, and iron overload).

Current estimates of the risk of infection per unit of blood are approximately 1 in 2 million for human immunodeficiency virus, 1 in 1 million for hepatitis C virus, and 1 in 100,000 for hepatitis B virus.[20] The most common transfusion-related infections are secondary to bacterial contamination, which occurs 12.6 times per 1 million units of allogeneic blood components transfused.[21] The risk of bacterial contamination is higher for packed cells than for whole blood. With RBC transfusion, gram-positive cocci (staphylococcal and streptococcal species) represent 58% of cases, gram-negative bacteria (*Yersinia enterocolitica*) represent 32%, and other bacteria represent 10%. In one study, 26.5% of cases of infection (49 of 185) were considered a serious threat, and 9.7% (18 of 185) had a fatal outcome. Overall, bacterial contamination accounted for 22% of all transfusion-related deaths.[21]

The incidence of major ABO mismatching is estimated at 1 in 138,673 RBC units.[21] Surprisingly, there is no significant difference in the incidence of major ABO mismatching between patients receiving allogeneic and autologous transfusion. The incidence of ABO mismatch-related death is around 1 per 2 million units transfused.[21] Despite advances in the understanding of red cell antigens, fatal acute hemolytic reactions still occur in 1 of every 250,000 to 1 million transfusions.[22]

Half of all deaths from acute hemolytic reactions are caused by ABO incompatibility. One in 1000 patients

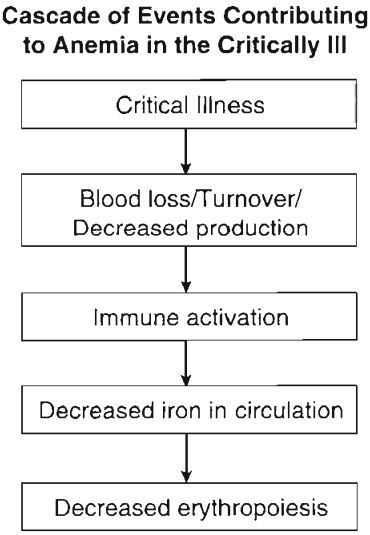

FIGURE 19–3. Summary of the cascade of events leading to anemia in the critically ill. (Adapted from Advancement in Critical Care Education (ACCE): Managing Anemia in the Surgical Patient. Princeton, NJ, DesignWrite, 2003, p 7, fig 1.)

demonstrates clinical manifestations of a delayed hemolytic transfusion reaction.[22] Hemolytic transfusion reaction occurs as a result of antigens that are not routinely detected by antibody assays before transfusion.

Transfusion-related acute lung injury is a serious complication with clinical symptoms similar to those of acute respiratory distress syndrome.[23] It is estimated that transfusion-related acute lung injury occurs in 1 of 5000 transfusions and has a mortality rate of 5% to 10%.[23] The pathogenesis of transfusion-related acute lung injury is still not well understood, but a two-hit hypothesis has been advanced to explain why some blood transfusion recipients develop the condition and others do not. The first hit is thought to be the priming of neutrophils, and the second hit is postulated to involve the transfusion of a lipid cytokine or an antibody that activates the primed neutrophils, leading to an inflammatory process.[23] Unfortunately, treatment is currently limited to supportive measures.

Transfused blood appears to be an immunosuppressive agent. Numerous clinical studies have examined the association of perioperative allogeneic blood transfusion with either cancer recurrence or postoperative bacterial infection,[24-32] as well as organ dysfunction. Clinical evidence of transfusion-associated immunomodulation was initially suggested by Opelz and colleagues in 1973, when improved renal allograft survival was demonstrated in patients transfused before transplantation.[25] Although several theories have been postulated to explain transfusion-associated immunomodulation, both animal and human data suggest that it is most likely secondary to the effect of transfused white blood cells (WBCs).

Seven randomized, controlled trials designed to investigate the impact of allogeneic blood transfusion on the incidence of postoperative infection have yielded contradictory findings.[26-32] Van de Watering and colleagues looked at the effect of leukocyte-depleted versus buffy coat–reduced blood transfusion in cardiac surgery patients.[29] Their study detected an association between WBC-containing allogeneic blood transfusion and postoperative mortality from causes other than postoperative infection. Multivariate regression analysis showed that the number of RBC units transfused was the most significant predictor of postoperative mortality. Patients who received leukocyte-depleted blood transfusion had a significantly reduced mortality. Jensen and colleagues, studying patients undergoing colorectal surgery, observed a 71% reduction in the incidence of postoperative infection in recipients of poststorage leukocyte-depleted transfusions.[28] Houbiers and colleagues, in a similar study, found no difference in the incidence of postoperative infection between the two groups.[31] The existing data from the various studies, although not compelling, justify a high degree of suspicion that an adverse transfusion-associated immunomodulation effect does exist. Because the evidence implicates allogeneic WBCs in the production of transfusion-associated immunomodulation, several western European countries and Canada have instituted the universal reduction of WBCs in all transfused blood components. Appropriately designed clinical studies are still needed to confirm the benefit of leukocyte-depleted blood transfusions.

Vamvakas and Carven reported that patients who received allogeneic transfusions perioperatively had significantly longer hospital stays.[33] These observations concur with the data collected by Taylor and coworkers, who reviewed the relationship between transfusion and infections in a medical-surgical-trauma ICU.[34] The nosocomial infection rate for the entire cohort was 6%. The nosocomial infection rates for the transfusion and nontransfusion groups were 15% and 3%, respectively ($P < 0.005$). The chance of infection increased 1.5-fold with each unit of packed RBCs transfused. After adjusting for age and the probability of survival, nosocomial infection still occurred at a consistently higher rate in patients who were transfused. Certainly, the fact that patients requiring transfusion are likely more ill remains a confounding factor in these studies.

TRANSFUSION OF THE CRITICALLY ILL

The overuse of transfusion is a significant problem. In 1995 Corwin and colleagues reported that 40% of transfusion events in the ICU had no clinical indication.[2] More recently, a large multicenter U.S. trial showed that patients who were transfused did not differ significantly with respect to their mean pretransfusion hemoglobin, admitting diagnosis, or indication for transfusion.[3] Thus, it appears that the hemoglobin value is still the major determinant in the decision to transfuse. Several questions need to be answered when we consider transfusing critically ill anemic patients: (1) Is a low hematocrit harmful to the critically ill patient? (2) What is the lowest tolerable hemoglobin concentration? (3) Will RBC transfusion benefit the anemic critically ill patient?[35]

A reasonable indication for the transfusion of RBCs is to augment the oxygen carrying capacity of the blood. Unfortunately, there is a lack of data defining the hemoglobin concentration in humans that hinders adequate oxygen delivery and initiates tissue hypoxia.[36] Studies in animals and humans show that the oxygen extraction ratio (O_2 consumption/O_2 delivery) progressively increases as a compensatory response to hemodilution. However, isovolemic hemodilution to a hemoglobin concentration of 5 g/dL in resting humans does not produce evidence of inadequate systemic oxygen delivery or adverse clinical effects.[36] This finding is consistent with data obtained by studying anemic patients who refuse transfusion.[37] Recently a Canadian trial demonstrated that a restrictive transfusion strategy (transfusion trigger: hemoglobin concentration of 7 to 9 g/dL) was at least equivalent if not superior to a liberal transfusion strategy (transfusion trigger: hemoglobin concentration of 10 to 12 g/dL).[38]

The optimal hemoglobin concentration in critical illness is unknown. Nelson and colleagues observed that postoperative anemia of less than 28% is associated with a significant increase in myocardial ischemia and morbid cardiac events among high-risk patients undergoing infrainguinal arterial bypass procedures.[39] Fang and colleagues reported that the lowest hematocrit during cardiopulmonary bypass (<14% for low-risk patients and <17% for high-risk patients) was an independent risk factor for mortality among patients undergoing coronary artery bypass grafting.[40] Similarly, Carson and colleagues studied the effect of anemia in Jehovah's Witnesses undergoing surgery.[41] They demonstrated that a low preoperative hemoglobin or a substantial operative blood loss was associated with an increase in the risk of death or serious morbidity only in patients with cardiovascular disease. Gould and colleagues investigated the impact of anemia on surgical mortality in a historical control group who refused blood for religious reasons.[42] Their study showed a rise in mortality in perioperative

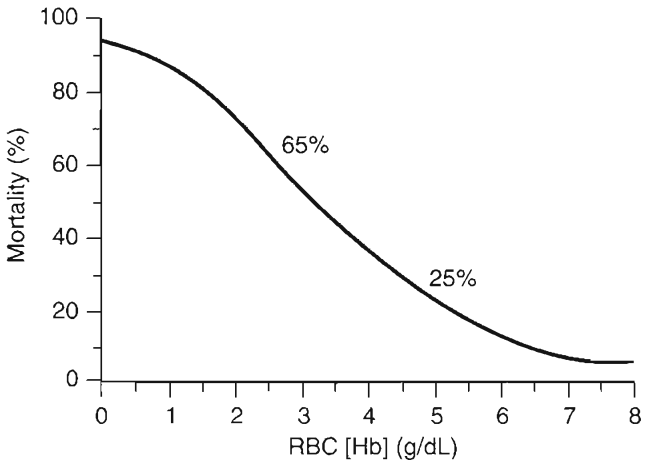

FIGURE 19–4. Mortality and hemoglobin levels in historical controls who refused blood for religious reasons. Note the sharp rise in mortality at hemoglobin levels less than 5 g/dL. RBC, red blood cell. (Adapted from Gould SA, Moore EE, Hoyt DB, et al: The life-sustaining capacity of human polymerized hemoglobin when red cells might be unavailable. J Am Coll Surg 2002;195:445-452, fig 4.)

patients as the hemoglobin level decreased below 5 g/dL (Fig. 19-4). The treatment of anemia in elderly patients (older than 65 years) is not as well defined as in other populations. Wu and colleagues demonstrated that blood transfusion is associated with a lower short-term mortality rate in elderly patients with acute myocardial infarction and a hematocrit less than 30.[43] Clearly, transfusion practices must be individualized to consider all disease processes and existing comorbidities.

Typically, blood is administered to improve oxygen delivery to the tissues. Although blood transfusion might acutely increase oxygen delivery, a matching improvement in tissue oxygen consumption is not necessarily seen, particularly in sepsis. For example, Dietrich and coworkers demonstrated that increasing oxygen carrying capacity with blood transfusion did not improve tissue oxygenation or decrease lactate levels in patients with shock.[44] The same conclusion was reached by Silverman and colleagues in a study evaluating the efficacy of dobutamine or packed RBC transfusion on splanchnic tissue oxygen utilization.[45] Indeed, blood transfusion may have an unfavorable impact on oxygen delivery in sepsis. Fitzgerald and coworkers concluded that storing rat RBCs for 28 days impairs their ability to improve tissue oxygenation when transfused into either control or septic rats.[46] This contrasted with an observation that transfusion of fresh blood acutely increases systemic oxygen uptake in this animal model. Marik and Sibbald showed that old blood (>15 days) transfused into septic patients was accompanied by splanchnic ischemia, as shown by gastric tonometry.[47] It is known that during storage, the concentration of 2,3-diphosphoglycerate (2,3-DPG) in RBCs progressively decreases. In addition, the adenosine triphosphate content of stored RBCs decreases, and the cells become less deformable. The microcirculation in septic patients is not normal, and old, poorly deformable RBCs may become entrapped in capillaries, promoting the development of tissue ischemia. Martin and colleagues observed a statistically significant association between the transfusion of old blood (>14 days) and increased duration of ICU stay.[48] The age of transfused RBCs was the only predictor of the length of ICU stay in patients who received transfusions. The implications of this association between adverse outcomes and the infusion of aged RBCs is worrisome, given that a typical unit of transfused blood in ICUs is between 16 (Europe) and 21 (U.S.) days old.[3,4] Finally, blood transfusion has been shown in several studies to be an independent predictor of multiorgan failure, even after correction for other indices of shock.[3,49]

To elucidate the possible advantages of transfusion in critically ill patients, Hebert and colleagues in Canada conducted a randomized, controlled clinical trial (the TRICC study) to determine whether a restrictive approach to red cell transfusion (transfusion trigger: hemoglobin concentration between 7 and 9 g/dL) was equivalent to a more liberal transfusion strategy (transfusion trigger: hemoglobin concentration between 10 and 12 g/dL) in critically ill patients.[38] The average number of transfusions was reduced by 54% when the lower threshold was used, and 33% of the patients in the restrictive group did not require transfusion. The 30-day mortality rate was similar in both groups. However, the death rate was significantly lower with the restrictive strategy among typical ICU patients (Acute Physiology and Chronic Health Evaluation [APACHE] II score = 20) and among patients younger than 55 years. A subsequent subgroup analysis of patients with cardiovascular disease found no significant mortality differences between the two transfusion strategies.[50] There was a trend, however, toward decreased survival with the restrictive strategy in patients with active or severe ischemic heart disease. Finally, there appears to be no difference in the duration of mechanical ventilation between the two transfusion policies.[51] Therefore, the TRICC study provides convincing evidence that restricting transfusion to critically ill patients with a hemoglobin concentration of 7 g/dL or less is safe and conserves this precious resource. Use of a restrictive transfusion approach at our busy trauma center reduced our yearly consumption of packed cells by about 25% (absent changes in the use of platelets or clotting factors), with no discernible impact on outcome.

Despite a restrictive strategy, 60% of ICU patients are still transfused. Based on the growing body of evidence suggesting the detrimental clinical effect of blood transfusion, new therapies that can increase hemoglobin levels in critically ill patients have emerged. Recombinant human erythropoietin may assist in augmenting red cell production in this population. Recently, Corwin and colleagues demonstrated a 19% reduction in blood transfusion among a group of critically ill patients who received high weekly doses of recombinant human erythropoietin compared with those receiving a placebo.[52] There were no significant differences in the frequency of adverse events or in mortality between the two groups. The effect of erythropoietin translated into only 0.6 unit per patient over 28 days.

ANNOTATED REFERENCES

Corwin HL, Gettinger A, Pearl RG, et al: Efficacy of recombinant human erythropoietin in critically ill patients: A randomized controlled trial. JAMA 2002;288:2827-2835.

The use of recombinant human erythropoietin is one of the new therapies that can increase hemoglobin levels in critically ill patients. In this randomized, prospective, multicenter trial, the authors showed a 19% reduction in the total units of RBCs transfused to critically ill patients receiving erythropoietin versus those receiving placebo.

Hebert PC, Wells G, Blajchman MA, et al: A multicenter, randomized, controlled clinical trial of transfusion requirement in critical care. N Engl J Med 1999;340:409-417.

To elucidate the possible advantages of transfusion in critically ill patients, these Canadian investigators conducted a randomized, controlled clinical trial that showed that a restrictive approach to red cell transfusion (transfusing at a hemoglobin of 7 to 9 g/dL) is equivalent to a more liberal transfusion strategy (transfusing at 10 to 12 g/dL).

Marik PE, Sibbald WJ: Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. JAMA 1993;269:3024-3029.

Although blood transfusion might acutely increase oxygen delivery, a matching improvement in tissue oxygen consumption is not necessarily seen, especially in sepsis. These authors showed that transfusing old blood (>15 days) in septic patients is accompanied by splanchnic ischemia, as shown by gastric tonometry.

Rogiers P, Zhang H, Leeman M, et al: Erythropoietin response is blunted in critically ill patients. Intensive Care Med 1997;23:159-162.

This study used enzyme-linked immunosorbent aassay to measure erythropoietin levels in critically ill patients with no renal failure and compare them with levels in ambulatory patients with iron deficiency anemia. It showed that erythropoietin is inappropriately low in critically ill patients with sepsis.

Vincent JL, Baron JF, Reinhart K, et al: Anemia and blood transfusion in critically ill patients. JAMA 2002;288.

This trial, one of the largest prospective observational studies, showed that 37% of patients admitted to the ICU are transfused. In addition, it provided evidence of an association among transfusion, diminished organ function, and mortality.

Chapter 20
THROMBOCYTOPENIA

William C. Aird

INCIDENCE

Thrombocytopenia is often classified according to whether platelets are being consumed, sequestered, or underproduced in the bone marrow. However, a more practical classification takes into account the clinical setting (Table 20-1).[1] In the ICU, thrombocytopenia occurs in up to 20% of medical and 35% of surgical admissions.[2] Although there are many causes of thrombocytopenia in this setting, the two most important ones are sepsis and heparin. Sepsis is a major risk factor, being associated with thrombocytopenia in 35% to 59% of cases.[2] The incidence of heparin-induced thrombocytopenia is influenced by the dose and type of heparin preparation, as well as the patient population receiving it. It is estimated that 2% of cardiac medical patients and 15% of orthopedic patients develop heparin-induced thrombocytopenia antibodies following exposure to unfractionated heparin, and up to one half of patients who undergo cardiac bypass surgery develop such antibodies. Only a minority of patients who form heparin-induced thrombocytopenia antibodies develop thrombocytopenia, and an even smaller fraction develop the clinical complication of thrombosis (reviewed in reference 1).

PATHOPHYSIOLOGY

Patients with sepsis may develop de novo ethylenediaminetetraacetic acid (EDTA)–dependent antibodies that cause platelet clumping in the test tube, with resultant pseudothrombocytopenia.[3] Immune mechanisms rarely contribute to sepsis-induced thrombocytopenia.[4] Nonspecific platelet-associated antibodies can be detected in up to 30% of ICU patients.[4] In these cases, nonpathogenic immunoglobulin G (IgG) presumably binds to bacterial products on the surface of platelets, to an altered platelet surface, or as immune complexes. A subset of patients with platelet-associated antibodies has autoantibodies directed against the integrin glycoprotein IIb/IIIa.[4] These antibodies have been implicated in the pathogenesis of immune thrombocytopenic purpura and, although not proved, may play a role in mediating sepsis-induced thrombocytopenia. Nonimmune platelet destruction is the most important cause of thrombocytopenia in severe sepsis. There is increased binding of platelets to the activated endothelium, resulting in their sequestration, activation, and destruction. Less commonly, thrombocytopenia is associated with underlying disseminated intravascular coagulation. Bone marrow specimens have demonstrated a high incidence of hematophagocytosis in patients with sepsis and thrombocytopenia.[5] The degree to which this pathologic process is a cause or simply a marker of sepsis-related thrombocytopenia is not clear.

Heparin-induced thrombocytopenia is a clinicopathologic syndrome that is diagnosed by the detection of circulating antibodies, usually of the IgG1 subclass, and thrombocytopenia with or without thrombosis. Heparin-induced thrombocytopenia antibodies, which recognize a cryptic autoantigen composed of multimolecular complexes of the chemokine platelet factor 4 (PF4) and heparin, may be detected by antigen assays or activation assays. Seroconversion occurs 5 to 10 days following initiation of heparin therapy. An important exception to this rule is that patients who have been treated with heparin in the past 100 days are at risk for developing rapid-onset heparin-induced thrombocytopenia promptly on re-exposure to heparin.[6] Heparin-induced thrombocytopenia occurs when platelet-bound PF4-heparin-IgG complexes interact with the Fcγ receptor type IIa (FcγRIIA), leading to platelet activation and aggregation.

In addition to sepsis and heparin-related mechanisms, other causes of thrombocytopenia should be considered in

TABLE 20–1. DIFFERENTIAL DIAGNOSIS OF THROMBOCYTOPENIA

Outpatients
Pregnancy
Immune thrombocytopenic purpura
Myelodysplastic syndrome
Hypersplenism
Antiphospholipid antibody syndrome
Hereditary thrombocytopenia
Non–ICU and MICU Inpatients
Drugs, including heparin
Sepsis
Disseminated intravascular coagulation
Dilutional thrombocytopenia
Post-transfusion purpura
Folate deficiency
Coronary Care Unit Inpatients
Heparin
Glycoprotein IIb/IIIa antagonists
Adenosine diphosphate receptor antagonists
Coronary artery bypass surgery
Intra-aortic balloon pump
Emergency Room Patients
Acute alcohol toxicity
Thrombocytopenic thrombotic purpura/hemolytic uremic syndrome
Immune thrombocytopenic purpura
Drugs

critically ill patients, including other drugs, dilutional thrombocytopenia following trauma or complicated surgery and multiple transfusions, acute folate deficiency,[7] and preexisting underlying disease (e.g., cancer, hypersplenism, immune thrombocytopenic purpura).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with thrombocytopenia may develop petechiae, purpura, bruising, or frank bleeding. The diagnosis of thrombocytopenia is made from the complete blood count. It is important to examine the peripheral blood smear to rule out platelet clumping. If such a phenomenon is observed, the platelet count should be repeated in blood drawn into a tube that contains an anticoagulant other than EDTA. If thrombocytopenia is associated with consumptive coagulopathy, any or all of the following laboratory tests may be abnormal: International Normalized Ratio, partial thromboplastin time, thrombin time, circulating concentration of D-dimer, plasma fibrinogen level, concentration of thrombin-antithrombin complexes, and plasma concentration of prothrombin fragment 1.2. The peripheral smear may show schistocytes. Although patients with sepsis may have increased platelet-associated IgG, this test is nonspecific and does not help in guiding therapy.

It is important to recognize that thrombocytopenia associated with sepsis, and particularly heparin-induced thrombocytopenia, can coexist with an underlying hypercoagulable state. Indeed, patients with heparin-induced thrombocytopenia are at far greater risk for thrombosis than for bleeding. These patients typically have mild to moderate reductions in platelet counts (median, 60,000/μL). Only 5% of cases are associated with platelet counts less than 15,000/μL.[8] It is important to recognize that thrombotic complications may occur with a "normal" platelet count (i.e., >150,000/μL). Findings suggestive of the diagnosis of heparin-induced thrombocytopenia in these patients is a 30% to 50% or greater fall in the platelet count within the normal range, or the presence of erythematous or necrotic skin lesions at subcutaneous heparin injection sites.

PROGNOSIS

Thrombocytopenia is a predictor of mortality in ICU patients and in patients with severe sepsis.[9,10] The degree and duration of thrombocytopenia, as well as the net change in the platelet count, are important determinants of survival.[10-12]

TREATMENT

Treatment of thrombocytopenia depends on the underlying mechanism. As a general rule, when thrombocytopenia is associated with an increased risk for bleeding and is not attributable to immune mechanisms, patients should be transfused with platelets to maintain a minimal platelet count. Although guidelines for prophylactic transfusions in patients with chemotherapy-induced thrombocytopenia have been established,[13] the threshold for transfusing in the ICU is not clear. This caveat notwithstanding (and in the absence of evidence-based guidelines), most patients are transfused to achieve a platelet count of 10,000/μL or greater. If the patient has concomitant coagulopathy (e.g., due to disseminated intravascular coagulation or liver disease), active bleeding, or platelet dysfunction (e.g., due to uremia), it may be prudent to employ a more liberal transfusion strategy with the goal of maintaining an even higher platelet count.

Patients with sepsis have an underlying shift in the hemostatic balance toward the procoagulant side. Indeed, platelets are activated in the setting of sepsis and likely contribute in important ways to the pathogenesis of the syndrome. Therefore, when considering the cost-effectiveness of platelet transfusion, it is important to consider the theoretic risk of accelerating the underlying pathophysiology (i.e., "adding fuel to the fire"). The best approach for treating sepsis-associated thrombocytopenia is to target the host response. Indeed, as long as the low platelet count is causally related to the host response, optimal therapy consists of some combination of low tidal volume ventilation,[14] activated protein C,[15] low-dose glucocorticoids,[16] intensive insulin therapy,[17] and early goal-directed therapy.[18]

The treatment of choice in heparin-induced thrombocytopenia is to discontinue all heparin, including heparin flushes, and to institute therapy with an alternative rapid-acting anticoagulant that either inhibits thrombin or reduces thrombin generation. Warfarin, low-molecular-weight heparin, ε-aminocaproic acid (ancrod), and, as a general rule, platelet transfusions should be avoided, because they may exacerbate the underlying prothrombotic state. Two direct thrombin inhibitors, lepirudin and argatroban, have been evaluated and approved by the Food and Drug Administration for the treatment of heparin-induced thrombocytopenia–related thrombosis.[19] Lepirudin may be given with or without a 0.4 mg/kg i.v. bolus, followed by 0.15 mg/kg/h adjusted to 1.5 to 2.5 times the patient's baseline activated partial thromboplastin time or the mean of the laboratory range. Argatroban is given at 2 μg/kg/min i.v. adjusted to 1.5 to 3 times the patient's baseline activated partial thromboplastin time or the mean of the laboratory range. The dose of lepirudin and argatroban should be reduced in renal insufficiency and hepatobiliary disease, respectively. Selected patients with life- or limb-threatening thrombosis may benefit from adjuvant therapies, including thrombolytic drugs, surgical thromboembolectomy, intravenous gammaglobulin, plasmapheresis and antiplatelet agents.

ANNOTATED REFERENCES

Aird WC: The hematologic system as a marker of organ dysfunction in sepsis. Mayo Clin Proc 2003;78:869-881.

This review places sepsis-associated thrombocytopenia in context with other hematologic changes and makes a distinction between adaptive and nonadaptive host responses.

Warkentin TE, Aird WC, Rand JH: Platelet-endothelial interactions: Sepsis, HIT, and antiphospholipid syndrome. Hematology (Am Soc Hematol Educ Program) 2003;497-519.

This review summarizes both thrombocytopenia in sepsis and heparin-induced thrombocytopenia. Figure 5 provides specific treatment recommendations for heparin-induced thrombocytopenia.

Chapter 21
COAGULOPATHY

William C. Aird

Hemostasis is typically divided into two components: primary and secondary. Primary hemostasis refers to the cellular (or platelet) response, whereas secondary hemostasis refers to the protein response (clotting cascade). In reality, both primary and secondary hemostasis are tightly interconnected, feed back on each other, and operate in unison. Nevertheless, from a conceptual standpoint, it is helpful to consider each limb of hemostasis separately. In this chapter, we review the clotting mechanism. The reader is referred to Chapter 20 for a discussion of the most common platelet disorder in the ICU: thrombocytopenia.

GENERAL PRINCIPLES

The blood clotting cascade is highly complex, consisting of a series of linked reactions in which a serine protease, once it is activated, is capable of activating its downstream substrate. For purposes of this chapter, the scheme can be simplified according to the following themes: (1) the final step in the clotting cascade is the conversion of fibrinogen to fibrin, a process that is mediated by a serine protease called thrombin; (2) fibrin is the "glue" that holds platelet plugs together and contributes to the host defense against pathogens; (3) there are two pathways—extrinsic and intrinsic—that converge to induce thrombin generation and fibrin formation; (4) blood coagulation is always initiated by the extrinsic pathway (via tissue factor) and is amplified through the intrinsic pathway; (5) the prothrombin time (PT) measures the integrity of the extrinsic (and common) pathways, and the activated partial thromboplastin time (aPTT) measures the integrity of the intrinsic (and common) pathways; and (6) every procoagulant step is balanced by a natural anticoagulant. Tissue factor pathway inhibitor neutralizes the extrinsic pathway; heparin is a cofactor for antithrombin III, which serves to inhibit serine proteases (most notably, factor Xa and thrombin) in the cascade; activated protein C functions with its cofactor protein S to inactivate the cofactors of the procoagulant response (factors Va and VIIIa); and the fibrinolytic pathway degrades preformed fibrin. In the final analysis, hemostasis represents a balance between anticoagulant and procoagulant forces.[1,2]

Disorders in hemostasis occur when the hemostatic balance shifts toward one side or the other, resulting in one of two clinical phenotypes: bleeding or thrombosis. The myriad causes, diagnostic workup, and treatment of coagulation disorders are beyond the scope of this chapter. In the sections that follow, we consider the coagulopathy that occurs in patients with sepsis. The reasons for choosing sepsis as the case study are several-fold: (1) sepsis is common in the ICU and accounts for the preponderance of coagulopathy; (2) a consideration of the mechanisms, diagnosis, and therapy of coagulopathy in this setting may be widely applicable to conditions in which the innate immune response is activated (e.g., sepsis, trauma, burns, postoperative systemic inflammatory response syndrome); and (3) recent therapeutic breakthroughs emphasize the importance of targeting the host response rather than the clotting cascade per se.

INCIDENCE

Previous studies demonstrated that the coagulation system is activated in the vast majority of patients with severe sepsis.[3] For example, circulating levels of D-dimers are elevated in virtually all patients with severe sepsis,[4] and protein C levels are decreased in up to 90% of such patients.[4,5] Acquired antithrombin III deficiency is also common in the setting of sepsis, with levels below 60% occurring in more than half of patients.[6,7] Although the operational definition varies among studies, disseminated intravascular coagulation (DIC) is estimated to occur in 15% to 30% of patients with severe sepsis, including those with septic shock.[8-13]

MECHANISMS

In sepsis, the clotting cascade is initiated through the up-regulation of tissue factor expression on circulating monocytes, tissue macrophages, and possibly subsets of endothelial cells.[14] At the same time, sepsis attenuates many of the natural anticoagulant mechanisms. For example, circulating levels of protein C and antithrombin III are reduced, and the fibrinolytic pathway is suppressed.[15,16] Moreover, sepsis-mediated down-regulation of thrombomodulin on the endothelial cell surface may impair the activation of protein C.[17] Together, these changes further tilt the balance toward the procoagulant side, resulting in thrombin generation, fibrin deposition, and clotting factor consumption. DIC represents the extreme in the pathophysiologic continuum. In addition to these systemic effects, sepsis results in local activation of the endothelium through the release of a number of inflammatory mediators. Once activated, the endothelium expresses a procoagulant phenotype. The nature and degree of this response vary among different sites of the vascular tree.[2,18,19] The systemic consumption of clotting factors may be accompanied by thrombocytopenia, and when sufficiently advanced, these processes may ultimately result in bleeding. Other factors that may contribute to sepsis-associated bleeding include trauma-related coagulopathy secondary to hypothermia, metabolic acidosis, or massive transfusions; vitamin K deficiency; liver dysfunction; and heparin treatment.[20]

Local activation of the coagulation system in sepsis is an integral component of the innate immune response and may

play a protective role in walling off infection.[21] However, in patients with severe sepsis, systemic activation of coagulation is harmful to the patient and is associated with increased mortality.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Severe sepsis is usually associated with a net procoagulant state, as evidenced by local or diffuse microvascular thrombi. These changes occasionally manifest as skin lesions, as occurs in purpura fulminans. More commonly, the coagulation cascade interacts with the inflammatory pathway to induce endothelial cell activation and secondary dysfunction of internal organs, including the liver, kidneys, lungs, and brain. Patients are at risk for bleeding when the consumption of clotting factors outstrips the production.[22,23] Bleeding is more common when the coagulopathy is exacerbated by concomitant thrombocytopenia, liver disease, heparin use, and invasive procedures. In large prospective studies, the incidence of serious bleeding in patients with severe sepsis varies between 2% and 6%.[7,24] The most sensitive laboratory markers of sepsis-associated coagulopathy include reduced circulating protein C levels and increased circulating D-dimer levels. However, protein C levels are not routinely measured, and elevated D-dimers are nonspecific. In general, coagulation factor levels are inversely correlated with the severity of sepsis.[7,6] One exception is factor VIII, an acute phase protein. Fibrinogen, another acute phase protein, may be elevated in the early stages of sepsis but is reduced in up to 50% of patients with severe sepsis.[3,5,25]

Marked activation of coagulation and secondary consumption of clotting factors may lead to DIC. No single test is sufficiently sensitive or specific to make the diagnosis of DIC. Recently, a scoring system was proposed that employs simple laboratory tests, including platelet count, elevated fibrin-related marker (e.g., soluble fibrin monomers, fibrin degradation products), prolonged PT (or International Normalized Ratio), and fibrinogen level.[26,27] Other markers of coagulation activation, such as thrombin-antithrombin complexes, fibrinopeptides and $F_{1,2}$, are considered investigational in this setting.

The PT or aPTT may be elevated for reasons other than sepsis-associated consumption of clotting factors (Table 21-1). As a general rule, increased clotting times are caused by inhibitors against one or more clotting factors or a congenital or acquired deficiency state. In the ICU, prolongation of the PT or aPTT is almost always related to an acquired deficiency state. An isolated increase in PT indicates factor VII (extrinsic pathway) deficiency and may be seen in early liver failure or during the initial stages of warfarin (Coumadin) therapy. An isolated increase in the aPTT points to a defect in the intrinsic pathway, namely, factor XII, XI, IX, or VIII. An increase in both PT and aPTT reflects an abnormality in the common pathway (factors X or V, prothrombin, or fibrinogen) or a combined deficiency in the extrinsic and intrinsic pathways. The latter occurs with heparin therapy, long-term warfarin treatment, vitamin K deficiency, advanced liver disease, DIC, or dilutional coagulopathy.

PROGNOSIS

Certain markers of coagulation activation have been correlated with negative outcome in patients with sepsis.[28] For example, low antithrombin III levels in patients with sepsis are predictive of poor survival.[25] Decreased protein C levels in severe sepsis have been shown to correlate with mortality, presence of shock, length of ICU stay, and ventilator dependence.[5] In clinical studies of multiple organ dysfunction, maximum PT and aPTT were shown to be longer in nonsurvivors than in survivors.[29] DIC is an independent predictor for mortality in patients with sepsis.[30]

TABLE 21-1. CAUSES OF INCREASED PROTHROMBIN TIME (PT) OR ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)

Increased PT—Defect in Extrinsic Pathway
Deficiency or inhibitor of factor VII
Early warfarin (Coumadin) therapy
Early liver disease
Increased aPTT—Defect in Intrinsic Pathway
Deficiency or inhibitor of factor XII, XI, IX, or VIII
Heparin (though usually affects PT as well)
Liver disease (though usually affects PT as well)
Lupus anticoagulant (may affect PT as well)
Increased PT and aPTT—Defect in Common Pathway or Combined Defect in Extrinsic and Intrinsic Pathways
Heparin (all serine proteases affected, especially II and X)
Disseminated intravascular coagulation (all factors, including pro- and anticoagulants, affected)
Liver disease (all factors except VIII affected)
Warfarin (factors II, VII, IX, and X affected)
Vitamin K deficiency (factors II, VII, IX, and X affected)
Direct thrombin inhibitors
Lupus anticoagulant

TREATMENT

The consumption of clotting factors with or without secondary DIC is rarely associated with a bleeding diathesis in patients with sepsis. Rather, the underlying coagulopathy reflects a procoagulant state and is associated with increased fibrin deposition in the microvasculature. Thus, transfusion therapy with platelets, fresh frozen plasma, or plasma components is indicated only in patients with active bleeding or in those with a high risk for this complication (e.g., other types of coagulopathy, trauma, surgery, or other invasive procedures).[23,27]

Based on an understanding of the underlying pathophysiology, there has been a shift in emphasis from procoagulant replacement to anticoagulant therapy. Initial studies with thrombin inhibitors were disappointing. Although these drugs clearly inhibit thrombin generation and fibrin formation, they do not appear to have an impact on organ dysfunction and survival.[31] In contrast, preclinical and early-phase clinical studies employing recombinant human protein C, antithrombin III, and tissue factor pathway inhibitor resulted in not only decreased thrombin generation but also improved survival.[8,32-35] One possible explanation for these findings is that the natural anticoagulants have a dual function: inhibition of coagulation and suppression of inflammation. Activated protein C, antithrombin III, and tissue factor pathway inhibitor have each been shown to modulate the inflammatory response under in vitro and in vivo conditions.[36-38]

Unfortunately, in phase 3 studies, infusions with antithrombin III or tissue factor pathway inhibitor failed to

improve 28-day all-cause mortality in patients with severe sepsis.[7] In contrast, the Protein C Worldwide Evaluation in Severe Sepsis trial, a large phase 3 study, confirmed the anticoagulant and anti-inflammatory properties of recombinant human activated protein C (drotrecogin alfa [activated]).[4] Most important, these effects translated into a survival advantage for patients with high-risk severe sepsis. At present, we do not know whether the different outcomes in the phase 3 trials of antithrombin III, tissue factor pathway inhibitor, and activated protein C are explained by differences in study design or whether they reflect important differences at the mechanistic level.

CONCLUSIONS

Most patients in the ICU have activation of the clotting cascade. This would be more apparent if we routinely tested patients with a sensitive assay of clotting activation, for example, protein C levels, markers of thrombin activation, or D-dimers. In the face of unrelenting coagulation activation, the clotting factors may become sufficiently consumed to create a bleeding diathesis. Important challenges for the intensivist are to (1) delineate and track a patient's position on the hemostatic scale (prothrombotic versus hemorrhagic), (2) understand that both phenotypes may occur concomitantly (e.g., microthrombi within internal organs and mucosal bleeding), and (3) target each component separately—that is, replenish the clotting factors in the face of severe of bleeding (e.g., plasma products) while attenuating the underlying host response (e.g., low tidal volume ventilation, activated protein C, low-dose glucocorticoids, intensive insulin therapy, and early goal-directed therapy).

ANNOTATED REFERENCES

Aird WC: Vascular bed–specific hemostasis: Role of endothelium in sepsis pathogenesis. Crit Care Med 2001;29:S28-S35.

This review emphasizes the notion of hemostasis as a balance between procoagulants and anticoagulants and applies the principle to an understanding of hemostatic changes in sepsis.

Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699-709.

This landmark study was the first to demonstrate a survival benefit of a drug in patients with severe sepsis. Clinicians who are involved in the care of patients with severe sepsis should be familiar with the inclusion and exclusion criteria that were used in this phase 3 clinical trial.

Faust SN, Levin M, Harrison OB, et al: Dysfunction of endothelial protein C activation in severe meningococcal sepsis. N Engl J Med 2001;345:408-416.

For those interested in the role of the endothelium in sepsis and the potential for bridging bench to bedside, this article is a must-read. It was previously shown that activated endothelial cells express lower levels of the natural anticoagulant thrombomodulin. In this study, the investigators demonstrated that a similar phenomenon occurs in the intact vasculature in patients with sepsis.

Levi M, Ten Cate H: Disseminated intravascular coagulation. N Engl J Med 1999;341:586-592.

This is an excellent and still timely review of DIC.

Taylor FB Jr, Toh CH, Hoots WK, et al: Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001;86:1327-1330.

There has been little consensus on the definition or diagnostic criteria of DIC. This paper represents an important first attempt to establish a set of criteria that may be tested prospectively in clinical trials.

Chapter 22
HYPERBILIRUBINEMIA

Mitchell P. Fink

Bilirubin is a byproduct of heme metabolism. Heme, which is largely derived from the hemoglobin in senescent red blood cells, is oxidized in the spleen, liver, and other organs by two isoforms of the enzyme heme oxygenase, in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) and molecular oxygen, to form biliverdin, carbon monoxide, and iron.[1] Subsequently, biliverdin is converted into bilirubin by the phosphoprotein biliverdin reductase, which also uses NADPH as a cofactor. Bilirubin is lipophilic molecule. To be excreted, bilirubin that is produced in extrahepatic organs is bound to albumin and transported to the liver. The liver takes up the bilirubin-albumin complex through an albumin receptor. Bilirubin, but not albumin, is transferred across the hepatocyte membrane and transported through the cytoplasm to the smooth endoplasmic reticulum bound primarily to ligandin or Y protein, a member of the glutathione S-transferase gene family of proteins. Within hepatocytes, bilirubin is converted to water-soluble derivatives, bilirubin monoglucuronide and bilirubin diglucuronide, by the enzyme uridine diphosphate-glucuronosyl transferase. These conjugated forms of bilirubin are secreted across the canalicular membrane into bile via an energy-dependent process. Conjugated bilirubin is excreted in the bile into the intestine, where it is broken down by gut flora to urobilinogen and stercobilin.

Total serum bilirubin consists of an unconjugated fraction and a conjugated fraction. The conjugated forms of bilirubin exist both free in the serum and bound covalently to albumin; the latter is known as delta-bilirubin.[2] Conjugated bilirubin is water soluble and reacts directly when certain dyes are added to the serum specimen. The unconjugated bilirubin does not react with the colorometric reagents until a solvent is added. Accordingly, the conjugated and unconjugated forms of bilirubin are often referred to as "direct" and "indirect" bilirubin. The sum of these two measurements is "total" bilirubin. The normal total bilirubin concentration in adults is less than 18 μmol/L (1.0 mg/dL). Although any total bilirubin concentration that is higher than the upper limit of normal constitutes hyperbilirubinemia, jaundice (i.e., yellow discoloration of the sclerae, mucous membranes, and skin) is usually not clinically apparent unless the serum total bilirubin level is greater than 50 μmol/L (2.8 mg/dL). Unconjugated or indirect hyperbilirubinemia is present when the total serum bilirubin concentration is above the upper limit of normal and less than 15% of the total is in the direct or conjugated form.

DIFFERENTIAL DIAGNOSIS

The long list of diagnoses depicted in Table 22-1 divides the causes of hyperbilirubinemia into two large groups, according to whether the predominant abnormality is an increase in the circulating concentration of unconjugated (indirect) bilirubin or an increase in the concentration of conjugated (direct) bilirubin. Although this classification scheme is useful under some circumstances, many of the diagnoses listed in Table 22-1 are extremely rare and very unlikely to be

TABLE 22–1. DIFFERENTIAL DIAGNOSIS OF HYPERBILIRUBINEMIA

A. Unconjugated hyperbilirubinemia
  1. Overproduction of bilirubin
    a. Hemolysis, intravascular: disseminated intravascular coagulation
    b. Hemolysis, extravascular
      (1) Hemoglobinopathies
      (2) Enzyme deficiencies such as glucose-6-phosphate dehydrogenase deficiency
      (3) Autoimmune hemolytic anemias
    c. Ineffective erythropoiesis
    d. Resorption of hematoma
    e. Massive transfusion
  2. Hereditary unconjugated hyperbilirubinemia
    a. Gilbert's syndrome (autosomal dominant)
    b. Crigler-Najjar syndrome type I (autosomal recessive)
    c. Crigler-Najjar syndrome type II (autosomal dominant)
  3. Drugs
    a. Chloramphenicol: neonatal hyperbilirubinemia
    b. Vitamin K: neonatal hyperbilirubinemia
    c. 5β-Pregnane-3α, 20α-diol: cause of breast milk jaundice

B. Conjugated hyperbilirubinemia
  1. Inherited disorders
    a. Dubin-Johnson syndrome (autosomal recessive)
    b. Rotor syndrome (autosomal recessive)
  2. Hepatocellular diseases and intrahepatic causes
    a. Viral hepatitis
    b. Alcoholic hepatitis
    c. Drug-induced hepatitis (e.g., due to isoniazid, nonsteroidal anti-inflammatory drugs, zidovudine)
    d. Cirrhosis
    e. Drug-induced cholestasis (e.g., due to prochlorperazine, haloperidol [Haldol], estrogens)
    f. Sepsis
    g. Postoperative jaundice
    h. Infiltrative liver disease: tumor, abscesses (pyogenic, amebic), tuberculosis, parasites (*Toxoplasma*), *Pneumocystis jirovecii* pneumonia, *Echinococcus*
    i. Primary biliary cirrhosis
    j. Primary sclerosing cholangitis
  3. Extrahepatic causes
    a. Gallstone disease
    b. Pancreatitis-related stricture
    c. Pancreatic head tumor
    d. Cholangiocarcinoma
    e. Primary sclerosing cholangitis

Adapted from Bernstein MD: Hyperbilirubinemia. In Rakel RE (ed): Saunders Manual of Medical Practice. Philadelphia, WB Saunders 1996, pp 371-373, with permission.

TABLE 22-2. CLASSIFICATION FOR ACUTE JAUNDICE ASSOCIATED WITH CRITICAL ILLNESS

I. Extrahepatic Bile Duct Obstruction
  A. Choledocholithiasis
  B. Common bile duct stricture
  C. Traumatic or iatrogenic common bile duct injury
  D. Acute pancreatitis
  E. Malignancy (e.g., ampullary carcinoma)
II. Increased Bilirubin Production
  A. Massive transfusion
  B. Resorption of blood collections (e.g., hematomas, hemoperitoneum)
  C. Acute hemolysis
    1. Disseminated intravascular coagulation
    2. Immune-mediated
III. Impaired Excretion due to Hepatocellular Dysfunction, Hepatitis, or Intrahepatic Cholestasis
  A. Drug- or alcohol-induced hepatitis
  B. Drug-induced intrahepatic cholestasis
  C. Drug-induced hepatocellular necrosis
  D. Gilbert's syndrome
  E. Sepsis and other causes of systemic inflammation
  F. Total parenteral nutrition
  G. Viral hepatitis

encountered by the intensivist caring for critically ill (adult) patients. A more useful classification scheme is depicted in Table 22-2. In this scheme, the causes of jaundice are lumped into three primary categories: extrahepatic obstruction to bile flow; increased bilirubin production; or impaired excretion secondary to hepatocellular necrosis and/or intrahepatic cholestasis and/or hepatitis. Often multiple mechanisms are involved at once.

The incidence of hyperbilirubinemia among critically ill patients is quite variable. Jaundice is present in more than 50% of patients with intra-abdominal sepsis, 33% of victims of severe polysystemic trauma, and from 3% to more than 20% of ICU patients recovering from cardiac surgery.[3–6] Determining the cause of hyperbilirubinemia of new onset is important when managing ICU patients, because some problems can be corrected. Exclusion of a mechanical cause for jaundice (e.g., obstruction of the common bile duct due to choledocholithiasis or stricture) assumes the highest priority because failure to correct this problem in a timely fashion can lead to serious morbidity or even mortality.

Iatrogenic injuries to the common bile duct are fortunately quite rare, although the incidence of this complication is greater after laparoscopic cholecystectomy than after open excision of the gallbladder.[7] Damage to the biliary tree, stricture of biliary anastomoses, or retained stones after cholecystectomy or common bile duct exploration present as hyperbilirubinemia and elevated circulating levels of alkaline phosphatase or gamma-glutamyl transpeptidase. Most often the diagnosis is made by detecting dilation of intrahepatic and extrahepatic bile ducts using ultrasonography.

By exceeding the capacity of the liver to conjugate and excrete bilirubin into the bile, hemolysis can produce jaundice. However, the liver can excrete about 300 mg/day of bilirubin,[8] so clinically significant hyperbilirubinemia is only apparent if the rate of hemolysis (i.e., number of red blood cells lysed per unit time) is fairly rapid. Approximately 10% of the erythrocytes in an appropriately crossmatched unit of packed red blood cells undergo rapid hemolysis, yielding about 250 mg of bilirubin.[9] Accordingly, transfusion of a single unit of packed red blood cells is not likely to increase serum total bilirubin concentration. However, transfusion of multiple units of blood over a short period almost inevitably leads to some degree of hyperbilirubinemia, particularly if hepatic function is already impaired. Other reasonably common causes of acute hemolysis in ICU patients include sickle cell disease and immune-mediated hemolytic anemia and disseminated intravascular coagulation.

Any condition that leads to extensive hepatocellular damage will increase circulating total bilirubin concentration. Conditions in this category that are commonly encountered in ICU patients include viral hepatitis, "shock liver," alcoholic hepatitis, and hepatocellular injury induced by drugs, especially acetaminophen.[10] In most forms of jaundice due to hepatic inflammation or hepatocellular damage, circulating levels of transaminases are elevated to a greater extent than is total bilirubin concentration. Making a diagnosis of acetaminophen overdose early is very important, because specific therapy using *N*-acetylcysteine can be lifesaving.[10]

Two other conditions that are commonly associated with jaundice in ICU patients are sepsis and total parenteral nutrition (TPN). Both are associated with the development of intrahepatic cholestasis. Hyperbilirubinemia is a common occurrence in patients with extrahepatic infections leading to the development of severe sepsis.[11,12] Persistent hyperbilirubinemia in septic patients is associated with a significantly increased risk of mortality.[12] Efforts to understand the pathophysiologic mechanisms responsible for cholestatic jaundice due to sepsis have largely focused on lipopolysaccharide (LPS)-induced alterations in the function and expression of various bile acid transporters.[13–16] Nevertheless, another factor that probably contributes to the development of intrahepatic cholestasis is back-leakage of bile from the canalicular spaces into the sinusoids.[17–19]

The basis for TPN-induced cholestasis is also probably multifactorial. Prolonged bowel rest and ileus may promote bacterial overgrowth and increased translocation of LPS into the portal vein on this basis. Phytosterols are present in the lipid emulsions used for TPN and have been associated with cholestasis, especially in premature infants.[20] Results from two retrospective studies suggest that administration of more than 1 g/kg/day of lipid emulsion is associated with increased incidence of hepatocellular dysfunction.[21,22] These data, however, were derived by studying patients receiving TPN at home for very prolonged periods and may not be applicable to ICU patients. In any case, TPN is associated with the development of jaundice and hepatocellular damage. Accordingly, except in rare cases, most ICU patients are better served by receiving enteral rather than parenteral nutrition.

Chapter 23

THE MANAGEMENT OF GASTROINTESTINAL BLEEDING

Omer Bajwa • Paul E. Marik

The cornerstone of management of gastrointestinal bleeding involves volume resuscitation, correction of coagulation disorders, and protection of the airway while initiating diagnostic procedures to determine the site of bleeding. Management is multidisciplinary, involving the emergency room physician, the gastroenterologist, the surgeon, and frequently the intensivist and interventional radiologist.

Upper gastrointestinal bleeding is twice as common in males as in females and its incidence increases with age.[1] The mortality rate for patients with upper gastrointestinal bleeding has remained relatively stable over the past 40 years, ranging from 6% to 10%.[2-4]

Significant improvements in the management of patients with gastrointestinal bleeding has been offset by the increasing number of cases in older patients, who frequently have significant comorbidities.[5-7] The risk of death depends on the patient's age, the presence of shock, comorbid medical conditions, the presence of major stigma of recent hemorrhage, and the underlying cause of the hemorrhage (Table 23-1). Scoring systems to predict mortality and risk of rebleeding are based on host factors, the patient clinical course, and endoscopic findings,[8] and the mortality rate is largely dependent on the cause. Variceal hemorrhage is associated with very high mortality rate: up to 30% of initial bleeding episodes are fatal, and as many as 70% of survivors have recurrent bleeding after a first variceal hemorrhage.[7,9] In contrast, bleeding peptic ulcer disease has a mortality rate of approximately 0.5% in patients younger than 60 years and 10.0% in patients older than 60 years.

CAUSES OF UPPER GASTROINTESTINAL BLEEDING

The source of upper gastrointestinal bleeding can be anywhere above the ligament of Treitz. Occasionally, it can arise outside the gastrointestinal tract. Significant bleeding from the nose, oropharynx, mouth, or lungs can be manifestation of upper gastrointestinal bleeding. Upper gastrointestinal bleeding can be classified into several broad categories based on anatomic and pathophysiologic factors:

1. Erosive or ulcerative
2. Portal hypertension
3. Arteriovenous malformation
4. Traumatic or post-surgical
5. Tumors

CAUSES OF LOWER GASTROINTESTINAL BLEEDING

Lower gastrointestinal bleeding refers to blood loss of recent onset originating from a site distal to the ligament of Treitz that results in hemodynamic instability, anemia, or the need for blood transfusion.[10] Causes can be grouped into several categories:

1. Anatomic
2. Vascular
3. Inflammatory
4. Neoplastic

In patients younger than 50 years of age, hemorrhoids are the most common cause of rectal bleeding.[11]

The reported incidence and differential diagnosis of lower gastrointestinal bleeding varies depending on a number of factors, including patient age and diagnostic method used. Although there are many reports on lower gastrointestinal bleeding, most are small studies from single institutions that may be biased by referral patterns and diagnostic methods used. Vernava and associates[12] analyzed the Department of Veterans Affairs databases over a 4-year period and reported that lower gastrointestinal bleeding was present in 17,941 patients or 0.7% of all discharges during that time period.

MAJOR CAUSES OF GASTROINTESTINAL BLEEDING

PEPTIC ULCER DISEASE

Peptic ulcer disease accounts for 50% of cases of upper gastrointestinal bleeding[10] and remains the most common cause of bleeding in patients with portal hypertension and varices.[13] Bleeding results from the development of a mucosal ulceration adjacent to a vessel, which can result from factors such as *Helicobacter pylori* infection, use of nonsteroidal anti-inflammatory drugs, and critical illness. Concurrent aspirin and oral anticoagulation use increases the risk of bleeding further.[14,15] Bleeding resulting from aspirin and nonsteroidal anti-inflammatory drug use is dependent on dose and duration of use.[16,17] The current practice of acid suppression with medical therapy (H_2-antagonists, proton-pump inhibitors) has not affected the predominance of peptic ulcer bleeding as the cause of acute hemorrhage.[18]

TABLE 23–1. RISK FACTORS FOR DEATH AFTER HOSPITAL ADMISSION FOR ACUTE UPPER GASTROINTESTINAL HEMORRHAGE

Advanced age
Shock on admission (pulse rate >100 beats/min; systolic blood pressure <100 mm Hg)
Comorbidity (particularly hepatic or renal failure and disseminated cancer)
Diagnosis (worst prognosis for advanced upper gastrointestinal malignancy)
Endoscopic findings (active, spurting hemorrhage from peptic ulcer; nonbleeding, visible blood vessel; large varices with red spots)
Rebleeding (increases mortality 10-fold)

STRESS ULCERS

Stress-related gastric ulcers were previously a common cause of acute upper gastrointestinal bleeding in patients who were hospitalized for life-threatening nonbleeding illnesses.[19] With more aggressive resuscitation and early enteral nutrition, bleeding from stress ulceration has become an uncommon problem.

ESOPHAGEAL VARICES

Gastroesophageal variceal hemorrhage is a major complication of portal hypertension resulting from cirrhosis and accounting for 10% to 30% of all cases of bleeding from the upper gastrointestinal tract.[20] The distal 2 to 5 cm of the esophagus contains superficial veins that lack support from surrounding tissues, and this is the most common site of varices (Fig. 23-1).[21] The dilation of distal esophageal varices depends on a threshold pressure gradient, which is most commonly measured by the hepatic venous pressure gradient, defined as the gradient between the wedged, or occluded, hepatic venous pressure and the free hepatic venous pressure (normal gradient <5 mm Hg). At a hepatic venous pressure gradient of less than 12 mm Hg, varices do not form.[22,23] Varices do not invariably develop in patients with gradients of 12 mm Hg or more; thus, this pressure gradient is necessary but not sufficient.[22,23] Gastroesophageal varices are present in 40% to 60% of patients with cirrhosis; their presence and size are related to the underlying cause, duration, and severity of cirrhosis.[24]

ESOPHAGITIS

Significant bleeding from esophagitis occurs in up to 8% of patients with upper gastrointestinal hemorrhage.[20,25-28] It more commonly causes occult blood loss rather than acute bleeding. Clinically obvious bleeding is most likely in patients with extensive ulcerative disease or with an underlying coagulopathy.

MALLORY-WEISS TEAR

Mallory-Weiss tears occur in gastric mucosa, although 10% to 20% can occur in esophageal mucosa. They account for approximately 5% to 10% of cases of upper gastrointestinal hemorrhage.[22,27-29] Although they are thought to be caused

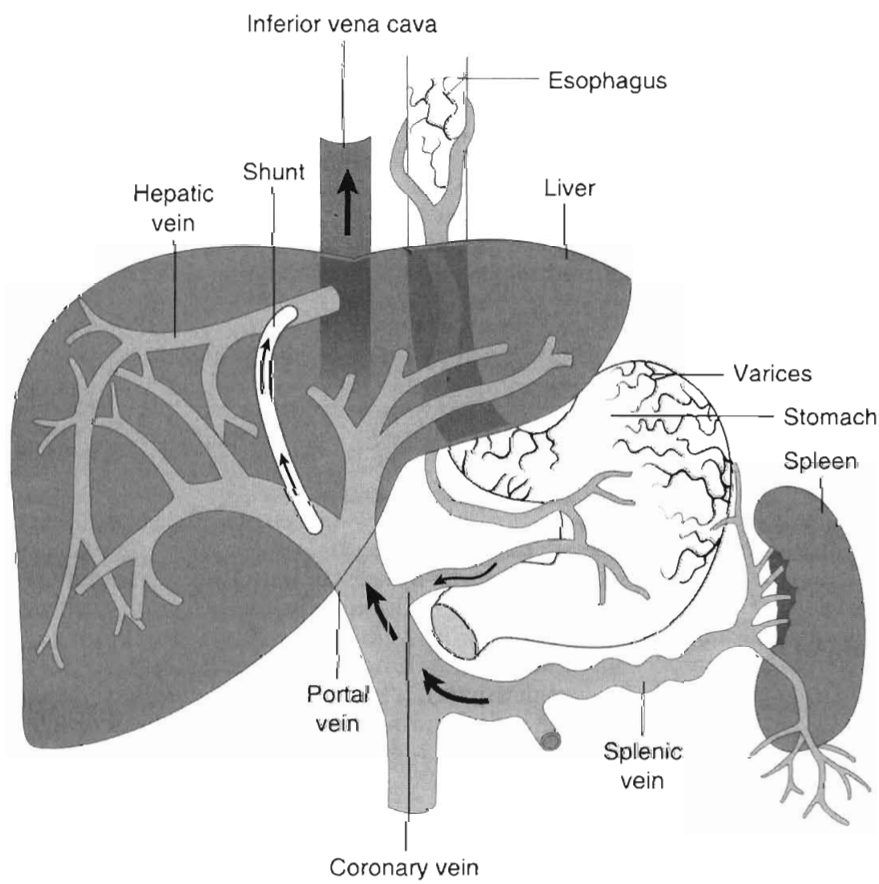

FIGURE 23–1. Transjugular intrahepatic portosystemic shunt (TIPS).

by retching, this history is obtained in less than one-third of patients.[27] Bleeding from Mallory-Weiss tears stops spontaneously in 80% to 90% of patients, and less than 5% of patients experience rebleeding, most often those with an underlying bleeding diathesis.[29,30]

ANGIODYSPLASIA

Angiodysplasia of the gastrointestinal tract is a common source of bleeding. The cause of these lesions is not clear. These lesions also occur in patients with Osler-Weber-Rendu syndrome. They are usually multiple and can occur anywhere from the stomach to the colon, although they are much more common in the colon.

DIVERTICULOSIS

The prevalence of diverticular disease is age-dependent, increasing from less than 5% at age 40, to 30% by age 60, to 65% by age 85. The high prevalence of the disease explains why diverticulosis is the most common cause of lower gastrointestinal bleeding even though less than 15% of patients with diverticulosis develop significant diverticular bleeding. Diverticular bleeding typically occurs in the absence of diverticulitis, and the risk of bleeding is not further increased if diverticulitis is present.[31] Risk factors for diverticular bleeding include[32]

1. Lack of dietary fiber
2. Aspirin and nonsteroidal anti-inflammatory drug use
3. Advanced age
4. Constipation

COLITIS

Infectious, ischemic, and idiopathic colitis (inflammatory bowel disease) can all manifest initially with hematochezia. Mucosal inflammation (colitis) is the common response to acute injury, resulting in activation of the immune system and inflammatory cascade. Establishing a specific diagnosis is paramount in the treatment of acute colitis, since therapy is dependent on the underlying disease process. The diagnosis requires an interpretation of the histologic and gross findings within its clinical context.

NEOPLASMS

Colon cancer is a relatively less common but serious cause of hematochezia. Neoplasm is responsible for approximately 10% of cases of rectal bleeding in patients older than 50 years of age but is rare in younger individuals.[33] Bleeding occurs as the result of overlying erosion or ulceration. The bleeding tends to be low grade and recurrent. Bright red blood suggests left-sided lesions; right-sided lesions can manifest with maroon blood or melena.

HEMORRHOIDS

Hemorrhoids are dilated submucosal veins in the anus located above (internal) or below (external) the dentate line. They are usually asymptomatic but can manifest with hematochezia, thrombosis, strangulation, or pruritus. Hematochezia results from rupture of internal hemorrhoids that are supplied by the superior and middle hemorrhoidal arteries. Hemorrhoidal bleeding is almost always painless. Bright red blood typically coats the stool at the end of defecation. Blood may also drip into the toilet or stain toilet paper. Occasionally, bleeding can be copious, causing great distress to the patient.

INITIAL MANAGEMENT OF GASTROINTESTINAL BLEEDING

Bleeding stops spontaneously in most patients, but aggressive management is required when bleeding does not quickly resolve or when patients are at high risk for rebleeding.[32] Priorities include achieving hemodynamic stability and the prevention of complications such as pulmonary aspiration.[34] The rate of bleeding dictates the urgency of management:

1. Patients with trace heme-positive stools and without severe anemia can be managed as outpatients.
2. Visible blood requires hospitalization and inpatient evaluation.
3. Persistent bleeding or rebleeding with hemodynamic instability necessitates admission to the intensive care unit (ICU).
4. Massive bleeding, defined as loss of 30% or more of estimated blood volume or bleeding requiring blood transfusion of 6 or more units in 24 hours, requires aggressive diagnostic and resuscitative methods in the ICU and the involvement of the intensivist, the gastroenterologist, and, frequently, the gastrointestinal surgeon.

In patients with upper gastrointestinal bleeding, the amount of blood loss can be estimated by measuring the return from a nasogastric tube. An approximate estimate of blood loss can be made by the hemodynamic response to a 2 L crystalloid fluid challenge:

1. If blood pressure returns to normal and stabilizes, blood loss of 15% to 30% has occurred.
2. If blood pressure rises but falls again, blood volume loss of 30% to 40% has occurred.
3. If blood pressure continues to fall, blood volume loss of greater than 40% has probably occurred.

The degree of blood loss can also be estimated clinically by an evaluation of the heart rate, blood pressure, respiratory rate, urine output, and mental status (Table 23-2). The clinical estimation of blood loss is somewhat more difficult in patients with cirrhosis who at baseline have a hyperdynamic circulation with a lower than normal systolic blood pressure and a widened pulse pressure.

History and Examination

A careful baseline cardiopulmonary evaluation is essential; this includes measurement of blood pressure and postural changes, heart rate, chest auscultation, and the ability of the patient to protect his or her airway. A digital rectal examination is always indicated to evaluate the quality of stool and look for the presence of blood, a mass, hemorrhoids, fissure, or fistula. Presence of significant comorbid disease must be determined.

The clinical features of the gastrointestinal bleeding provide clues to the probable source of bleeding within the gastrointestinal tract (Table 23-3). When small amounts of bright red blood are passed per rectum, the lower gastrointestinal tract

TABLE 23–2. CLINICAL INDICATORS AS TO DEGREE OF BLOOD LOSS

Blood loss (mL)	<750	750–1500	1500–2000	>2000
Blood loss (%bv)	<15%	15–30%	30–40%	>40%
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure*	Normal	Decreased	Decreased	Decreased
Pulse rate	<100	>100	>120	>140
Respiratory rate	14–20	20–30	>30	>35
Urine output (mL/hr)	>30	20–30	<20	<10
Mental status	Anxious	Anxious	Anxious and confused	Confused and lethargic
Fluid replacement	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood

*Pulse pressure may be widened in patients with cirrhosis.

can be assumed to be the source. In patients with large-volume maroon stools, nasogastric tube aspiration should be performed to exclude upper gastrointestinal bleeding, although in approximately 15% of patients with upper gastrointestinal bleeding, nasogastric aspirate fails to reveals blood or "coffee ground" material. Concern that placement of a nasogastric tube may induce bleeding in patients with coagulopathies is outweighed by the benefits of the information obtained. A nasogastric tube should be inserted in *all* patients with upper gastrointestinal bleeding to monitor ongoing bleeding and to decompress the stomach. There are no data to suggest that nasogastric tube placement initiates or potentiates bleeding in patients with esophageal varices. Although there are no published reports of nasogastric tubes causing band dislodgment or variceal bleeding, cautious placement of a small nasogastric tube is recommended after variceal banding.

Iced-saline lavage does not prevent or decrease upper gastrointestinal bleeding.[35] Gastric lavage with lukewarm tap water is as safe as lavage with saline and considerably cheaper.[36] Coffee-ground material or a frankly bloody gastric aspirate confirms an upper gastrointestinal source of bleeding, while a non-bloody yellow-green nasogastric aspirate that contains duodenal secretions suggests the absence of bleeding proximal to the ligament of Treitz.[37] However, in up to 50% of patients with a bleeding duodenal ulcer, a nonbloody gastric aspirate is obtained,[35,36] possibly because of insufficient reflux of blood from the duodenum through the pylorus. Similarly, an intermittently bleeding upper gastrointestinal lesion may result in a nonbloody gastric aspirate. The color of the gastric aspirate is of prognostic significance. Patients with coffee-ground or black gastric aspirates and whose stool is melanotic have a reported mortality rate of 9%.[38] However, patients who have bright red blood per gastric aspirate and red blood per rectum have a 30% mortality rate.[38] Red blood per rectum from an upper gastrointestinal source usually signifies rapid bleeding.[39]

TABLE 23–3. CLINICAL INDICATORS OF GASTROINTESTINAL BLEEDING AND THE PROBABLE SOURCE LOCATION WITHIN THE GASTROINTESTINAL TRACT

Clinical Indicator	Probability of Upper Gastrointestinal Source	Probability of Lower Gastrointestinal Source
Hematemesis	Almost certain	Rare
Melena	Probable	Rare
Hematochezia	Possible	Probable
Blood-streaked stool	Rare	Almost certain
Occult blood in stool	Possible	Possible

After the gastric contents have been aspirated, the nasogastric tube should be left in place. The nasogastric tube allows monitoring of ongoing bleeding and is essential to prevent pulmonary aspiration. Once there is no longer any evidence of bleeding, the nasogastric tube can be removed. Maintaining this tube for a prolonged period, especially when the tube is attached to suction, may injure gastric mucosa and exacerbate the gastrointestinal hemorrhage.[40]

INITIAL RESUSCITATION

The first priority in the management of any patient with gastrointestinal bleeding is volume resuscitation. Two large-bore peripheral intravenous lines or a large-bore central line is essential. Volume resuscitation should be initiated with normal saline (a 2-L volume challenge) followed by lactated Ringer's solution. Large-volume resuscitation with normal saline alone will cause a hyperchloremic metabolic acidosis and is associated with coagulation abnormalities. Colloidal solutions have a limited role in patients with acute gastrointestinal bleeding. Patients with an estimated blood loss in excess of 15% to 30% (about 1 L) require blood transfusion (see Table 23-2). In addition, patients with a preexistent coagulopathy (due to liver disease or use of anticoagulants) require transfusion with fresh frozen plasma. Platelet transfusion is indicated if the platelet count is less than 50,000/mm^3. Therefore, a complete blood count including platelet count, blood typing, a prothrombin time and partial thromboplastin time, in addition to blood chemistries and liver function tests should be obtained at the time of line placement. In patients with massive ongoing bleeding, type O blood can be used until cross-matched blood is obtained.

The end-points of resuscitation include normalization of the patient's blood pressure and pulse and indices of end-organ perfusion (mentation, urine output, skin perfusion). Vasopressor agents should be avoided (at least initially) because pressor-mediated vasoconstriction in a hypovolemic patient can cause severe end-organ ischemia.[41] Patients with a history of congestive heart failure, renal failure, or cirrhosis require close monitoring during volume resuscitation; overly aggressive volume resuscitation may precipitate acute pulmonary edema and respiratory failure. A pulmonary artery catheter may help titrate volume expansion in these patients.[42]

Once venous access has been established, a nasogastric or orogastric tube should be placed. Gastric lavage should be performed in all patients with upper gastrointestinal bleeding to remove particulate matter, fresh blood, and clots to facilitate

endoscopy and to decrease the risk of massive aspiration. The risk of aspiration is especially high in patients with massive bleeding or those who have an altered mental status. Endotracheal intubation is recommended in these patients. In addition, endotracheal intubation facilitates endoscopy. In patients with severe upper gastrointestinal bleeding and clinical evidence or a history of advanced liver disease or a history of previous variceal bleeding, an octreotide infusion should be commenced prior to endoscopy (see treatment of variceal hemorrhage).

TRIAGE: WHO TO ADMIT TO THE INTENSIVE CARE UNIT?

At the time of presentation to hospital, patients should be stratified into a high risk (high risk of rebleeding, requiring surgery, and dying) or low risk group. Patients with one or more of the following criteria are stratified as high risk:

1. Systolic blood pressure of less than 100 mm Hg on presentation
2. Severe comorbid disease (e.g., cardiac, pulmonary, renal)
3. Evidence of active, ongoing gastrointestinal hemorrhage
4. Prothrombin time greater than 1.5 times normal

The rate of rebleeding is approximately 3% in the low-risk group and 25% in the high-risk group. Patients in the low-risk group therefore do not require admission to an ICU and can be adequately managed on a general medical floor. The decision regarding ICU admission should, however, be individualized based on the patient's risk stratification, age, comorbid diseases, clinical presentation, and endoscopic findings.[43] Patients with active bleeding and two or more comorbidities have a greater than 10% mortality rate and should be observed in the ICU.[44] Patients with coronary artery disease, regardless of the severity of the gastrointestinal bleeding, are best managed in the ICU because hypovolemia and hypoperfusion from gastrointestinal bleeding can precipitate myocardial ischemia.[45] Admission to the ICU should be considered when endoscopic stigmata of recent hemorrhage, particularly visible vessels, are noted.

FURTHER MANAGEMENT OF UPPER GASTROINTESTINAL BLEEDING

Over the past 20 years, endoscopy has developed as the modality of choice for determining diagnosis, prognosis, and therapy for upper gastrointestinal bleeding. Endoscopy should be performed only after the patient has received adequate volume resuscitation and has achieved a degree of hemodynamic stability but within 6 to 12 hours of presentation. In patients who have had relatively minor bleeding, endoscopy can be performed on a semi-elective basis.

Nonvariceal Bleeds. A meta-analysis of a large number of studies of nonvariceal bleeds demonstrated that endoscopic intervention decreased the mortality rate.[46] The main techniques are injection therapy and thermocoagulation. Employed as the sole therapy in the past, injection therapy is currently followed by thermocoagulation. Although sclerosing agents have been used, epinephrine-containing solutions are now preferred.[47]

Variceal Bleeding. Variceal bleeding stops spontaneously in more than 50% of patients; however, in those who continue to bleed, the mortality rate approaches 70% to 80%. Sclerotherapy is effective for controlling acute bleeding but is associated with a high complication rate, including the risk of ulceration and stricture formation.[48] The risk of secondary ulceration and rebleeding following endoscopic injection sclerotherapy of gastric varices has been reported to be much higher than for esophageal varices.[49] Therefore, treatment of gastric varices without active bleeding or adherent clots should be avoided.

Without treatment to obliterate the varices, there is a 60% to 70% risk of rebleeding. The risk for acute recurrent bleeding is highest within the first 24 to 72 hours of the initial bleed and decreases with time, similar to peptic ulcer hemorrhage.[50,51] Another option is variceal band ligation[51-53]; advantages over injection sclerotherapy include fewer local and systemic complications, lower rebleeding rates, fewer endoscopic treatment sessions to obliterate varices, and lower mortality rate.[54-58]

The diagnostic and therapeutic value of endoscopy in patients with upper gastrointestinal bleeding is often limited by the presence of residual blood or clots. Failure to identify the cause of bleeding at the initial endoscopy examination due to residual blood often necessitates a second endoscopy within several hours with a resultant delay in diagnosis that can increase morbidity and mortality.[59] To avoid this problem, gastric lavage is usually performed with a large-diameter nasogastric tube just before endoscopy.[60] Erythromycin induces rapid gastric emptying in healthy subjects and in patients with diabetic gastroparesis.[60-62] An infusion of 250 mg erythromycin prior to endoscopy improves esophagogastroduodenal cleansing and enhances the quality of the endoscopic findings.[61]

FURTHER MANAGEMENT OF BLEEDING PEPTIC ULCERS

PHARMACOLOGIC THERAPY

Gastric acid-suppressing agents such as histamine receptor-2 blockers (H_2 blockers) have long been available as treatment options for patients with peptic ulcer disease. In acutely bleeding patients, these agents have not been shown to reduce the number of transfusions, episodes of further bleeding or rebleeding, or the need for surgery.[63]

During the past 10 years, proton pump inhibitors have been widely used to suppress gastric acid secretion in patients with a variety of acid-related disorders.[64] Data from a number of studies[65-71] suggest that intravenous proton pump inhibitors reduce the risk of recurrent upper gastrointestinal bleeding; however, they may not affect other outcome variables. Somatostatin is effective for controlling hemorrhage from esophageal varices,[72,73] but its efficacy in the setting of nonvariceal upper gastrointestinal hemorrhage has not been demonstrated.[74]

ROLE OF SURGERY

Although surgical intervention for peptic ulcer bleeding has become less commonplace than in the past, the indications for operation remain unchanged, including severe hemorrhage unresponsive to initial resuscitative measures; unavailability or failure of endoscopic or other nonsurgical therapies to control persistent or recurrent bleeding; and a coexisting

second indication for operation, such as perforation, obstruction, or suspicion of malignancy.[75,76]

Patients in a trial randomized to endoscopic retreatment had significantly fewer complications and tended to have decreased transfusion requirements, 30-day mortality rate, and use of the ICU compared with patients randomized to surgery.[77] Nevertheless, 10% to 12% of patients with acute ulcer hemorrhage still require operative intervention for adequate hemostasis.[78]

FURTHER MANAGEMENT OF ESOPHAGEAL VARICES

PHARMACOLOGIC INTERVENTIONS

Vasopressin causes direct splanchnic and systemic vasoconstriction mediated via the V_1 receptor on vascular smooth muscle and thereby decreases portal venous flow and portal pressure.[79] Vasopressin may also compress esophageal submucosal vessels and decrease esophagogastric collateral blood flow by contracting esophageal smooth muscle and increasing lower esophageal sphincter tone.[79,80] Vasopressin can be administered either intravenously or directly into the superior mesenteric artery; the simpler route is preferred.[81] As with other potent vasoconstrictors, vasopressin must be administered via a central venous line. It is infused continuously, at an initial dose of 0.4 U/min, with gradual increments to a maximum of 1.0 U/min.[82] Higher doses are associated with increased toxicity without further benefit. Vasopressin achieves hemostasis in about 55% of patients.[83] Systemic side effects occur in 20% to 30% of patients. Ischemic side effects include myocardial ischemia, cerebral ischemia, and acrocyanosis.[82] Vasopressin is also associated with congestive heart failure, cardiac arrhythmias, hyponatremia, hypertension, and phlebitis at the venous infusion site. Vasopressin should be used extremely cautiously in patients with coronary artery disease or prior congestive heart failure. Concomitant administration of nitroglycerin, either intravenously or sublingually, improves vasopressin safety and efficacy.[84] The combination of vasopressin and nitroglycerin more effectively controls bleeding and reduces toxicity but does not reduce mortality as compared with vasopressin alone.[85] Vasopressin should not be administered for longer than 24 hours. Terlipressin, a synthetic vasopressin analog, has been used instead of vasopressin to attempt to reduce the toxicity.[86] Terlipressin is as effective as vasopressin in achieving hemostasis and may be associated with a lower incidence of adverse side effects.[82,87]

Somatostatin causes splanchnic vasoconstriction, reduces azygos blood flow, reduces portal collateral circulation, and decreases portal pressure.[88] Somatostatin has been successfully used as an alternative to vasopressin to control variceal bleeding.[89] Octreotide, a synthetic somatostatin analog, is more commonly used than somatostatin. Randomized, controlled trials have shown greater control of variceal bleeding with octreotide, as compared with control, but no improvement in survival.[90] Octreotide produces modest systemic hemodynamic effects and few cardiovascular complications.[89] Octreotide is administered as a 50-μg bolus, followed by infusion at 50 μg/h. If bleeding is controlled, the infusion is continued for 5 days, then discontinued without tapering. Several studies have shown that somatostatin and octreotide are as effective as endoscopic sclerotherapy.[89,91,92]

BALLOON TAMPONADE

Variceal hemorrhage that is unresponsive to combination therapy with octreotide and endoscopic therapy should be temporarily controlled by balloon tamponade. Balloon tamponade initially controls the hemorrhage in 60% to 90% of cases.[93,94] Rebleeding occurs in approximately 50% of cases after balloon deflation, when balloon tamponade is used alone.[95] Balloon tamponade should be only a temporizing measure, before more definitive therapy is instituted (transjugular intrahepatic portosystemic shunt or surgery). Endotracheal intubation and adequate sedation is essential before placement of the balloon.[96,97] Balloon tamponade is associated with significant morbidity, particularly when used by inexperienced clinicians. Relative contraindications to balloon tamponade include an esophageal stricture, recent caustic ingestion, recent esophageal surgery, large hiatal hernia, recent sclerotherapy, an unproven variceal source of bleeding, and an improperly trained support staff.[98,99] Esophageal rupture occurs in about 3% of cases. Other complications include pulmonary aspiration, alar necrosis, nasopharyngeal bleeding, and balloon impaction.[95,98,99]

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

Transjugular intrahepatic portosystemic shunt (TIPS) is an intrahepatic shunt between the hepatic and portal veins created by angiographic methods (see Fig. 23-1). The shunt is kept patent by a fenestrated metal stent. This low-resistance channel between the portal and hepatic (systemic) veins decompresses the portal vein, similar to a surgical side-to-side portacaval shunt, but avoids the need for general anesthesia and laparotomy.

Approximately 10% to 20% of patients fail to stop bleeding with endoscopic treatment combined with somatostatin infusion.[100-103] Others rebleed in the first few days after cessation of the index bleed. A second attempt at endoscopic hemostasis is sometimes effective and is generally recommended.[104] When two attempts at hemostasis fail, however, the risk of mortality rises exponentially.[105-107] Even though emergency surgery is highly effective in arresting hemorrhage

TABLE 23–4. COMPLICATIONS OF TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS)

Technique-Related Complications	Complications Related to Portosystemic Shunting	Stent-Related Complications
Neck hematoma	Hepatic encephalopathy	TIPS-associated hemolysis
Cardiac arrhythmias	Increased risk of bacteremia	Infection of stent
Perihepatic hematoma	Liver failure	Stent stenosis or ruptured liver capsule malfunction
Extrahepatic puncture of portal vein		

and preventing rebleeding, it is associated with a mortality rate of approximately 50%.[108-112] A recent study enrolled patients who were actively bleeding and who were considered to be poor-risk candidates for surgery.[113] Patients were initially stabilized with balloon tamponade, and a TIPS was placed within 12 hours. The balloon was deflated within 12 to 24 hours after TIPS placement. TIPS was placed successfully in all but one patient. The 5-week survival rate among this extremely high risk group of patients was 60%, compared with 10% for historical control subjects. Patients without pulmonary aspiration had a 90% survival rate at 5 weeks. These data have been corroborated by smaller series and provide the basis for the use of TIPS for esophageal variceal hemorrhage refractory to emergency endoscopic treatment and pharmacologic treatment in patients who are poor surgical candidates.[114-117]

The role of TIPS in treating active hemorrhage uncontrolled by first-line therapy in patients who are good surgical candidates (i.e., with well-preserved liver function and absence of complications of bleeding) remains controversial. In the absence of well-defined clinical guidelines, the choice of therapy is often dictated by the available expertise.

NONSELECTIVE BETA-BLOCKERS

Nonselective beta blockers (propranolol, nadolol) have been used to prevent recurrent bleeding. Treatment with these agents can reduce the risk of recurrent bleeding and death from bleeding by about 40%. Sympathetic adrenergic activity regulates splanchnic arteriolar resistance.[118] Alpha-adrenergic agents, acting locally, cause vasoconstriction, whereas beta-adrenergic agents cause vasodilation. Blockade of beta-adrenergic receptors allows unrestricted alpha-adrenergic activity, producing splanchnic arteriolar vasoconstriction and decreasing portal venous inflow. Propranolol is the prototypic nonselective beta blocker.[119]

After an oral or intravenous dose of propranolol, portal pressure decreases by 9% to 31%,[120-127] as measured by the hepatic venous pressure gradient. This decrease is primarily due to a decrease in hepatic wedge pressures, with a small contribution from increased systemic venous pressures.[123,128] It has been suggested that a decrease in heart rate and cardiac output also contributes to the decrease in portal venous inflow.[121-124] Findings suggest that the portal decompressive effect of propranolol is a specific splanchnic effect rather than a consequence of its systemic effects.[129] In the long term, tachyphylaxis occurs in 50% to 70% of patients,[144] which is clinically important because only those with a sustained decrease in portal pressures can benefit from beta blockade.[130,131] Patients whose hepatic venous pressure gradient increases above 12 mm Hg lose the protective benefit of beta blockade and are at an increased risk of bleeding. The underlying reason for this problem, in large part, is a concomitant increase in portocolateral venous resistance. In principle, the latter could be prevented by adding a venodilator after starting beta-blocker therapy. Nitrates such as isosorbide mononitrate have been shown to act synergistically with beta blockers in reducing hepatic venous pressure gradient. The cumulative risk of hemorrhage was decreased from 29% in those receiving nadolol alone to 12% in those who received the combination of nadolol and isosorbide mononitrate.[132] Nitrates, however, may worsen the vasodilation of cirrhosis and may impair tissue oxygenation, presumably by dilation of arteriovenous channels in the peripheral circulation. Restriction of combination therapy to patients selected on the basis of a failure of beta blockers therefore seems prudent.

Several other nonselective beta blockers have also been used, including nadolol, sotalol, betaxolol, and mepindolol. Nadolol has a longer half-life of biologic activity[132,133] and can be administered once a day. It is more hydrophilic than propranolol; this hydrophilicity limits its intestinal absorption after oral administration as well as its ability to cross the blood-brain barrier.[134,135] Propranolol is administered orally twice a day. The dose should be increased slowly until the heart rate decreases by 25% from baseline but not below 55 beats/minute. Once a stable dose is achieved, propranolol can be changed to a once-a-day, sustained-release form[136] that is equally effective.[137-143]

SURGICAL MANAGEMENT

Surgery for bleeding esophagogastric varices continues to be the most reliable method to control acute hemorrhage and prevent its recurrence. Operative approaches generally consist of either decompression of the high-pressure portal venous system into the low-pressure systemic venous system by creation of a shunt or devascularization of the distal esophagus and proximal stomach with or without disconnection of the portal and azygous venous systems. In most instances, surgical procedures are used for prevention of recurrent hemorrhage rather than treatment of the initial bleeding episode. Because of the effectiveness of endoscopic therapies, emergency surgery for variceal hemorrhage in most centers is reserved for patients who have failed initial nonsurgical treatment and have reasonable hepatic function.[144]

ANTIBIOTICS IN VARICEAL BLEEDING

Bacterial infections are common in patients with cirrhosis. The overall incidence of bacterial infections in cirrhotic patients admitted with gastrointestinal hemorrhage is 44%. Spontaneous bacterial peritonitis is the most common manifestation of infection, which is usually caused by enteric Gram-negative bacteria (mainly *Escherichia coli*). Mortality has been shown to be higher in these patients than in noninfected patients.[145,146] It has also been shown that infections also predispose to recurrent variceal hemorrhage.[147] A meta-analysis of five trials of short-term antibiotic prophylaxis in patients with variceal bleeding showed both a decrease in the number of infections in treated patients and improved survival.[148] The current recommendation is oral administration of either levofloxacin (500 mg every day) or ciprofloxacin (500 mg q12h) for 7 days in all patients with cirrhosis admitted with an upper gastrointestinal bleed.

FURTHER MANAGEMENT OF LOWER INTESTINAL BLEEDING

The management of acute lower gastrointestinal hemorrhage is a challenging task that requires an efficient, disciplined, and orderly evaluation, choosing among several sophisticated diagnostic tools, while concurrently stabilizing the patient and planning definitive therapy. The source of the bleeding lesion can be extremely difficult to ascertain, as even massive hemorrhage can spontaneously stop, thereby thwarting even the most sophisticated and carefully planned efforts at localization. Eliciting a medical history and identifying pertinent

risk factors help in determining the cause of lower intestinal bleeding. Use of aspirin or nonsteroidal anti-inflammatory drugs use is strongly associated with diverticular bleeding. Bleeding associated with antecedent hypovolemia should raise the possibility of ischemic colitis, whereas prior radiation therapy for prostate or pelvic cancer suggests radiation proctitis, which can appear months or years after radiation. A history of severe constipation should raise the possibility of a stercoral ulcer, and a recent colonoscopic polypectomy suggests post-polypectomy bleeding.

A careful digital rectal examination and sigmoidoscopy should be done to exclude anorectal pathology and to confirm the patient's description of the symptoms. Of rectal carcinomas diagnosed by proctoscopy, 40% are palpable on digital rectal examination.[149]

COLONOSCOPY

The role of colonoscopy in the evaluation and management of lower gastrointestinal bleeding has evolved over the past two decades. The practice of early and rapid diagnosis and treatment of bleeding by colonoscopy has gained widespread support, in part because of evidence that total colonic preparation with an oral purge is safe, even in elderly patients.[150-152] Elderly patients generally prefer colonoscopy to double-contrast barium enemas, and the yield and value of colonoscopy are well justified.[153] Endoscopic therapy is applied to lower gastrointestinal bleeding in 12% to 27% of cases.[154,155] Modes of endoscopic therapy for acute lower intestinal bleeding, in particular for angiodysplasia and diverticular disease, include thermal contact probes, laser, monopolar electrocautery (hot biopsy forceps), injection sclerotherapy, and band ligation.

SCINTIGRAPHY AND ANGIOGRAPHY

If the source of bleeding is not detected on colonoscopy, a bleeding scan followed by angiography should be considered if bleeding is severe. Although not as precise in identifying the site of bleeding as angiography, scintigraphy is safe and more sensitive, detecting active bleeding reliably at rates less than 0.1 mL/min.[156,157] Angiographic extravasation of contrast material can be seen with bleeding rates as low as 0.5 mL/min. Angiographic demonstration of a tumor, neovascularization, or vascular lesions may identify a presumed source of bleeding in the absence of extravasation. The rate of localizing the site of lower intestinal bleeding ranges from 28% to 77%.[158] A major limitation of diagnostic and therapeutic angiography is the risk of renal failure from intravenous contrast material.

Angiography may permit transcatheter administration of vasoconstrictor therapy for lower gastrointestinal bleeding.[159] Rates of initial hemostasis range from 62% to 100% with this technique, although bleeding can recur in 16% to 50% of patients in the short term. Efficacy rates in controlling colonic bleeding are somewhat higher (83%) compared with small bowel bleeding (71%). In one series, 41% of patients had complications from intra-arterial vasopressin, including fluid retention, hyponatremia, transient hypertension, sinus bradycardia, and transient arrhythmias (premature contractions and atrial fibrillation). Major complications occurred in 9% to 21% of patients and included pulmonary edema, serious arrhythmias, myocardial ischemia, and hypertension requiring treatment.[160]

Transcatheter embolization with various embolic agents, including surgical gelatin sponges, microcoils, polyvinyl alcohol particle, and detachable balloons, has been used to control massive lower intestinal bleeding. This technique has been associated with abdominal pain, fever, and mesenteric infarction. Ischemic complications appear to be more common when embolization is performed for colonic than for upper gastrointestinal hemorrhage because of the relatively sparse colonic collateral circulation. Embolic therapy may have utility in patients with coronary artery disease or in other situations in which vasopressin is relatively contraindicated or has failed and may be an alternative to emergency surgery in high-risk patients.

SURGERY

Age, probably by association with increased comorbidity, is an important risk factor for postoperative mortality. The postoperative mortality rate in patients undergoing surgery for colorectal cancer is 3.7% in patients aged 70 to 79 years, 9.8% in those aged 80 to 89 years, and 12.9% in those older than 90.[161] Surgery is generally considered in patients with acute lower intestinal bleeding, when the blood transfusion requirement is greater than 4 U during 24 hours, or when bleeding recurs. Accurate preoperative localization of the bleeding site is essential for successful segmental colonic resection. Blind segmental resection of the colon or segmental resection based solely on tagged red blood cell scan localization is associated with substantial risk of rebleeding and morbidity.[162] High morbidity and mortality rates are associated with blind limited resection and emergency total abdominal colectomy. The rebleeding rate for blind limited resection is 33%.[162] The mortality rate for total abdominal colectomy ranges from 5% to 33%, whereas the mortality rate for blind limited resection can be 57%.[154,155]

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Chapter 24
ILEUS

Vishal Bansal • Juan B. Ochoa

DEFINITION

Ileus is defined as the absence of physiologic motility of the bowel leading to a disturbance in the progression of bowel contents through the gastrointestinal tract.

Ileus must be distinguished from mechanical bowel obstruction, which is defined as the presence of anatomic barriers, either extrinsic or intrinsic, that prevent the normal progression of bowel contents through the gastrointestinal tract.

PATHOPHYSIOLOGY

NORMAL GASTROINTESTINAL MOTILITY

During fasting states, the coordinated contractions of the gastrointestinal tract are called migrating motor complexes and are divided into three phases[1]:

1. Resting phase
2. Intermittent contractions of moderate amplitude
3. High-pressure waves

When a food bolus is introduced into the intestine, organized migrating motor complexes disappear and digested food (chyme) is propelled through the gastrointestinal tract by spikes in the contraction of smooth muscle in the wall of the gut. Longitudinal progression of intestinal contents (made up by food and secretions) occurs through the integration of several complex processes. Specifically, activation of the sympathetic nervous system decreases gastrointestinal motility. Activation of the parasympathetic nervous system increases gastrointestinal motility.[2] The interstitial cells of Cajal are distributed throughout the tunica muscularis and are electrically coupled with one another. These cells are responsible for the pacemaker activity of the gastrointestinal tract.[1] Myenteric and submucosal nerve plexi integrate with the autonomic nervous system. Nitric oxide produced by neuronal nitric oxide synthase produces smooth muscle relaxation and decreases gastrointestinal motility. Multiple endocrine substances affect gastrointestinal motility. Some of these substances, including motilin, gastrin, and cholecystokinin, increase gastrointestinal motility. Other hormones, notably somatostatin and glucagon, decrease gastrointestinal motility. Activation of the innate immune system can impair gastrointestinal motility in patients with sepsis or after surgical manipulation of the small bowel and colon. Inflammatory mediators, such as nitric oxide and prostaglandins, have direct inhibitory effects on normal contractile activity.[3]

CLINICAL CONSEQUENCES OF ILEUS

Ileus results in the inability to tolerate enteral feeding, nausea, vomiting, constipation, and obstipation. Accumulation of fluid and air in the bowel results in abdominal distention. Symptoms and consequences of ileus can range from minimal to life-threatening. Serious consequences of ileus include intestinal ischemia, intestinal perforation, and abdominal compartment syndrome. Intolerance of enteral feeding compromises the ability to provide adequate nutritional support to critically ill patients.

DIAGNOSIS

Tools to aid clinicians in identifying and diagnosing gastrointestinal dysfunction are poorly developed. Ileus is suggested by the presence of the following signs and symptoms: abdominal distention, nausea, vomiting, high output from a nasogastric (Salem sump) tube, high gastric residual volumes during enteral tube feeding, abdominal pain, absent bowel sounds, constipation, or obstipation. No clear guidelines exist to determine what is an abnormal degree of abdominal distention or an excessive amount of nasogastric output. The true incidence of ileus in cases of critical illness is unknown. Radiologic findings suggestive of ileus are increased air in the small intestine, bowel distention, and presence of air-fluid levels.

Ileus is often diagnosed by challenging the patient with an enteral diet. Gastric ileus (i.e., absence of normal gastric emptying) is observed in as many as one third of all critically ill patients and is more common in hemodynamically unstable patients. Thus, clinicians often attempt to place feeding tubes into the small bowel, where success in achieving nutritional goals is more common.

Three types of clinical ileus are observed:

1. Adynamic ileus
2. Spastic ileus observed rarely in diseases such as porphyria or lead poisoning
3. Ischemic ileus, identified in hemodynamically unstable patients with low flow states and classified as nonocclusive mesenteric ischemia

TREATMENT

1. *Adequate hemodynamic resuscitation* helps to ensure adequate organ blood flow. It is especially important to reduce infusion of exogenous catecholamines, if at all

possible, because these agents promote development of ileus.

2. *Judicious administration of intravenous fluids.* Excessive fluid resuscitation can promote bowel edema, decreasing intestinal blood flow and increasing intra-abdominal pressure.
3. *Maintaining or restoring normal circulating electrolyte levels is crucial.* Hypokalemia, in particular, inhibits normal muscle contraction and nerve depolarization.
4. *Avoiding narcotics.* Morphine and other opioids decrease coordinated contractions of the gut and decrease forward propulsion of chyme. These effects may be especially important in postoperative patients.
5. *Avoiding prolonged starvation.* Starvation is associated with mucosal atrophy. Early use of the gastrointestinal tract (within the first 24 to 48 hours of the onset of critical illness) is associated with achieving caloric goals earlier, earlier time to bowel movements, and overall shorter lengths of hospital stay. The initial goal of early enteral nutrition is to prevent development of intestinal mucosal atrophy, and thus a low rate (10-20 mL/h) of enteral feeding is all that is necessary.
6. *Do not assume that a patient has ileus and should not be fed enterally.* Passage of flatus and the presence of bowel sounds are not reliable indicators of normal gastrointestinal motility.[4] Virtually all hemodynamically stable postoperative patients should be fed enterally as soon as hemodynamic stability and resuscitation are achieved.
7. *Total parenteral nutrition (TPN) is not an adequate substitute for enteral nutrition.* TPN rarely achieves adequate nitrogen retention in patients with critical illness. There are no data to support indiscriminate use of TPN in patients with ileus.[5]
8. *Use of nonsteroidal anti-inflammatory agents.* In surgical patients, the use of systemic ketorolac is associated with early bowel movements, increased tolerance to oral diet, and a significant decrease in narcotic use. In animals subjected to surgical manipulation of the gastrointestinal tract, ketorolac is associated with faster gastric emptying and restoration of normal migrating motor complexes.[6]
9. *In the intensive care unit, the use of metoclopramide has not been shown to provide clinical benefit.* Erythromycin, used because of its molecular similarity to motilin, can be used in some cases, but its efficacy is disappointing.
10. *Newer agents are being tested for clinical use to aid in the prevention of or to hasten the resolution of ileus.* These agents include narcotic antagonists, nitric oxide synthase inhibitors, and protein tyrosine kinase inhibitors.

CONCLUSION

Ileus can lead to significant clinical adverse consequences and mortality, especially if the problem is not recognized and adequately treated. The criteria and tools for the diagnosis of ileus are poorly developed, and this fact hinders progress in this area. Inappropriately diagnosing ileus often leads to unnecessary, prolonged starvation of patients or inappropriate use of TPN. Significant progress in the understanding of the mechanisms that lead to the development of ileus will permit the implementation of logical treatments.

Chapter 25
DIARRHEA

Juan B. Ochoa • Vishal Bansal

Diarrhea is one of the most common abnormal manifestations of gastrointestinal dysfunction in the intensive care unit (ICU). The reported incidence ranges from 2% to 63% of cases.[1] Although many definitions exist in the literature, diarrhea is best defined as bowel movements that, because of increased frequency, abnormal consistency, or increased volume, are deleterious to the well-being of the patient.

CRITERIA

Several criteria are used to diagnose diarrhea[1]:

1. *Abnormal frequency.* Normal frequency is described as one or two bowel movements per day. Three or more bowel movements per day is abnormal.
2. *Abnormal consistency.* Stool that is either nonformed or contains excessive fluid content is abnormal. The normal water content of stool is 60% to 85% of total weight.
3. *Volume.* Stool volume varies according to the amount and type of food intake. Insoluble fiber adds bulk. Normal volume is approximately 200 g per bowel movement. Volumes greater than 500 g are abnormal.

PATHOPHYSIOLOGY

There are several classification systems for diarrhea, a situation that suggests that no classification system is ideal for helping clinicians care for patients. Perhaps the most useful approach is to classify diarrhea based on pathophysiology.

1. *Increased mucosal secretion that overwhelms mucosal absorption.* On average, up to 9 L of fluid is secreted into the gastrointestinal lumen. To this volume must be added the normal oral intake. Less than 1% of the total fluid volume is normally excreted as stool. Thus, the small and large intestine have an amazing capacity to absorb fluid. In the intestinal mucosa, passive and active transport of sodium determines the absorption of water. Increased formation of cyclic adenosine monophosphate within enterocytes inhibits absorption of sodium and promotes the active secretion of fluids into the lumen.[2] Thus, diarrhea caused by excessive secretion of fluids is called "secretory" diarrhea. Secretory diarrhea characteristically contains large amounts of fluid and is described as "watery." Secretory diarrhea is observed in patients with cholera or rotavirus infections and can also be observed in endocrine disorders, such as carcinoid syndrome or the syndrome associated with vasoactive intestinal peptide–secreting tumors.
2. *Increased mucus secretion from the large bowel.* Production of large amounts of mucus and other secretions from the large bowel characteristically leads to a different type of diarrhea. This form of diarrhea is observed in patients with colonic infections, such as *Clostridium difficile* colitis and amebiasis.[3]
3. *Diarrhea due to increased osmotic load.* Many substances that are taken orally and are not fully absorbed can exert a significant osmotic force overwhelming the physiologic absorptive capacity of the mucosa. Many patients with diarrhea in the ICU fall into this category. Subclassifications of osmotic diarrhea exist.
   a. *Osmotic diarrhea caused by medications.* Sorbitol, a poorly absorbed sugar alcohol, is used in the formulation of many orally administered drugs. Thus, sorbitol is frequently and inadvertently given to patients in the ICU when medications are administered via a feeding tube. Sorbitol often is overlooked as a causative factor leading to diarrhea.[4] Other osmotic agents include GoLYTELY solution and magnesium-containing medications.
   b. *Incomplete digestion and malabsorption.* The incidence of malabsorption among patients in the ICU is unknown. However, malabsorption may play an important role in ICU-acquired diarrhea in a variety of circumstances. Incomplete protein digestion (azotorrhea) is one cause of malabsorption leading to diarrhea. A key step in protein breakdown occurs in the stomach, catalyzed by the digestive enzyme pepsin. This enzyme is active only at low pH. In the ICU, virtually all patients receive medications (H_2 blockers and proton pump inhibitors) to increase gastric pH.[5] In addition, feeding tubes frequently bypass the stomach, delivering nutrients directly into the proximal small intestine. Poor digestion of carbohydrates can also contribute to diarrhea in the ICU. In addition to sorbitol, other enterally administered carbohydrates, including glucose, lactose, or fructose, can overwhelm the absorptive capacity of the small bowel causing an osmotic influx of fluid into the gut lumen. Inadequate digestion of fats is a third factor that promotes diarrhea on the basis of malabsorption. Steatorrhea (diarrhea caused by undigested fats) is characteristically observed in patients with pancreatic insufficiency. Inadvertent lack of mixing pancreatic enzymes with the food bolus can occur in patients with intestinal bypass or pancreatic fistulas or in patients that have undergone a pancreatectomy. Steatorrhea is also observed in patients with biliary diversion. Diarrhea due to an excessive load (overfeeding) of any of the above components (protein, carbohydrate, or fat) can be observed in the ICU.

Iatrogenic overfeeding occurs in up to 33% of patients in the ICU and is a result of inappropriate estimation of caloric and protein needs or inadequate metabolic surveillance.[6] Administration of an excessive load of any of these substances also can occur with specialized formulas that contain altered amounts of one or more of these components.

4. *Atrophy of the gastrointestinal tract.* Atrophy of the brush border is associated with decreased capacity for digestion and absorption. Atrophy is observed in malnourished patients; thus, diarrhea is often observed in patients with hypoalbuminemia. Mucosal atrophy also occurs when oral intake of food is discontinued for days or weeks. This cause of mucosal atrophy is a particular problem in surgical patients because prolonged periods of "bowel rest" are still frequently ordered.
5. *Abnormal motility.* Intestinal dysmotility (ileus) is a frequent problem in the ICU. The use of promotility agents (e.g., erythromycin) can inadvertently cause diarrhea in these patients.
6. *Abnormal gut flora.* The normal colonic flora is essential for the proper functioning of the large bowel. Systemic administration of antibiotics markedly alters the microbial ecology of the colonic lumen, possibly leading the development of diarrhea.

DIAGNOSIS

Careful and complete evaluation of diarrhea is necessary for good patient care. Unfortunately, diarrhea is often ignored or hastily treated. Diagnostic laboratory tests are inadequate, making it more difficult to properly diagnose and treat diarrhea. The following questions constitute a useful approach for managing patients with suspected diarrhea:

- Does the patient really have diarrhea? Clinicians rarely will question the diagnosis of diarrhea. Most often, the diagnosis is made by the nurse at the bedside.
  A concerted effort at defining diarrhea is essential:
- Can an iatrogenic cause explain the presence of diarrhea? Is the patient receiving a promotility agent or a stool softener? Is the patient receiving medications with a high concentration of sorbitol?
- Is the patient being fed excessively?
- Is the patient intolerant to any of the components of the diet?
- Is a specialized diet providing an excessive amount of a substance, such as fat, that the patient is having difficulty digesting?
- Is bypassing the stomach or inhibiting HCl secretion affecting the digestion of protein?
- Is the patient on any medications that can cause diarrhea?

Seek to determine whether diarrhea is caused by altered absorptive capacity:

- Could the patient have gut atrophy due to prolonged bowel rest?
- Is the patient malnourished?
- Does the patient have a condition (e.g., pancreatitis) that alters secretion of digestive enzymes?
- Does the patient have a chronic disease process (e.g., short gut syndrome) that alters absorption?

Seek to determine whether the patient might have an infectious cause of diarrhea:

- Is there any evidence of contamination of tube feeds?
- Are the tube feedings being administered via a closed system?
- Has the patient tested positive for *C. difficile* toxin?
- Has the patient been treated with multiple antibiotics, possibly leading to derangements in the colonic microbial ecology?

TREATMENT

Treatment depends on identification of the underlying cause or causes. Once identified, the causes of diarrhea should be eliminated, modified, or treated. This is particularly important when iatrogenic causes of diarrhea are identified. For example, antibiotics that are not needed (e.g., prophylactic antibiotics) should be discontinued.[7] Modification of the diet may be important, especially if the absorptive capacity is being overwhelmed by excessive quantities of a nutrient (often fat). Digestive aids, such as pancreatic enzymes or bile substitutes, should be administered to patients with a disease process (or treatment) that is associated with decreased production of these factors.

Agents that inhibit gastrointestinal motility, such as loperamide, should be used with caution. These agents are often ordered empirically but can worsen the underlying problem, especially when the problem causing diarrhea is an infection.

Bulk-forming agents are sometimes given to patients to improve the consistency of the fecal bolus. The proper amount of these agents must be prescribed, since bulk-forming therapeutics can also be a cause of diarrhea.[8]

Antibiotics to treat infectious diarrhea should be used with caution. If the diarrhea is causing minimal discomfort and is of no physiologic consequence, waiting for results from tests for *C. difficile* toxi may be prudent, rather than starting treatment for this infection empirically.[9]

Restoring normal colonic flora has become an increasingly frequent practice in the ICU. The administration of prebiotics and probiotics has been suggested by a number of different authors.[10,11] The side effects and complications associated with this new form of therapy are not clear at this point. The use of soluble fiber may have a role in restoring normal colonic function and flora.

When dealing with diarrhea, clinicians often stop administration of enteral nutrition or decrease the rate of enteral feeding. This strategy is reasonable only if the patient is being overfed or if the patient exhibits intolerance to the diet. Only very rarely is it appropriate to stop oral intake and start total parenteral nutrition as a treatment for diarrhea.

CONCLUSION

Diarrhea is a poorly studied clinical manifestation of gastrointestinal dysfunction in the ICU. The incidence of diarrhea is unknown due to lack of consistent definitions and a concerted effort to study the problem. We also have little understanding of the pathophysiology of diarrhea in the ICU. Despite these limitations, the cause of diarrhea often becomes obvious with a careful clinical evaluation of the patient.

Chapter 26
RASH AND FEVER

Burke A. Cunha

GENERAL CONCEPTS

The diagnostic approach to an ICU patient with a rash depends on whether the patient was admitted with the rash or acquired it in the hospital. Rashes are seldom the primary cause for an ICU admission. The best clinical approach to a patient ill enough to be admitted to the ICU with a rash acquired in the community is to analyze features of the rash. Its distribution and nature—maculopapular, vesicular, bullous, or petechial-purpuric—determine the range of diagnostic possibilities. Rashes are the dermatologic manifestation of an underlying infectious or noninfectious process, and patients admitted to the ICU with rash usually also have fever. Epidemiologic factors, patient age, and associated physical and laboratory findings all help narrow the diagnosis.[1-5]

Rashes acquired after hospitalization, either on the ward (requiring transfer to the ICU) or de novo in the ICU, represent a different set of diagnostic possibilities. The clinician must decide whether the rash is part of the basic underlying process that prompted the ICU admission or is the result of an unrelated process superimposed on the basic problem. For example, a patient in the ICU with an acute myocardial infarction may develop a rash on the basis of contact dermatitis or due to a hypersensitivity reaction to an antiarrhythmic medication.[6] Rash and fever in the ICU should always prompt an infectious disease consultation; in the absence of critical illness, patients with rash may also be referred for dermatologic consultation. As with community-acquired rashes, a patient who develops a rash in the ICU should be approached syndromically. In addition to the distribution of the rash, laboratory features and pulse-temperature relationships are of diagnostic importance. A history focusing on recent surgical procedures and medications is essential.[1,4]

COMMUNITY-ACQUIRED RASHES

Patients with rash who are ill enough to be hospitalized or transferred to the ICU are best approached diagnostically by analyzing the nature and distribution of the exanthem.

MACULOPAPULAR RASHES

Important causes of maculopapular rashes associated with serious illness include systemic lupus erythematosus (SLE), toxic shock syndrome (TSS), overwhelming staphylococcal bacteremia or sepsis, overwhelming pneumococcal bacteremia or sepsis, and drug reactions superimposed on an underlying disorder (e.g., myocardial infarction, pulmonary edema, acute pancreatitis, gastrointestinal hemorrhage, adrenal insufficiency, overzealous diuresis). SLE can be a particularly vexing problem, because acute exacerbations of SLE can produce symptoms and signs that clinically mimic bacteremia, community-acquired pneumonia, acute bacterial meningitis, or acute peritonitis. Blood cultures and radiology findings differentiate uninfected SLE flare from SLE flare with infection. TSS can occur in any patient colonized or infected with a TSS-1 producing strain of *Staphylococcus aureus*. TSS is an obvious component of the differential diagnosis in the presence of staphylococcal infection but may not come to mind when there are no signs of clinical infection (e.g., staphylococcal colonization of the nares).[5,7,8]

VESICULAR RASHES

Vesicular eruptions limit the diagnostic possibilities. A vesicular rash can represent chickenpox or reactivation of varicella-zoster virus manifesting as herpes zoster (shingles). Herpes zoster can be localized or disseminated. Disseminated shingles may resemble chickenpox, but patients with herpes zoster have a prior history of chickenpox. Before the appearance of the rash, localized herpes zoster can be a difficult diagnostic problem, presenting with acute thoracic or abdominal pain, depending on the dermatomal distribution. The appearance of vesicles in the same dermatomal distribution as the preceding pain confirms the diagnosis.[7,8]

BULLOUS RASHES

Bullous lesions can be caused by *Vibrio vulnificus* or gas gangrene (clostridial myonecrosis). Patients with either of these bullous disorders are critically ill. Bullous lesions are painful and tense, and the lesions are accompanied by diarrhea. Establishing their cause depends on obtaining a proper history. Patients with *V. vulnificus* have ingested undercooked shellfish, usually originating from the Gulf of Mexico. Clostridial myonecrosis occasionally presents after a crush injury or trauma to an extremity, when previously embedded clostridial spores become activated.[1,5,7]

PETECHIAL-PURPURIC RASHES

Petechial-purpuric rashes are associated with some of the most virulent and lethal infectious diseases. Petechiae can also accompany benign viral infections (e.g., enteroviral infections) and noninfectious disorders (e.g., drug fever). The presence of a petechial or purpuric rash requires evaluation by an experienced infectious disease consultant. Meningococcemia with or without meningitis,

Rocky Mountain spotted fever, dengue fever, dengue hemorrhagic fever, dengue shock syndrome, and arbovirally transmitted hemorrhagic fevers are all potentially lethal infections. Dengue fever can have hemorrhagic manifestations, but such findings are not synonymous with dengue hemorrhagic fever or dengue shock syndrome. Dengue fever should be considered in the differential diagnosis if the patient has lived in or visited an area where the disease is endemic. A history of recent travel to Latin America, Asia, or Africa should prompt the clinician to consider arboviral hemorrhagic fevers.

The two potentially fatal infectious diseases that are most likely to be confused are meningococcemia and Rocky Mountain spotted fever (Table 26-1).[1,7,9-12] Rocky Mountain spotted fever is diagnosed on the basis of the rash distribution and a history of recent tick exposure. Meningococcemia is suggested by rapid onset of disease, asymmetrical distribution of lesions, and irregularly shaped petechial-purpuric lesions. Overwhelming pneumococcal sepsis can also resemble meningococcemia. The former does not occur in normal hosts, however, and is invariably related to impaired splenic function. Therefore, in a patient with fever, rash, hypotension, and an obvious splenectomy scar, diagnosis is not a problem. Making the correct diagnosis in a timely fashion can be more challenging in patients with diminished splenic function or with congenital asplenia. Clinicians should be familiar with the disorders associated with diminished splenic function, which predispose to pneumococcal bacteremia or sepsis (Table 26-2).[5,7,8]

TABLE 26–1. DIFFERENTIAL DIAGNOSIS OF MENINGOCOCCEMIA AND ROCKY MOUNTAIN SPOTTED FEVER

Key Diagnostic Findings	Meningococcemia	Rocky Mountain Spotted Fever
Clinical Features		
Onset of rash ≤12 h into illness	+	–*
Nontender macular/petechial rash	–	+
Tender petechial rash	+	–
Relative bradycardia	–	+
Hypotension on admission	–†	–‡
Severe headache	–	+§
Conjunctival suffusion	–	+
Periorbital edema	–	+
Deafness	–	+
Abdominal pain	–	+
Splenomegaly	–	+
Edema of dorsum of hands/feet	–	+
Leg/muscle tenderness	–	+
Laboratory Features		
Thrombocytopenia	+	+
Leukopenia	–	+¶
Leukocytosis	–	+
↑ Erythrocyte sedimentation rate	–	+
↑ SGOT/SGPT	–	+

* Usually day 3 to 5.
† Only with Waterhouse-Friderichsen syndrome.
‡ Later, following excessive fluids or myocarditis.
§ Frontal or retro-orbital.
¶ Generalized.
SGOT/SGPT, aspartate transaminase/alanine transaminase.
Adapted from Woodward TE, Cunha BA: Rocky Mountain spotted fever. In Cunha BA (ed): Tickborne Infectious Diseases. New York, Marcel Dekker, 2000, pp 121-137.

TABLE 26–2. DISORDERS ASSOCIATED WITH DECREASED SPLENIC FUNCTION

Chronic alcoholism	Congenital asplenia
Chronic active hepatitis	Sickle cell trait/disease
Myeloproliferative disorders	Splenic infarct
Waldenström's macroglobulinemia	Systemic mastocytosis
Non-Hodgkin's lymphoma	Rheumatoid arthritis
Sézary syndrome	Necrotizing vasculitis
Celiac disease	Thyroiditis
Regional enteritis	Steroid therapy
Ulcerative colitis	Gammaglobulin therapy
Immunoglobulin A deficiency	Amyloidosis
Intestinal lymphangiectasia	Splenectomy
	Hyposplenism of the elderly
	Disorders that decrease splenic artery flow

Adapted from Cunha BA: Severe community-acquired pneumonia. J Crit Illness 1997;12:711-721.

Table 26-3 presents the differential diagnostic features of community-acquired rashes that accompany conditions warranting ICU admission. It is important to remember that arthropod-borne hemorrhagic fevers may resemble meningococcemia.[13-15]

HOSPITAL-ACQUIRED RASHES

Two types of rashes are commonly seen in the ICU: vesicular-bullous and maculopapular.

VESICULAR-BULLOUS RASHES

Vesicular-bullous eruptions can be drug related, but gas gangrene is a diagnosis that should not be overlooked. Patients with severe drug reactions have multiple bullous lesions or can develop Stevens-Johnson syndrome; in either case, the rash is not rapidly progressive. In contrast, in patients with gas gangrene, the vesicular or bullous eruptions spread rapidly (over hours). Gas gangrene in the ICU is likely to be a complication of gastrointestinal surgery performed during the past few days. Skin near the bullous lesions is extremely tender; patients with gas gangrene have little fever but often experience watery diarrhea. Rapidly progressive hemolytic anemia due to lysis of red blood cells by clostridial lethicinases completes the clinical syndrome of gas gangrene. Despite the terminology, gas in tissues is not a prominent feature of gas gangrene. There is no gross crepitus or gas visible on radiographs. Small gas bubbles present in the muscle fascicles usually are not clinically obvious. Copious amounts of gas in the soft tissues or on radiographs should suggest a mixed aerobic-anaerobic infection by gas-producing organisms (e.g., necrotizing fasciitis)—an entity that is clinically distinct from gas gangrene. Mixed aerobic-anaerobic soft tissue infections occur most often in diabetes; although these infections are serious, they are not as rapidly progressive as gas gangrene. Mixed aerobic-anaerobic soft tissue infections do not involve primarily the muscle, as does clostridial myonecrosis.[1,4,5,7,8]

MACULOPAPULAR RASHES

Maculopapular rash as a result of surgical TSS is uncommon but occasionally occurs in the ICU setting. The typical surgical TSS patient develops a wound infection days after an operation.

TABLE 26–3. COMMUNITY-ACQUIRED RASHES IN THE ICU

Type of Rash	Central > Peripheral	Peripheral > Central	Palms and Soles	Appearance of Rash after Fever	Clinical Features	Comments
Petechial-Purpuric Rash						
Meningococcemia	+	+	–	1-2 h	Irregular distribution of painful, irregular petechial lesions Early, spares palms and soles Generalized headache Hypotension (if Waterhouse-Friderichsen syndrome) Leukocytosis Thrombocytopenia	History of recent mild upper respiratory tract infection common in late winter–early spring May present alone or with meningococcal meningitis
Rocky Mountain spotted fever	–	+	+	3-5 days	Painless macular-petechial rash begins in wrists, ankles Conjunctival suffusion Severe frontal headache Periorbital edema Bilateral relative bradycardia Edema of dorsum of hands, feet Splenomegaly in some Hypotension late (due to excessive i.v. fluids, myocarditis) Leukocytosis Thrombocytopenia	Late spring–early fall Recent history of tick exposure No lung involvement unless CHF (late)
Hemorrhagic/toxic smallpox	+	–	–	1-3 days	Fever, headache, and vomiting precede the appearance of petechial hemorrhage in a "swimming trunk" distribution	Hemorrhagic smallpox presents with petechial lesions and profound toxemia Patients may expire before vesicular lesions develop
Overwhelming pneumococcal bacteremia	–	+	+	1-2 days	Diffuse asymmetrical purpuric lesions Hypotension, shock early Leukopenia Thrombocytopenia Howell-Jolly bodies on peripheral smear	Occurs in asplenic patients (e.g., trauma, staging procedures for lymphoma, sickle cell anemia) Source of pneumococcal pneumonia may not be clinically apparent
Dengue hemorrhagic fever, dengue shock syndrome	+	–	+	3-4 days	Rash begins on thorax Palpable pinpoint petechiae on trunk Pain on eye movement Severe headache, myalgias Generalized adenopathy may be present "Camel-back" fever curve Leukopenia Thrombocytopenia	Recent travel history to Caribbean, Latin America, Asia
Arboviral hemorrhagic fevers	+	–	+	3-4 days	Acute onset with prominent hemorrhagic manifestations Severe headache, myalgias "Camel-back" fever curve Possibly abdominal pain, generalized adenopathy Encephalopathy, lethargy common Sore throat, cough Conjunctivitis Nausea, vomiting, diarrhea Abdominal pain ↑ SGOT/SGPT Leukopenia Thrombocytopenia Generalized adenopathy may be present	History of recent travel to Africa, Latin America, or Asia Rapidly fatal
Overwhelming staphylococcal bacteremia	–	+	+	3-5 days	Asymmetrical hemorrhagic lesions or infarcts in distal extremities	Usually obvious staphylococcal focus or *S. aureus* ABE

Continued

TABLE 26–3. COMMUNITY-ACQUIRED RASHES IN THE ICU—CONT'D

Type of Rash	Central > Peripheral	Peripheral > Central	Palms and Soles	Appearance of Rash after Fever	Clinical Features	Comments
					Leukopenia Thrombocytopenia No relative bradycardia Heart murmur if source is ABE	
Maculopapular Rashes						
Toxic shock syndrome (TSS)	+	–	+	1-2 days	Conjunctivitis Scarlatiniform maculopapular rash Bilateral periorbital edema Edema of the dorsum of hands, feet Oral, vaginal erythema Leukocytosis Thrombocytopenia ↑ SGOT/SGPT ↑ BUN/creatinine	Recent or current history of tampon use, menses May have only streptococcal colonization with TSS-1 strain Severe cases may have persistent hypotension despite fluid replacement
Systemic lupus erythematosus (SLE)	+	+	–	With flare	Rash usually facial, but may involve extremities Possibly severe abdominal pain On SPEP, α_2-globulins ↑ in SLE flare, but not in infection LFTs normal in SLE flare; if SGOT/SGPT elevated, test for CMV Leukopenia, lymphopenia, thrombocytopenia suggest SLE flare Microscopic hematuria, ↑ serum creatinine also indicative of SLE flare	Flare usually occurs when steroids tapered CMV may induce SLE flare Associated signs of cerebritis, pneumonitis, peritonitis, or serositis with SLE flare Migratory pulmonary infiltrates with effusion characteristic of SLE pneumonitis Rule out infection to diagnose SLE flare Infections common in SLE, but not during SLE flare
Cutaneous anthrax	–	+	±		Circular, raised lesions may initially be pruritic before ulcerating Painless lesions may be accompanied by painful regional adenopathy	Well-developed anthrax lesion is surrounded by a raised "gelatinous halo" Initial painless ulcer has central necrosis and evolves into an eschar
Drug rash	+	–	+	Days to weeks	Erythema multiforme, Stevens-Johnson syndrome in severe cases ↑ ESR Eosinophils usually present; eosinophilia less uncommon Mildly ↑ SGOT/SGPT ↑ WBC (with left shift) Relative bradycardia Negative blood cultures (excluding contaminants)	"Sensitizing" medication, usually not an antibiotic
Measles	+	–	–	2-3 days	Toxic appearance Intense red or purple confluent rash begins on face (3 days head to feet) Cough prominent Conjunctivitis (Giant cell) pneumonia Leukopenia ± Thrombocytopenia ± ↑ SGOT/SGPT Pseudoappendicitis	Occurs in spring Koplik's spots present before rash
Vesicular Rashes						
Chickenpox	+	+	+	2-3 days	Lesions appear in crops for first 3 days, then stop Vesicles are in different stages of development Vesicles lying on skin surface have "dew drop on rose petal" appearance	Critically ill adults usually have varicella pneumonia

TABLE 26–3. COMMUNITY-ACQUIRED RASHES IN THE ICU—CONT'D

Type of Rash	Central > Peripheral	Peripheral > Central	Palms and Soles	Appearance of Rash after Fever	Clinical Features	Comments
					Vesicles surrounded by "red halo" are pruritic ↑ Basophils No leukopenia No thrombocytopenia ± ↑ SGOT/SGPT	
Typical smallpox	–	+	+	5-7 days	Macular lesions start at hairline, followed by papules, vesicles, and pustules that rapidly cover the face and spread to the extremities Relative sparing of the trunk	Pustules in each anatomic region are in same stage of development, but stage differs from region to region Pustule of smallpox is umbilicated and deep in the dermis
Herpes zoster (shingles)				3-4 days		Before the appearance of the rash, the pain of dermatomal zoster may mimic an acute abdomen, pneumonia, pulmonary edema, or myocardial infection Acutely ill adults usually have disseminated varicella-zoster virus
Bullous Lesions						
Vibrio vulnificus	+	–	–	1-3 h	Painful hemorrhagic, bullous rash on trunk, buttocks Watery, profuse diarrhea Abdominal pain No muscle involvement No anemia	Primary septicemia from ingestion in patients with liver disease or severe wound infection from water containing "halophilic vibrios"

ABE, acute bacterial endocarditis; BUN, blood urea nitrogen; CHF, congestive heart failure; CMV, cytomegalovirus; ESR, erythrocyte sedimentation rate; LFT, liver function test; SGOT/SGPT, aspartate transaminase/alanine transaminase; SPEP, serum protein electrophoresis; WBC, white blood cell.
Adapted from Cunha BA: Approach to the patient with fever. In Samiy AH, Douglas RG Jr, Barondess JA (eds): Textbook of Diagnostic Medicine. Philadelphia, Lea & Febiger, 1987, pp 132-141.

Drainage from the wound is serosanguineous rather than purulent.

Staphylococcal sepsis is usually related to an intravascular device or source. Staphylococcal acute bacterial endocarditis may present initially with maculopapular lesions that become hemorrhagic or gangrenous. The diagnosis should be suggested by a peripheral location of lesions with an irregular outline in the setting of staphylococcal bacteremia.

Cholesterol emboli can be released into the systemic circulation during cardiopulmonary bypass. Thus, after open-heart surgery a patient may develop cholesterol emboli syndrome, which presents as a maculopapular rash with a livedo reticularis–like appearance. The rash occurs on the extremities and can be accompanied by myocardial infarction, acute pancreatitis, acute renal failure, or stroke due to organ ischemia caused by cholesterol emboli. Excluding drug rashes, cholesterol emboli syndrome is the only rash in the ICU associated with peripheral eosinophilia.

Drug rash is a drug hypersensitivity reaction associated with a skin rash. Most patients who develop drug rash do so after receiving new medications in the hospital. Drug-induced rashes are usually maculopapular, generalized, and pruritic and can involve the palms and soles; fever is almost always present. Mild transaminasemia and peripheral eosinophilia complete the clinical presentation. The clinical problem is that drug rash is often superimposed on one or more underlying medical disorders that brought the patient to the ICU in the first place. Even after discontinuing therapy with the offending drug, the rash and fever can take days to weeks to resolve.[16]

Many patients develop contact dermatitis while in the ICU. This condition is very common and must be differentiated from a drug rash. Patients with contact dermatitis do not have fever; in addition, the rash of contact dermatitis is limited to a localized area (e.g., the back), whereas a drug rash is never asymmetrical or limited to only one extremity or anatomic region. Contact dermatitis is not accompanied by eosinophilia or increased serum transaminase levels.

The types of hospital-acquired rashes and their differential diagnoses are presented in Tables 26-4 and 26-5.

TABLE 26–4. HOSPITAL-ACQUIRED RASHES IN THE ICU

Type of Rash	Central > Peripheral	Peripheral > Central	Palms and Soles	Appearance of Rash after Fever	Clinical Features	Comments
Maculopapular Rashes						
Overwhelming staphylococcal sepsis	–	+	+	3-5 days	Asymmetrical hemorrhagic lesions or infarcts in distal extremities Positive blood cultures Leukopenia ± thrombocytopenia	Usually obvious staphylococcal focus or *S. aureus* acute bacterial endocarditis
Surgical toxic shock syndrome	+	–	+	1-2 days	Surgical wound nonpurulent with serosanguineous discharge Scarlatiniform, maculopapular rash Extremity edema Oral, vaginal erythema Watery diarrhea Liver, renal dysfunction Negative blood cultures, leukocytosis ± thrombocytopenia	Recent history of surgical wound infection Severe cases may have persistent hypotension despite fluid replacement
Cholesterol emboli syndrome	–	+	–	Hours-days	"Livedo reticularis" rash on extremities Multisystem organ dysfunction: myocardial infarction, pancreatitis, CVA, intestinal ischemia Eosinophilia a key diagnostic clue Negative blood cultures Leukocytosis No thrombocytopenia	Recent cardiothoracic or carotid surgical procedure
"Surgical" scarlet fever	+	–	–	1-2 days	Diffuse sunburn-like rash "Sandpaper" skin Rash subsides in 6-9 days "Strawberry" tongue Leukocytosis ± thrombocytopenia Eosinophilia Group A streptococci in wound cultures ↑ ASO/anti-DNAse titers	Group A streptococcal wound infection due to erythrotoxin-producing strains
Drug rash	+	–	+	Days to weeks	↓ Platelets common Relative bradycardia Erythema multiforme, Stevens-Johnson syndrome in severe cases Mildly ↑ serum transaminases ↑ ESR Eosinophils usually present; eosinophilia less uncommon, may be pruritic Thrombocytopenia common Negative blood cultures (excluding skin contaminants)	"Sensitizing" medication, usually not an antibiotic ↑ WBC with left shift common, mimicking infection
Bullous Lesions						
Gas gangrene (clostridial myonecrosis)	–	–	–	Hours to days	Low-grade or no fever Patients very apprehensive Intense local pain Relative tachycardia Little or no gas on auscultation Bullous, hemorrhagic rash Leukocytosis No thrombocytopenia Rapidly progressive hemolytic anemia Watery diarrhea Radiograph shows small bubbles in muscle	Related to recently fecally contaminated wound Gross gas on auscultation or radiograph argues against diagnosis of clostridial myonecrosis

ASO, antistreptolysin O; CVA, cerebrovascular accident; ESR, erythrocyte sedimentation rate; WBC, white blood cell.
Adapted from Cunha BA: Approach to the patient with fever. In Samiy AH, Douglas RG Jr, Barondess JA (eds): Textbook of Diagnostic Medicine. Philadelphia, Lea & Febiger, 1987, pp 132-141.

TABLE 26–5. DIFFERENTIAL DIAGNOSTIC FEATURES IN ACUTELY ILL PATIENTS WITH RASH AND FEVER

Rash and Shock
TSS
MC
Fulminant pneumococcal sepsis in an asplenic patient
Overwhelming *S. aureus* bacteremia
Arboviral hemorrhagic fevers
Hemorrhagic smallpox
ABE
DHF
DSS
Rash and Periorbital Edema
RMSF
Rash and Conjunctival Suffusion
RMSF
DHF, DSS
Arboviral hemorrhagic fevers
TSS
Rash and Abdominal Pain
V. vulnificus
Cholesterol emboli syndrome
RMSF
SLE
DHF, DSS
Arboviral hemorrhagic fevers
Rash and Diarrhea
V. vulnificus
Gas gangrene
TSS
DHF, DSS
Arboviral hemorrhagic fever
Rash and CVA
SLE
Cholesterol emboli syndrome
S. aureus ABE
Rash and Mental Status Changes
SLE (if cerebritis)
RMSF
MC
S. aureus ABE
Rash and Pulmonary Infiltrates
RMSF
SLE
Rash and Relative Bradycardia
RMSF
Arboviral hemorrhagic fevers
Rash on Palms and Soles
RMSF
DF
TSS
Rash and Vesicular Lesions
Chickenpox
Typical smallpox
VZV (localized/disseminated)
Rash and Bullous Lesions
V. vulnificus
Gas gangrene
Livedo Reticularis–Like Rash
SLE
Cholesterol emboli syndrome
Hemorrhagic Rash
MC
RMSF
Cholesterol emboli syndrome
DHF, DSS
Arboviral hemorrhagic fevers
Hemorrhagic smallpox
Rash and Edema of Hands, Feet
TSS
RMSF

ABE, acute bacterial endocarditis; CVA, cerebrovascular accident; DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; RMSF, Rocky Mountain spotted fever; SLE, systemic lupus erythematosus; TSS, toxic shock syndrome; VZV, varicella-zoster virus.

Chapter 27
CHEST PAIN

David T. Huang

Chest pain in the ICU is a common complaint that demands urgent evaluation. It is also a somewhat different entity from chest pain seen in the office, ward, or emergency department (ED). Although ICU patients typically are sicker and their problems more complex, management is expedited. ICU patients have already been identified as being critically ill, and they are already in the most resource-rich area of the hospital. The keys to proper management of chest pain in the ICU are a rapid and focused assessment of immediate problems, a careful consideration of the differential diagnosis, a logical evaluation plan, and empirical treatment while awaiting a definitive diagnosis.

INITIAL APPROACH

An ICU patient with chest pain should be seen as soon as possible. When performing the initial evaluation (Fig. 27-1), a good policy is to obtain a fresh set of vital signs and determine whether anything else has changed. First, ensure the adequacy of the basic ABCs: airway, breathing, and circulation. Ensure that the patient has intravenous access and is on a cardiac monitor. Next, take a moment to note the patient's cardiac rhythm and arterial oxygen saturation (pulse oximetry). Check the ventilator settings and, if an arterial catheter or pulmonary artery catheter is in place, the systemic arterial or pulmonary arterial pressure waveforms, respectively. Determine whether the patient appears obtunded, dyspneic, mottled, cool, or diaphoretic. Auscultate the chest and precordium, listening for heart murmurs, friction rubs, and the presence and quality of breath sounds. Seek to identify immediate life-threatening problems, such as tension pneumothorax, ventricular arrhythmias, or arterial hypoxemia, before moving on to perform a more detailed assessment. If life-threatening problems are suspected, evaluation and treatment must be performed almost concurrently. Other chapters in this textbook discuss these time-urgent conditions in greater detail.

HISTORY

If the patient is stable after the initial evaluation, obtain a more detailed history. If the patient can communicate, start with an open-ended question, such as "What's going on, Mr. Jones?" Physicians typically interrupt their patients after about 23 seconds,[1] so force yourself to simply listen for at least 1 minute before saying anything else. The most pertinent information will usually come out during those 60 seconds. Next, fully characterize the chest pain. In one study, only 42% of patients with confirmed thoracic aortic dissections were asked even basic questions about their pain.[2] Omitting one or more of these basic questions during the initial evaluation was associated with a delayed diagnosis. The mnemonic OLDCAAR can help clinicians avoid this mistake (Table 27-1).

The patient's bedside nurse should also be queried about recent changes in the patient's status (e.g., mental status, respiratory pattern, cardiac rate and rhythm). Last, a quick "chart dissection" should be performed, focusing on the initial history and physical examination, past medical history (paying special attention to cardiac risk factors and prior surgical procedures), reason for ICU admission, and the last few progress notes. Do not waste time asking the patient or nurse questions that can be answered by reading the medical record.

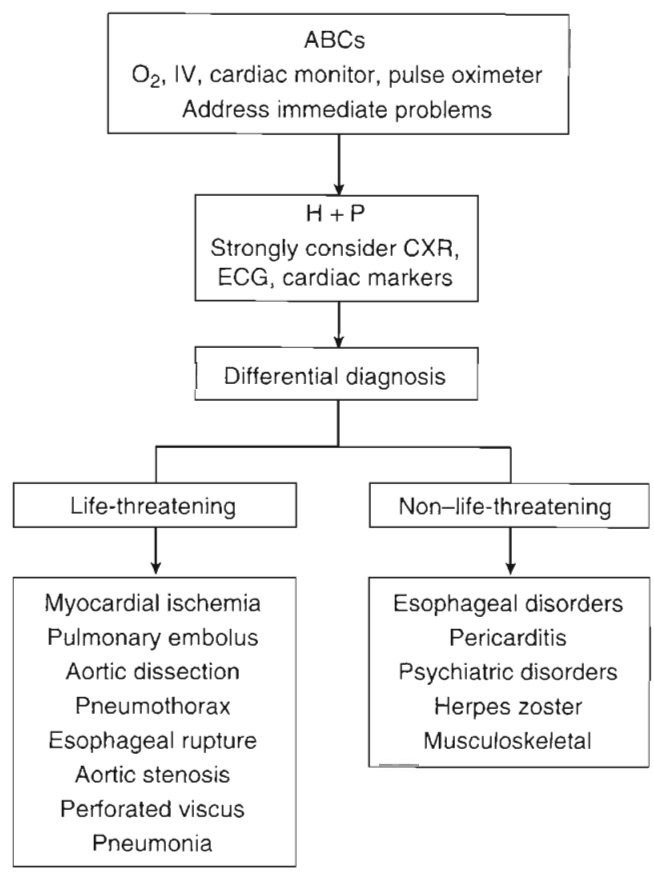

FIGURE 27–1. Approach to chest pain in the ICU. ABC, airway, breathing, circulation; CXR, chest x-ray; ECG, electrocardiogram; H + P, history and physical examination; IV, intravenous access.

TABLE 27–1. OLDCAAR MNEMONIC FOR EVALUATING PAIN

Domain	Suggested Questions
Onset	Sudden vs gradual? Maximal pain at onset?
Location	Generalized or localized? Can you point with one finger to where it hurts?
Duration	When did it start? Just now, or did the pain occur earlier, but you didn't want to bother anyone? Is it constant or intermittent? If intermittent, is there a trigger, or is it random?
Character	Sharp? Dull? Ache? Indigestion? Pressure? Tearing? Ripping?
Associated symptoms	"Dizzy"—vertiginous or presyncopal? Diaphoresis? Palpitations? Dyspnea? Nausea or vomiting?
Alleviating/ **A**ggravating	Position? Belching? Exertion? Deep breathing? Coughing?
Radiation	To the back? Jaw? Throat? Arm? Neck? Abdomen?

PHYSICAL EXAMINATION

Disrobe the patient to ensure optimal visualization, looking particularly for obvious chest wall asymmetry or deformities. Seek to identify areas of point tenderness or crepitus. Next, focus on the cardiac, pulmonary, and abdominal examinations. Check the blood pressure in both arms as you talk to the patient. Assess for asymmetry in pulse quality of the carotid, femoral, and radial pulses. There is a difference in the blood pressure recorded from the right and left upper extremities in about one third of patients with aortic dissection.[3] Check for pulsus paradoxus and jugular venous distention. Listen for asymmetry and quality of breath sounds in conjunction with a review of ventilator settings, if applicable. Evaluate the heart for diminished heart sounds, new murmurs, friction rubs, or gallops. Examine the abdomen for tenderness, pulsatile masses, and absent or abnormal (i.e., high-pitched) bowel sounds. Last, palpate and inspect the lower extremities for tenderness or size differential. Unfortunately, the physical examination is relatively insensitive, and supplemental tests are frequently necessary.[3]

DIAGNOSTIC ADJUNCTS

Unless the cause of new chest pain is obvious (e.g., tension pneumothorax, herpes zoster with visible lesions), a portable chest x-ray (CXR) and 12-lead electrocardiogram (ECG) and rhythm strip should almost always be obtained. In addition, serial measurements of circulating levels of creatinine phosphokinase MB or, preferably, troponin T or troponin I should be strongly considered to exclude a myocardial infarction (MI).

The CXR should be examined for pneumothorax; a widened mediastinum; new infiltrates; effusions; free subdiaphragmatic air; rib fractures; subcutaneous emphysema; malpositioned endotracheal, nasogastric, orogastric, or chest tube; and aortic silhouette abnormalities. Both the ECG and the CXR should be compared with the most recent study before the onset of chest pain.

The ECG and rhythm strip should be evaluated principally for arrhythmias and signs of ischemia, such as inverted T waves, ST segment depression or elevation, and new Q waves. More subtle ECG findings relevant to specific causes of chest pain are discussed in the next section.

An intravenous contrast–enhanced spiral computed tomography (CT) scan is helpful for excluding the diagnosis of pulmonary embolism and may detect other pathologic findings as well. In many centers, it is the diagnostic test of choice for pulmonary embolism. The ventilation-perfusion ($\dot{V}/\dot{Q}$) radionuclide lung scan is an alternative method of diagnosing pulmonary embolism. The $\dot{V}/\dot{Q}$ scan can be a useful alternative to spiral CT in patients with a history of allergic reaction to intravenous contrast material or those at high risk for contrast-induced nephropathy. Pulmonary angiography remains the gold standard for detecting pulmonary embolism, but it is an invasive procedure with a low but real risk of iatrogenic complications.

Echocardiography can be useful for assessing not only left and right ventricular function but also regional wall motion abnormalities, pulmonary hypertension, valvular disease, pericardial effusion, cardiac tamponade, and aortic dissection. Transthoracic echocardiography is usually the first step, followed by transesophageal echocardiography, if necessary. However, transthoracic echocardiography does not visualize the aorta well and can be limited by obesity, emphysema, and chest deformity. For patients in urgent need of aortic visualization, transesophageal echocardiography may be indicated as the initial choice.

DIFFERENTIAL DIAGNOSES

There are three rules to live by:

1. Do not assume that the admission diagnosis is necessarily correct or inclusive. MI can present as gastrointestinal complaints, especially among African Americans.[4] Conversely, the actual diagnosis among patients admitted with presumed (but unconfirmed) MI includes pneumonia, perforated duodenal ulcer, or acute cholecystitis, among myriad other possibilities.
2. Do not be biased by the type of ICU the patient happens to be in. For example, aortic dissection can present as a stroke, prompting admission to a neurologic ICU. Acute serious abdominal problems can occur in medical ICU patients. Indeed, a recent retrospective review of abdominal catastrophes in a medical ICU concluded, "delays in surgical evaluation and intervention are critical contributors to mortality rate in patients who develop acute abdominal complications in a medical ICU."[5]
3. Do not close your mind to alternative diagnoses, even if the diagnosis seems obvious.

ACUTE LIFE-THREATENING PROBLEMS

Myocardial Ischemia

The spectrum of myocardial ischemia ranges from angina to frank MI. Because coronary artery disease is highly prevalent in ICU patients, whether previously diagnosed or occult, a high index of suspicion for ischemia is mandatory. Enumeration of the patient's risk factors (hypercholesterolemia, hypertension, smoking history, family history, age, diabetes mellitus) is useful. The classic signs of myocardial ischemia include chest pain, diaphoresis, palpitations, nausea, syncope or near syncope, vomiting, and dyspnea. Pain often radiates to the neck, arm, or jaw. Unfortunately, myocardial ischemia can also present in much more subtle ways. The type of chest pain is variable and has been described as sharp, dull, tearing, or crushing. Many patients do not even report pain but describe only pressure or simply

an odd feeling. Importantly, MI can often present as gastrointestinal symptoms alone, such as "gas," "heartburn," or simply nausea. A retrospective review of 434,877 patients with confirmed MI found that 33% did not have chest pain.[6] Further, patients without chest pain had higher in-hospital mortality rates, possibly due to delays in care. These atypical presentations are more common in patients with heart failure, a previous stroke, or diabetes and in the elderly, women, and minorities.[4,6]

An ECG should be obtained, and supplemental oxygen and pain relief should be provided, if myocardial ischemia is deemed possible. Unless contraindicated, antiplatelet therapy in the form of aspirin 162 to 325 mg p.o or clopidogrel 75 mg p.o. (if aspirin allergy is present) should also be administered. The ECG should be compared with the most recent previous one and examined for ST segment elevation or depression, new Q waves, and T wave inversion. Unfortunately, many MIs are associated with equivocal ECG findings,[7] in which case serial cardiac enzymes and serial ECGs are necessary for diagnosis. Nitroglycerin and morphine should be used to relieve pain, checking the blood pressure before and after each dose. If pain is not relieved with these measures, alternative diagnoses such as aortic dissection should be considered. However, if the diagnosis of MI is strongly suspected, an interventional cardiology consultation should be obtained because persistent chest pain is an indication for urgent cardiac catheterization.[8]

Pulmonary Embolus

Most ICU patients have at least one risk factor for pulmonary embolus (prolonged bed rest, postoperative state, hypercoagulable state, trauma, burns, heart failure); therefore, pulmonary embolus, like MI, should be strongly considered in this population. Pulmonary embolus can present in multiple ways, but most frequently as pleuritic chest pain and dyspnea or tachypnea. Other presentations include syncope, hemoptysis, diaphoresis, cough, and hypoxia. Although pulmonary embolus is often associated with a widened alveolar-arterial (A-a) gradient, this finding is not very useful among ICU patients because it is neither specific (ICU patients often have many other reasons for hypoxia) nor sensitive (the A-a gradient is normal in approximately 25% of patients with pulmonary embolus).[9] Large pulmonary emboli that significantly occlude the pulmonary circulation present with obstructive cardiogenic shock, hypotension, and a sudden rise in central venous, right ventricular, and pulmonary arterial pressures. Echocardiography can be useful in this setting to confirm the diagnosis by demonstrating right heart failure and right ventricular dilatation with septal shift and subsequent left ventricular outflow obstruction.

The CXR is insensitive for diagnosing pulmonary embolus, so more advanced studies are typically required (CT, V/Q scan, pulmonary angiography). For each test, the risks of iatrogenic complications and complications during transport must be taken into account.

Aortic Dissection

The risk factors for aortic dissection overlap considerably with those for myocardial ischemia; therefore, this entity should always be considered among "rule out MI" patients (Table 27-2). Persistent chest pain without ECG changes is a potential clue that aortic dissection may be present.

The basic pathophysiology involves a tear of the aortic intima, leading to a false lumen between the intima and adventitia. A recent systematic review noted that the vast majority of patients complain of severe chest pain (90%) of sudden onset (84%).[3] The review also noted that 28% have a diastolic murmur (due to aortic regurgitation), 31% have a pulse deficit or blood pressure differential (>20 mm Hg), and 17% have focal neurologic deficits. The physical examination should search for these findings.

TABLE 27–2. AORTIC DISSECTION RISK FACTORS

Atherosclerosis risk factors (hypertension, diabetes, smoking, age, hypercholesterolemia)
Connective tissue disorders (Marfan's syndrome, Ehlers-Danlos syndrome)
Cocaine
Bicuspid aortic valve
Coarctation of the aorta
Trauma
Previous cardiac surgery (especially aortic valve replacement)
Intra-aortic catheterization
Giant cell arteritis

Patients with aortic dissection were once thought to experience a tearing or ripping sensation. However, the International Registry of Acute Aortic Dissection reported in its series of 464 patients that pain was most commonly described as "sharp."[10] Further, only about half the patients described back pain. Therefore, the absence of tearing or ripping pain radiating to the back should not exclude the diagnosis of aortic dissection.

Although a normal CXR does not rule out aortic dissection, the presence of certain findings can be helpful. These findings include a wide mediastinum, separation of intimal calcification from the outer border of the aortic knob by 1 cm or greater, deviation of the trachea to the right, and blurring of the aortic margin. Comparison to the most recent CXR is key. Contrast-enhanced spiral CT is usually the best confirmatory test, but if the risk of transport is too high, bedside transesophageal echocardiography should be performed. Immediate management should focus on blood pressure control, ideally using beta-adrenergic blockade with or without a vasodilator, such as sodium nitroprusside.

Pneumothorax

ICU patients are at high risk for pneumothorax due to iatrogenic complications from central venous catheterization and thoracentesis; preexisting and acquired pulmonary disease, particularly emphysema, asthma, and acute respiratory distress syndrome; and barotrauma secondary to mechanical ventilation. It is absolutely critical to diagnose pneumothorax in patients receiving positive pressure mechanical ventilation, because positive airway pressure can transform a simple pneumothorax into a tension pneumothorax. The cardinal signs of tension pneumothorax are hypotension, jugular venous distention, absence of breath sounds and hyperresonance to percussion on the affected side, and tracheal deviation (away from the affected side). Treatment is immediate needle (14 gauge) decompression, followed by chest tube placement. Needle decompression is quickly accomplished by inserting a large-bore (16 or 18 gauge) needle through the second or third anterior interspace in the midclavicular line of the involved hemithorax.

Simple pneumothorax presents similarly but less dramatically with hypoxia, dyspnea or tachypnea, pleuritic chest pain, decreased breath sounds with hyperresonance, and increased

peak airway pressure. An upright, expiratory CXR should be obtained in cases of suspected pneumothorax. If only a supine film is possible, the deep sulcus sign (hyperlucent, lowered hemidiaphragm with an unusually sharp cardiac border) can help make the diagnosis. Loculated pneumothoraces due to underlying pulmonary adhesions can be difficult to visualize on a CXR. In such cases, chest CT should be obtained promptly; left undiagnosed and untreated, simple pneumothorax can lead to tension pneumothorax. Communication with the radiologist is essential. If the diagnosis of a loculated pneumothorax is confirmed, CT-guided placement of a chest tube or pigtail catheter should be undertaken.

Esophageal Rupture

Prompt recognition is required, because esophageal rupture can lead to potentially lethal mediastinitis. Although usually suggested by a clear history of caustic substance ingestion, forceful vomiting, or iatrogenic trauma (secondary to orogastric lavage, esophageal stricture dilatation, nasogastric tube placement, esophageal intubation, endoscopy), less obvious causes can lead to a delay in diagnosis. Any sudden increase in intra-abdominal pressure can lead to esophageal rupture, and seizures and blunt abdominal trauma have been reported as inciting events. Patients with esophageal disease such as cancer, Barrett's esophagus, and varices are especially vulnerable to rupture.

Physical examination may reveal subcutaneous emphysema or the classic finding of mediastinal crackling on auscultation (Hamman's crunch). CXR may show pneumothorax, pneumomediastinum or pneumoperitoneum, pleural effusion, or subcutaneous emphysema. In victims of blunt abdominal trauma, several findings should increase the suspicion of esophageal rupture: left pneumothorax without associated rib fractures, pain or shock out of proportion to the injury, and particulate matter in the chest tube.[11] A water-soluble contrast study or esophagoscopy confirms the diagnosis.

Aortic Stenosis

The main physiologic effect of aortic stenosis is to impede left ventricular ejection, leading ultimately to left ventricular hypertrophy. Critical aortic stenosis results when this compensatory mechanism can no longer overcome the valvular stenosis or when the hypertrophy itself causes diastolic failure or excessive myocardial oxygen demand. The classic symptoms of angina, syncope, and dyspnea result. Clues suggesting critical aortic stenosis on physical examination include narrow pulse pressure, systolic murmur radiating to the carotid, S_4 gallop, and an aortic ejection click. CXR and ECG may show signs of left ventricular hypertrophy, but the definitive test is a Doppler echocardiogram. If positive, cardiac catheterization should be performed to look for concomitant coronary artery disease and to confirm the echo results. The urgency of these tests is determined by the severity of symptoms; once angina, heart failure, or syncope occurs, a prompt workup is required. Aortic valve replacement is the definitive therapy. Temporizing medical management focuses on cautiously decreasing afterload and treating angina with the careful administration of nitrates, angiotensin-converting enzyme inhibitors, and diuretics. Close hemodynamic monitoring is essential if these drugs are given, because decreases in diastolic pressure can worsen myocardial ischemia.

Miscellaneous

A perforated viscus sometimes presents as chest pain, but fortunately, this is usually easily picked up as free subdiaphragmatic air on an upright CXR. However, retroperitoneal perforations do not show up as free air under the diaphragm on CXR.

Pneumonia is often accompanied by pleuritic chest pain. Referred shoulder pain can result from diaphragmatic irritation by lower lobe pneumonia.

NON–LIFE-THREATENING PROBLEMS

All the following entities should be considered diagnoses of exclusion and should be considered only after life-threatening causes have been ruled out.

Esophageal Disorders

Owing to the shared innervation of the heart and esophagus, visceral pain originating from these two organs can be similar in character. Thus, it can be difficult to differentiate between myocardial ischemia and relatively benign esophageal disorders such as gastroesophageal reflux disease and esophageal dysmotility syndromes. The diagnosis of esophageal disease is supported by a history of pain precipitated by lying flat or the ingestion of hot or cold liquids or food. The diagnosis of an esophageal disorder is also supported if the pain is relieved by antacids. Nitroglycerin can relieve pain due to myocardial ischemia or esophageal spasm, so response to this drug it is not useful as a diagnostic tool. Confirmatory tests include esophageal manometry and esophageal pH monitoring. Alternatively, an empirical trial of a proton pump inhibitor can be tried first. Last, sometimes a nasogastric tube with the distal tip in the esophagus can produce pain, especially when left on suction.

Musculoskeletal Disorders

Chest wall pain is diagnosed with direct palpation or by asking the patient to press with his or her arms against resistance. Usually these maneuvers elicit pain from the affected area. Costochondritis and myofascial syndromes often have specific trigger points that can stimulate pain. Occult rib fractures should be sought carefully by examining the CXR. According to some reports, up to 15% of patients with MI also have chest wall pain, so unless a very specific, localized, and reproducible area of pain can be found, a cardiac workup should be performed.[12] The insertion points for each chest tube and central line should also be inspected. If chest pain is elicited on physical examination, the clinician should specifically ask the patient whether the pain is the same as the spontaneously occurring pain. A negative reply demands further workup.

Pericarditis

Although pericarditis itself is rarely life-threatening, other entities in the differential diagnosis, such as MI and cardiac tamponade, can be. Pain due to pericarditis is typically pleuritic, sharp or stabbing, and retrosternal or precordial, with radiation to the back, neck, shoulders, or arms. Pain is often relieved by leaning forward and worsened by lying flat. More useful in differentiating pericarditis from ischemia is the presence of a pathognomonic but often transitory triphasic (systole, early diastole, and presystole) friction rub. A pericardial rub sounds similar to hair being rubbed together and has been described as high-pitched. It is best heard with the

diaphragm of the stethoscope at the cardiac apex, with the patient seated and leaning forward.

Characteristic ECG findings also help differentiate pericarditis from MI. Both entities demonstrate ST segment elevation, but with pericarditis, ST segment depression is absent in the reciprocal leads, except occasionally in aV_R and V_1. Absence of Q waves, concave (instead of convex) ST segment elevation, PR depression, and upright T waves also strongly favor pericarditis.[13] Careful ECG review, auscultation, and history are the key to distinguishing between these two disorders and avoiding potentially fatal complications of contraindicated therapy (administration of a thrombolytic agent to patients with pericarditis can precipitate hemotamponade) or missing a diagnosis of life-threatening MI.

Pericarditis can lead to pericardial effusion. If it is large or acute, pericardial effusion can lead to cardiac tamponade. Pericardial effusion can present similarly to pulmonary embolus with dyspnea or tachypnea, tachycardia, and chest pain or pressure. ECG findings of electrical alternans and low voltage, coupled with cardiomegaly on CXR, strongly favor pericardial effusion. Pulsus paradoxus may also be present. Beck's triad (jugular venous distention, hypotension, muffled heart tones) points to a more emergent condition. Note that cardiac tamponade and tension pneumothorax share the first two components of Beck's triad, but the latter condition is characterized by normal heart tones, decreased breath sounds, and hyperresonance of the involved hemithorax. Beck's triad is not always present in patients with tamponade. For instance, if the patient is hypovolemic, jugular venous distention may not be apparent. Tamponade should be suspected when the clinical condition looks like congestive heart failure but breath sounds are clear. The ECG and CXR findings discussed for pericardial effusion are useful, but urgent echocardiography should be ordered to confirm the diagnosis. If the patient is in extremis and the clinical picture strongly suggests tamponade, pericardiocentesis should be performed. Volume loading should be done concurrently, because it can partially overcome the hemodynamic effects of tamponade.

Last, it is important to determine the underlying cause of the pericarditis. Possibilities include infection, malignancy, trauma, autoimmune disorders, and connective tissue disorders; it can also be idiopathic.

Psychiatric Disorders

Anxiety disorders, somatization, and panic attacks can all present with chest pain. Panic attacks, in particular, can be associated with symptoms that closely mimic those of MI. Both conditions are commonly associated with diaphoresis, tachypnea, dyspnea, palpitations, presyncope, and a sense of impending doom. Many patients with panic attacks have had extensive cardiac and gastrointestinal workups in the past, and obtaining these reports is helpful. Nonetheless, the dictum that "psychiatric patients get sick too" should be remembered. Psychiatric patients with real cardiac or pulmonary disease can be especially challenging to diagnose, and a thorough, empathic history is essential. Depression is often a comorbid psychiatric condition and should be appropriately treated.

Herpes Zoster

Inspection of the patient's thorax usually makes the diagnosis of herpes zoster, although pain precedes skin manifestations by 1 to 3 days. The lesions are limited to a single dermatome and start as a maculopapular rash that quickly changes to the characteristic vesicular lesions. Acyclovir is the treatment.

CONCLUSION

Attention to immediate problems, a thorough history and physical examination, and consideration of each life-threatening possibility are the key steps to managing chest pain in the ICU. The test battery of a CXR, ECG, and serial cardiac enzymes should be used liberally but intelligently. A high index of suspicion for occult disease is necessary for complex ICU patients.

ANNOTATED REFERENCES

Canto JG, Shlipak MG, Rogers WJ, et al: Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. JAMA 2000;283:3223-3229.

This study of 434,877 patients with confirmed MIs found that fully one third of MI patients do not complain of chest pain at presentation. These atypical patients tended to be older, female, and diabetic and to have prior heart failure. Most important, the in-hospital mortality for these patients was more than double that of patients who presented with chest pain.

Gajic O, Urrutia LE, Sewani H, et al: Acute abdomen in the medical intensive care unit. Crit Care Med 2002;30:1187-1190.

This retrospective cohort study found that delays in surgical evaluation and intervention were independent, statistically significant correlates of mortality. Interestingly, it also found that risk factors for surgical delay included opioid use, mechanical ventilation, no peritoneal signs, antibiotics, and altered mental state. This suggests that a heightened index of suspicion for an acute abdomen may be necessary in ICU patients with these risk factors.

Hagan PG, Nienaber CA, Isselbacher EM, et al: The International Registry of Acute Aortic Dissection (IRAAD): New insights into an old disease. JAMA 2000;283:897-903.

The IRAAD is composed of 12 international referral centers, from which 3 years of data and 464 patients were analyzed. A key finding was that classic presentations such as tearing or ripping chest pain (50.6%), aortic regurgitation (31.6%), and pulse deficit (15.1%) were frequently absent, leading the authors to urge clinicians to maintain a high index of suspicion.

Klinger D, Green-Weir R, Nerenz D, et al: Perceptions of chest pain differ by race. Am Heart J 2002;144:51–59.

In this study of 215 patients with confirmed MI, African-American patients attributed their initial symptoms to a gastrointestinal cause 61% of the time, versus 26% in white patients.

Marvel MK, Epstein RM, Flowers K, Beckman HB: Soliciting the patient's agenda: Have we improved? JAMA 1999;281:283-287.

Although this study was conducted in primary care offices and not in an ICU, it emphasizes the importance of the basic history-taking process and listening to patients. It found that physicians interrupted their patients after a mean of only 23.1 seconds and that late-arising patient concerns were more common when physicians did not solicit questions during the interview.

Section II

BASIC SCIENCE

Chapter 28
REGULATION OF GENE EXPRESSION

Edward Abraham

KEY POINTS

1. Effective transcription requires assembly of a transcriptional apparatus that consists of RNA polymerase (Pol II), the enzyme that translates DNA sequences into RNA, with activator and coactivator proteins.
2. The stability of messenger RNA (mRNA) plays an important role in determining the final levels of gene products.
3. Cellular activation results in a sequence of signaling events, in which the initially activated kinases become capable of phosphorylating serine or tyrosine residues in downstream kinases or regulatory proteins. As a result of such kinase activity, transcriptional factors, nuclear coactivator proteins, and other regulatory molecules become phosphorylated, inducing enhanced transcriptional activity.
4. Dephosphorylation of regulatory proteins is an important negative regulatory event, resulting in down-regulation of transcriptional events, leading to a return to baseline levels of transcriptional activity.
5. The transcriptional regulatory factor nuclear factor-κB (NF-κB) is a central participant in modulating the expression of many of the immunoregulatory mediators involved in sepsis, acute lung injury, acute renal failure, and other organ system dysfunctions associated with critical illness and other inflammatory conditions, such as rheumatoid arthritis and inflammatory bowel disease.
6. The regulation of gene transcription is modulated positively by transcriptional activators and negatively by transcriptional repressors.
7. Interactions between transcriptional factors and chromatin structure determine that genes are transcribed at appropriate times and levels in response to cellular activation.

The expression of gene products is regulated at multiple steps. The initial events involve activation of intracellular kinases that phosphorylate transcriptional factors, regulatory cytoplasmic and nuclear proteins, resulting in enhanced gene transcription and messenger RNA (mRNA) production. Examples of such cascades are the phosphorylation of the p65 subunit of the transcriptional factor nuclear factor-κB (NF-κB), which increases transcriptional activity,[1,2] or of the inhibitory protein IκB-α,[3,4] which facilitates the degradation of IκB-α and nuclear translocation of NF-κB. Similarly, phosphorylation of the transcriptional factor cyclic adenosine monophosphate (cAMP) responsive element binding (CREB) protein on serine 133 by phosphokinase A, calmodulin kinases, or extracellular regulated kinases or through other kinase-mediated events enhances its transcriptional activity.[5,6] In the case of NF-κB, liberation from IκB-α allows NF-κB dimers to translocate to the nucleus, where they can interact with specific sequences in the promoter regions of genes and help initiate transcription.[7,8] CREB is normally bound to promoter sequences, but is not transcriptionally active unless phosphorylated on serine 133.[5,6]

Although availability in the nucleus of specific transcriptional factors is necessary for their interaction with binding sequences of the promoters and subsequent gene transcription, it is not sufficient. Evidence indicates that the presence of transcriptional factors in different locations in the nucleus is associated with different transcriptional activity.[9] Such information shows that it is not enough for a transcriptional factor simply to reach the nucleus to initiate transcription, but rather that there are differences between nuclear locations and that the transcriptional factor must find its way to the correct site before it can participate in gene expression.

Effective transcription requires assembly of a transcriptional apparatus that consists of RNA polymerase (Pol II), the enzyme that translates DNA sequences into RNA, with activator and coactivator proteins (Fig. 28-1). Pol II, when in the appropriate configuration with additional scaffolding, activator, and coactivator proteins, is required for transcription of genes from the 5′ end of their coding sequence. The transcriptional machinery cannot gain access to relevant promoter sites and initiate transcription unless chromatin surrounding the DNA is modified through acetylation, methylation, and association with many proteins, of which one of the most important seems to be ubiquitin.[10] Ubiquitin is a highly conserved 76-amino acid protein that is linked covalently to lysine residues in other proteins, including histones associated with DNA. Modifications in histones accomplished by addition of methyl and acetyl groups and of ubiquitin are required to expose DNA and allow access of the transcriptional apparatus to relevant promoter sequences, where it can initiate transcription.[11-13]

When mRNA is produced, its stability plays an important role in determining the final levels of gene products.[14-16] mRNA that remains available for translation for longer periods generally is associated with greater amounts of translated proteins. Post-translational events, including modification of protein length and structure, also are involved, in

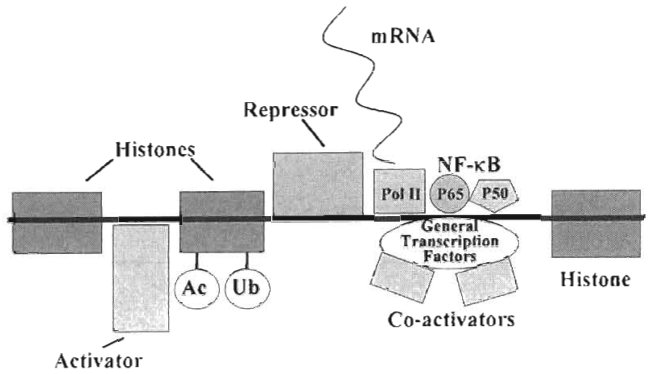

FIGURE 28–1. Regulation of gene transcription involves an interplay of histones, DNA, activators, repressors, and transcriptional machinery, primarily to allow RNA polymerase (Pol II) to produce mRNA. For transcription to occur, histones are acetylated and ubiquitylated, and a transcriptional apparatus, consisting of RNA polymerase, transcriptional factors (e.g., NF-κB), activators, and coactivators is assembled. The modifications of histones allow RNA polymerase to have access to relevant sequences in the promoter regions of genes and to initiate transcription from the 5′ end of the gene's coding sequence.

modifying intracellular and extracellular protein levels. An example of such post-translational regulation concerns the activity of caspase-1 in cleaving pro-interleukin (IL)-1β or pro-IL-18 to the mature extracellularly secreted forms of IL-1β and IL-18.[17-19]

KINASE-INDUCED PHOSPHORYLATION EVENTS AND GENE ACTIVATION

Phosphorylation of proteins by kinases often leads to their participation in signaling events that result in modified cellular activity. Kinase cascades become activated through receptor occupancy with their specific ligands, such as the interaction of lipopolysaccharide with the type 4 Toll-like receptor (TLR4) (Fig. 28-2).[17,20-22] Alterations in the intracellular milieu, including changes in oxidation state induced by increased concentrations of reactive oxygen intermediates in or around cells, also can result in the activation of kinases. Exposure of cell populations to hydrogen peroxide can produce increased activity of the inhibitor of NF-κB kinase (IKK) complex, resulting in enhanced nuclear concentrations of the NF-κB transcriptional factor.[23]

Cellular activation results in a sequence of signaling events, where the initially activated kinases become capable of phosphorylating serine or tyrosine residues in downstream kinases or regulatory proteins. As a result of such kinase activity, transcriptional factors, nuclear coactivator proteins, and other regulatory molecules become phosphorylated, inducing enhanced transcriptional activity. An example of such a cascade is the phosphorylation of the transcriptional coactivator TATA Box binding protein (TBP), a nuclear coactivator that participates in the transcriptional apparatus. Phosphorylation of TBP through activation of p38-related kinases allows enhanced association with NF-κB and increased transcription of NF-κB-dependent genes.[24]

In the same way that phosphorylation of regulatory proteins leads to increased transcriptional activity, dephosphorylation is an important negative regulatory event, resulting in down-regulation of transcriptional events, leading to a return to baseline levels of transcriptional activity. An example of the importance of dephosphorylation in modulating transcription is provided by data showing that the serine/threonine protein phosphatase 2A (PP2A) participates in regulating the activity of the activating protein 1 (AP-1) transcriptional complex.[25] In particular, AP-1 is formed and becomes transcriptionally active when phosphorylated c-Jun associates with c-Fos. Phosphorylation of c-Jun is under the regulatory control of the c-Jun N-terminal kinase (JNK). PP2A is a key regulator of JNK through its ability to dephosphorylate JNK, decreasing JNK's activity and ability to phosphorylate c-Jun. Activation of PP2A can also down-regulate AP-1-dependent transcription through its effects in dephosphorylating c-Jun.

Kinase-mediated phosphorylation is involved in enhancing nuclear accumulation of transcriptional factors, a necessary event for the initiation and enhancement of transcription. Nuclear translocation of the transcriptional factor NF-κB depends on IKK-mediated phosphorylation of inhibitory IκB cytoplasmic molecules, which leads to their destruction in the 26S proteosome and liberation of NF-κB to move into the nucleus.[4,26,27] This issue is discussed in more detail in the next section of this chapter.

NUCLEAR FACTOR κB

NF-κB is a prototypical transcription factor involved in acute inflammatory responses associated with critical illness. The transcriptional regulatory factor NF-κB is a central participant in modulating the expression of many of the immunoregulatory mediators involved in sepsis, acute lung injury, acute renal failure, and other organ system dysfunctions associated with critical illness and other inflammatory conditions, such as rheumatoid arthritis and inflammatory

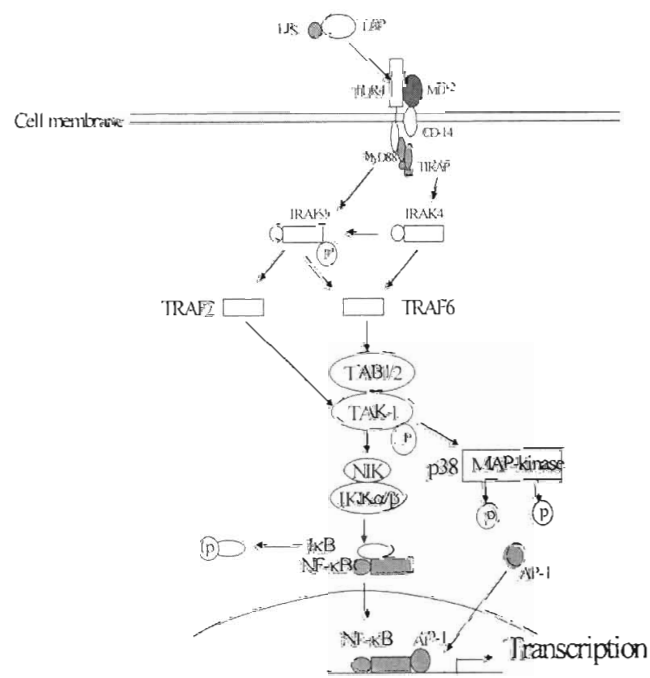

FIGURE 28–2. Interaction of lipopolysaccharide (LPS) and the LPS binding protein (LBP) with the type 4 Toll-like receptor (TLR 4) initiates a sequence of intracellular signaling events, involving activation of kinases that associate with scaffolding proteins, which ultimately leads to gene transcription through the activation of transcriptional regulatory factors, such as NF-κB and AP-1.

bowel disease. Signaling pathways initiated by engagement of TLRs, such as TLR 2 and TLR 4, by bacterial products or of cytokine receptors, including those for tumor necrosis factor (TNF)-α and IL-1, lead to nuclear accumulation of NF-κB and enhanced transcription of genes responsible for the expression of cytokines, chemokines, adhesion molecules, apoptotic factors, and other mediators of the acute inflammatory response associated with multiple organ system dysfunction in sepsis, acute lung injury, pancreatitis, burns, and other ICU conditions.[7,8,26,28,29]

In the active DNA binding form present in the nucleus and involved in transcriptional events, NF-κB is a dimer composed of members of the Rel family. Five mammalian members of this family have been identified: NF-κB1 (p50 and its precursor p105), NF-κB2 (p52 and its precursor p100), c-Rel, Rel A (p65), and Rel B. All of these proteins share a highly conserved Rel homology domain of approximately 300 amino acids composed of two immunoglobulin-like sequences. The Rel homology domain is responsible for dimerization of the NF-κB subunits, interaction with inhibitory IκB molecules, and DNA binding.

Various combinations of NF-κB have different transcriptional efficiency. The p50:p65 heterodimer promotes transcription, whereas p50:p50 homodimers suppress gene activation through preventing access to gene promoters by the transcriptionally active p50:p65 heterodimers.[30] Additionally, there is evidence that phosphorylation of the NF-κB subunits, particularly of p65, is important in optimizing transcriptional potential.[1]

NF-κB dimers normally are retained in the cytoplasm through interaction with inhibitors of the IκB family. Seven IκB molecules have been identified: IκB-α, IκB-β, IκB-γ, IκB-ε, Bcl-3, p100, and p105. Through their association with NF-κB cytoplasmic heterodimers and homodimers, IκB molecules mask the nuclear localization sequence of NF-κB and prevent its movement to the nucleus. Although IκB molecules initially were thought to reside only in the cytoplasm, more recent evidence shows that they shuttle in and out of the nucleus and have important roles in regulating the presence and activity of NF-κB dimers in the nucleus and the cytoplasm (Fig. 28-3).[31]

Cellular activation that leads to nuclear translocation of NF-κB and enhanced transcription of NF-κB-dependent genes can be induced by multiple stimuli, including LPS, peptidoglycans, and lipotechoic acid (from gram-positive bacteria); cytokines (e.g., TNF-α, IL-8, and IL-1β); T-cell and B-cell mitogens; complement fragments (e.g., C5a); reactive oxygen species; G-protein coupled receptor agonists; and other mediators associated with infection, ischemia, and stress responses. In a critically ill patient, in whom such proinflammatory stimuli are present at increased levels, the degree of NF-κB activation has been shown to correlate with patient outcome. In particular, nuclear concentrations of NF-κB in peripheral blood mononuclear cells from septic patients are higher in patients who subsequently die than in survivors.[32,33] Similar patterns of NF-κB activation, with greater nuclear accumulation being associated with a worse clinical outcome, specifically mortality or prolonged time on the ventilator, have been shown to be present among neutrophils from patients with acute lung injury.[34] These associations between enhanced nuclear levels of NF-κB and worse clinical outcome are not surprising because increased levels of many of the proinflammatory mediators under the regulatory control of NF-κB, such as TNF-α or IL-8, have

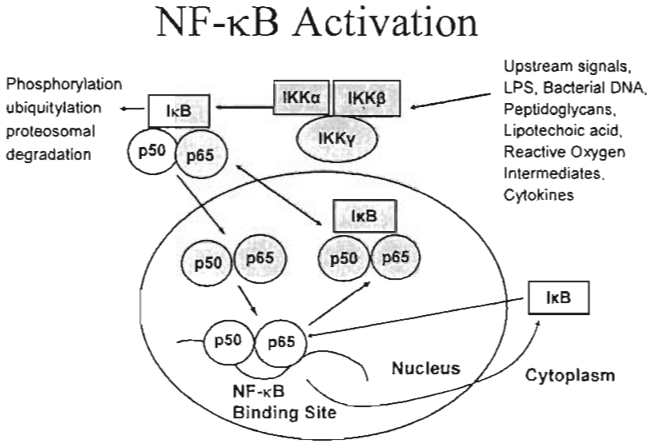

FIGURE 28–3. Multiple mediators associated with critical illness lead to activation of the IKK complex, which then phosphorylates IκBs, such as IκB-α, resulting in degradation of IκB and liberation of NF-κB dimers to move into the nucleus. The IKK complex consists of the kinases IKKα and IKKβ and the scaffolding protein IKKγ. In the nucleus, NF-κB binds to specific sites in promoter regions, where it can initiate transcription, including that of IκB-α. IκBs are primarily present in the cytoplasm, but are able to enter the nucleus, where they can facilitate the disassociation of NF-κB from binding to promoter sites and facilitate movement of NF-κB to the cytoplasm.

been shown to participate in acute inflammatory responses and organ dysfunction in sepsis, acute lung injury, and many other critical illnesses.

After cellular activation by appropriate stimuli, IκB molecules associated with NF-κB in the cytoplasm (particularly IκB-α) are phosphorylated, linked to the protein ubiquitin (i.e., ubiquitylated), and degraded by the 26S proteosome. Degradation of IκB molecules permits nuclear translocation of NF-κB, where it binds to specific sequences in the promoter regions of genes, participates in the formation of a transcriptional apparatus consisting of activator and coactivator proteins (including CREB binding protein (CBP) and RNA polymerase), and initiates transcription (see Fig. 28-3).

Phosphorylation of IκB occurs through activation of IKK.[4,26,29] Three components of IKK have been identified: the serine/threonine kinases IKKα and IKKβ and a regulatory subunit called IKKγ or NEMO. Many different protein kinases activate IKK, including Akt, PKCζ, MEKK1, MEKK2, MEKK3, NIK, COT/TPL-2, and TAK1. Although p38 has been shown to increase NF-κB-dependent transcription, it is unclear if this kinase has a role in enhancing nuclear translocation of NF-κB or whether its activity is primarily due to phosphorylation of NF-κB-associated coactivator proteins, such as TBP, or to enhancing phosphorylation of NF-κB subunits, such as p65. TAB1, an adapter protein that associates with p38α, is able to activate the kinase TAK1, leading to downstream phosphorylation and enhancement of activity of the IKK complex.[21,24,35,36]

Many of the genes regulated by NF-κB participate in inflammatory reactions leading to organ dysfunction and death in critically ill patients with conditions such as sepsis, acute lung injury, hemorrhage, burns, and pancreatitis.[7,8,26,28,37-40] A partial list of NF-κB inducible genes is provided in Table 28-1. Several of the cytokines under the regulatory control of NF-κB, such as IL-1 and TNF-α, also are able to induce further activation of this transcriptional factor, leading to potentiation of inflammatory responses

TABLE 28–1. NF-κB INDUCIBLE GENES INVOLVED IN CRITICAL ILLNESS

Class	NF-κB-Dependent Genes
Cytokines	IL-1α and IL-1β
	TNF-α
	G-CSF
	GM-CSF
	IL-6
	IFN-β
Chemokines	MIP-1α
	MIP-2
	IL-8
Adhesion molecules	ICAM-1
	VCAM-1
	E-selectin
	ELAM-1
Coagulation factors	Tissue factor
	Tissue factor pathway inhibitor
Others	Inducible nitric oxide synthase
	Cyclooxygenase-2
	IκB-α
	C3 complement
	Complement factor B

in the critically ill patient and further enhancement of NF-κB-dependent gene expression.

ROLES OF UBIQUITIN AND CHROMATIN IN MODULATING TRANSCRIPTION

The regulation of gene transcription is modulated positively by transcriptional activators and negatively by transcriptional repressors. Transcriptional activators function through facilitating direct contact of components of the general transcriptional apparatus, such as TBP, with histone-modifying moieties, such as histone acetyl transferases, and activator and coactivator proteins, such as CBP. These interactions result in modifications of chromatin structure, allowing direct access of the transcriptional complex, which includes RNA polymerase, to DNA, where the gene then can be transcribed (see Fig. 28-1). Transcriptional repressors antagonize many of these steps by deacetylating histones, blocking the recruitment or assembly of the transcriptional apparatus, or interacting with transcriptional co-repressors.

Interactions between transcriptional factors and chromatin structure determine that genes are transcribed at appropriate times and levels in response to cellular activation. The ubiquitin system is composed of a family of proteins that are capable of linking covalently to target proteins.[10,21,41] *Ubiquitylation* is the process by which ubiquitin is conjugated to a substrate protein and is essential for regulating transcription and facilitating access of transcriptional factors to relevant promoter sites. After phosphorylation on serines 32 and 36, IκB-α is ubiquitylated, an essential step that facilitates its recognition and breakdown in the 26S proteosome, allowing NF-κB to move to the nucleus and initiate transcription.[20,21,41] Modification of chromatin through covalent association with ubiquitin influences other chromatin modifications, such as acetylation and methylation, involved in transcriptional control.

Ubiquitylated forms of histones H1, H2A, and H2B are associated specifically with actively transcribed genes, providing a marker of transcriptionally active chromatin. Ubiquitylation of H2B is required for methylation of the histone H3 at lysine residues 4 and 79, which is required for telomeric gene silencing, the transcriptional down-regulation of the expression of genes proximal to the telomere.[10] It also is likely that histone ubiquitylation is involved in the activation of genes. Ubiquitylation of the linker histone H1 seems to be involved in enhancing activity of the general transcription factor TFIID complex.[10]

COORDINATION OF STEPS INVOLVED IN GENE EXPRESSION

The final step in the transcriptional regulatory process is initiation of transcription at the 5′ end of a gene by RNA polymerase II (Pol II), resulting in production of mRNA, which, after migrating to the cytoplasm, is translated to protein.[42,43] As described earlier, access of RNA polymerase to relevant gene sequences is a highly regulated event, involving a balance between stimulatory events initiated by cellular activation through receptor-ligand interaction, kinase activation, phosphorylation of regulatory proteins, modification of histones, and down-regulatory processes that occur through phosphatases and other kinases able to modulate the phosphorylation, acetylation, and ubiquitylation that lead to gene expression. Exquisite control of gene expression is achieved through the interplay of these multiple regulatory processes. Additional fine-tuning of protein production is accomplished through post-transcriptional events, involving control of mRNA stability, translational rates, and post-translocation modification of proteins.

Despite the regulatory processes that are available to modulate gene expression, critical illness often is associated with altered and pathologic production of immunoregulatory and other molecules that induce the development of organ dysfunction. Gene polymorphisms that lead to overexpression of regulatory molecules, such as plasminogen activator inhibitor-1 (PAI-1), which is involved in coagulation cascades, or of proinflammatory or anti-inflammatory mediators, such as TNF-α or IL-1ra, are associated with outcome from severe infections.[44-48] Similarly, increased activation of kinases, such as Akt, or of transcriptional factors, such as NF-κB, in neutrophils or other cell populations correlates with worse outcome from acute lung injury.[34] Future use of gene expression arrays and proteomics, which would permit identification of genes and proteins whose expression is altered in cell populations from patients at risk for or with a critical illness, are likely to help not only in early diagnosis, but, more importantly, also should permit therapies to be tailored to correct the alterations in gene and protein expression that contribute to organ system dysfunction and death in critically ill patients.

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Chapter 29

THE NEUTROPHIL: BALANCING ANTIMICROBIAL EFFECTIVENESS AND THE POTENTIAL FOR DAMAGE TO THE HOST

Theo J. Morales • Tomoko Suzuki • Gregory P. Downey

KEY POINTS

1. Neutrophils are key cells in the innate immune system serving in host defense.
2. The importance of each step in neutrophil functioning is demonstrated by a variety of disease states that result from deficiencies in these specific functions.
3. "Excessive" or unregulated neutrophil activation may contribute to the host cell damage seen in a variety of inflammatory based diseases such as acute respiratory disease syndrome (ARDS).
4. Proteases, reactive oxygen and nitrogen species, and lipid metabolites from activated neutrophils may all contribute to the host damage seen in ARDS.
5. Signal transduction pathways involving the enzyme PI3 kinase, various mitogen-activated protein kinases, especially the p38 pathway, and ultimately the transcription factor NF-κB have been implicated in contributing to the increased neutrophil activity seen in ARDS.
6. Modification of neutrophil function to achieve the optimal balance between adequate host defense and minimal host damage remains on the horizon.

Neutrophils contribute to host defense primarily through the recognition and destruction of pathogenic microorganisms, a functional role that is achieved through a series of rapid and coordinated responses, including chemotaxis, phagocytosis, and release of cytotoxic products. These responses are initiated by the interaction of cell surface receptors with specific ligands found on microbial targets or in the inflammatory milieu and the consequent induction of intracellular signaling pathways that couple such activating stimuli to physiologic antimicrobial responses. Paradoxically, these cellular and biochemical events may also result in damage to host tissues in inflammatory conditions, including ischemia-reperfusion injury, sepsis, acute lung injury (ALI), and the acute respiratory distress syndrome (ARDS). Therefore, to maximize host defense capabilities while minimizing damage to host tissues ("collateral damage"), neutrophil microbicidal responses must be tightly regulated. Notwithstanding the potential role of the neutrophil in inflammatory injury, it is important that the primary function of this "professional phagocyte" in host defense and in resolution of inflammation and tissue remodeling by clearance of debris is not eclipsed. In this chapter we briefly focus on the functions of neutrophils and then discuss the evidence implicating neutrophils in ARDS and ALI with ramifications for potential treatment options on the horizon.

NEUTROPHIL PRODUCTION

Neutrophils, so named because they stain in a neutral manner with Wright's stain, are crucial players in inflammation and the innate immune response. Formed in the bone marrow, the neutrophil progresses through defined stages of development from the myeloblast, promyelocyte, myelocyte, metamyelocyte, and band cell eventually to the mature polymorphonuclear neutrophil (PMN) (Fig. 29-1). This progression takes about 9 days. It is generally accepted that only the myeloblast, promyelocyte, and myelocyte are capable of cell division. Studies suggest approximately 100 billion neutrophils are produced in an adult per day. This can increase 1000-fold in times of need through the action of cytokines such as granulocyte-macrophage colony-stimulating factor. Once in the bloodstream neutrophils have a half life of approximately 7 hours.[1] A large group of mature neutrophils remain in the bone marrow for up to 2 days and outnumber circulating neutrophils 20 to 1. In addition, a portion of mature neutrophils marginate preferentially in the pulmonary vasculature. The reasons for this include the relatively large size of neutrophils compared with pulmonary capillaries, the organization of the pulmonary capillary bed, the lower pressure and shear stress of the pulmonary as compared with the systemic circulation, the less deformable nature of neutrophils as compared with red blood cells, and the fact that the pulmonary vasculature receives the entire cardiac output.[3]

The importance of the neutrophil in immune function is emphasized by various congenital and acquired conditions that result in neutropenia.[4] These patients are at risk for severe skin, lung, and other invasive bacterial and fungal infections.

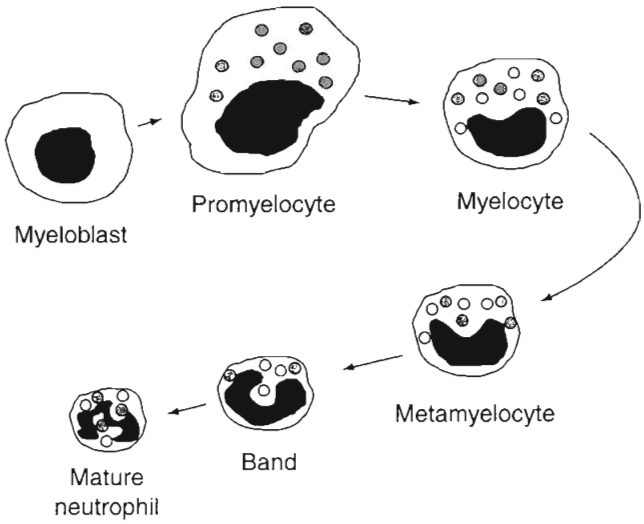

FIGURE 29–1. Progression from myeloblast to myelocyte takes 4 to 6 days. Promyelocytes develop azurophilic granules and myelocytes develop specific granules. Maturation from myelocyte to mature neutrophil takes 5 to 7 days. (Adapted from Skubitz KM: Neutrophilic leukocytes. In Lee FJ et al [eds]: Wintrobe's Clinical Hematology. Philadelphia, Lippincott Williams & Wilkins, 1000, pp 300-350; and Abramson SL, Malech HL, Gallin JI: Neutrophils. In Crystal WJ [ed]: The Lung: Scientific Foundations. New York, Raven, 1991, pp 553-563.)

BASIC NEUTROPHIL FUNCTION

The physiologic functions of neutrophils that are involved in their antimicrobial role are described individually.

ADHESION

To eradicate microorganisms, circulating neutrophils must move out of the vasculature into the infected tissues. Adhesion of neutrophils to vascular endothelium is the first step in this process.[1,5] Neutrophils and endothelial cells express a variety of cognate adhesion molecules on their respective surfaces (Table 29-1), the expression of which is regulated by various stimuli present in an inflammatory milieu. Selectins mediate the initial rolling and tethering of a circulating neutrophil to the vascular endothelium. L-selectin is expressed on neutrophils whereas P- and E-selectin are found on endothelial cells. The interaction between selectins and their cognate ligands serves to tether neutrophils, slowing them in their journey through the microvasculature, where they sense chemoattractants and other inflammatory agonists, leading to firm adhesion mediated by integrins interacting with endothelial ligands. The major integrins expressed by neutrophils are β_2 integrins (CD11/CD18), although recent studies have indicated that activated neutrophils also express $\alpha_4\beta_1$ integrins.[6] Endothelial cells express intercellular adhesion molecules (ICAMs), which are members of the IgG superfamily and are ligands for β_2 integrins and mediate firm adhesion. After adhering to the endothelium, neutrophils spread and then move between or through endothelial cells and migrate along chemoattractant gradients toward the invading pathogens. Gap junctions form between neutrophils and endothelial cells and serve to facilitate cell communication to assist in transmigration.[7]

The importance of adhesion molecules in innate immunity is illustrated by the propensity to infections in congenital diseases where these molecules are deficient or absent. Leukocyte adhesion deficiency (LAD) type I is the result of a deficiency of β_2 integrins.[4,8] As a consequence, neutrophils cannot adhere and migrate to sites of infection, resulting in a predisposition to recurrent, severe infections, despite a high neutrophil count, and delayed umbilical stump separation in the newborn. LAD type II, secondary to defective selectins,[4] is an autosomal recessive condition with characteristic physical features, short stature, and a predisposition to recurrent infections as well.

TABLE 29–1. SELECTED NEUTROPHIL AND ENDOTHELIAL ADHESION MOLECULES

	Other Names		Ligands
Neutrophil Integrins			
$\alpha_2\beta_1$			Collagen, laminin
$\alpha_3\beta_1$			Collagen, laminin, fibronectin, tenascin
$\alpha_4\beta_1$	VLA-4	CD49d/CD29	VCAM-1, fibronectin
$\alpha_5\beta_1$	VLA-5	CD49e/CD29	Fibronectin
$\alpha_6\beta_1$	VLA-6	CD49f/CD29	Laminin
$\alpha_9\beta_1$			VCAM-1, tenascin
$\alpha_L\beta_2$	LFA-1	CD11a/CD18	ICAM-1 to 3
$\alpha_M\beta_2$	Mac-1	CD11b/CD18	ICAM-1, C3bi, fibrinogen, factor x
$\alpha_X\beta_2$	P150,95	CD11c/CD18	Fibrinogen, C3bi
$\alpha_V\beta_3$			Vitronectin
Neutrophil Selectins			
L-selectin	LAM-1	CD62L	Sialylated carbohydrates
Endothelial Selectins			
E-selectin	ELAM-1	CD62E	Sialylated carbohydrates
P-selectin	GMP-140, PADGEM	CD62P	Sialylated carbohydrates
Endothelial Ig Family			
ICAM-1		CD54	LFA-1, Mac-1
ICAM-2		CD-102	LFA-1

Data from references 1, 27, and 79.

CHEMOTAXIS

Once out of the vasculature, neutrophils must be able to find their way rapidly to areas of inflammation and infection. This process of directional motility along a chemoattractant gradient is known as chemotaxis. Many chemoattractants bind to G-protein–coupled 7 transmembrane spanning domain receptors (e.g., receptors for fMLP, C5a, platelet-activating factor, leukotriene B_4, interleukin [IL]-8), leading to dissociation of the G-protein complex and activation of signal transduction cascades.[9] Ultimately, polymerization and reorganization of the actin cytoskeleton occurs, driving extension of a pseudopodia or lamellipodia, which are sheet-like protrusions of membrane rich in actin filaments.[10] Adenosine triphosphate–dependent contraction mediated by myosin then contracts the cytoskeleton toward the leading pseudopodium.[1] Cycles of protrusion, adhesion, contraction, and de-adhesion are repeated, allowing the neutrophil to move through the extracellular membrane. Defective actin polymerization is one cause of a primary chemotactic disorder manifest clinically as recurrent infections, typically of fungal origin.[8]

PHAGOCYTOSIS

The process of phagocytosis, or engulfment of particles greater than 3 μm, is important both for removal of dead cells and for microbial killing.[11] Importantly, most microbial killing occurs inside the neutrophil. Phagocytosis occurs when the neutrophil internalizes microscopic particles through extensions of the plasma membrane that surround the particle and fuse around it, isolating the particle in a nascent phagosome (Fig. 29-2).[12,13] This serves to compartmentalize both the pathogen and the leukocyte-derived cytotoxic products that are destined to kill and digest the pathogen.

Neutrophils can recognize invading microbial pathogens by virtue of specific membrane receptors that recognize highly conserved motifs on pathogens not normally present on higher-order eukaryotic cells (e.g., specific carbohydrates, glycolipids such as lipopolysaccharide, glycoproteins, and proteins).[11] Collectively, these receptors are termed *pathogen-associated molecular pattern (PAMP) receptors.*[14] Phagocytes also express receptors that recognize specific host proteins such as antibodies or complement that coat ("opsonize") the pathogen. These "phagocytic receptors" include receptors for the Fc fragment of antibodies (Fc receptors) and complement receptors such as CR3 that recognize pathogens coated with antibodies or complement, respectively. Importantly, opsonization improves phagocytic efficiency dramatically.[12] There is no known specific inherited disorder resulting in a primary phagocytic defect.[8]

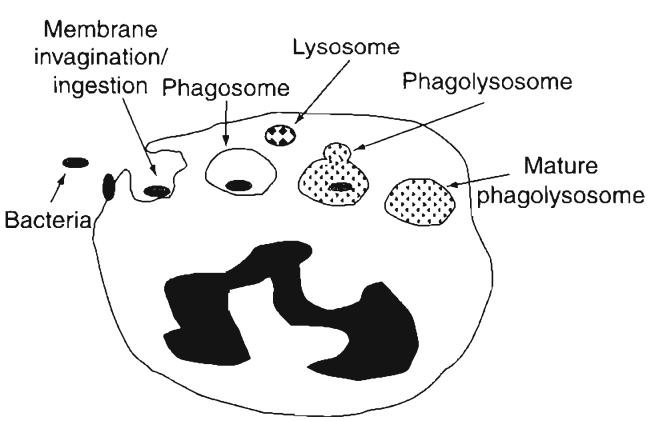

FIGURE 29–2. Process of phagocytosis.

MICROBIAL KILLING

As previously stated, most microbial killing occurs inside the neutrophil in specialized compartments (phagosome, phagolysosome). In this way, potentially damaging effects of neutrophil products on host cells are minimized. The neutrophil can effectively kill microbes by releasing various molecules and compounds into the phagosome. Stimulated neutrophils, through the action of NAPDH oxidase, produce potent oxidants, including superoxide (O_2^-) and hydrogen peroxide (H_2O_2). These reactive oxygen species can be converted by myeloperoxidase to generate the hypohalous acids such as HOCl (bleach) that are extremely potent antimicrobial products. Nonoxidative killing mechanisms include acidification of the phagosome (pH 3.5 to 6), lysozyme (hydrolyses cell walls), lactoferrin (binds iron), various proteases (including elastase, collagenase, gelatinase, cathepsin G, and proteinase-3), and defensins (small microbicidal cationic peptides).[1,15]

Neutrophils contain four types of intracellular granules: azurophilic (primary), specific (secondary), and gelatinase (tertiary) granules and secretory vesicles.[1] The compounds contained in these granules aid in microbial killing and facilitate cell adhesion and locomotion by delivery of granule-associated proteins to the phagosome or to the cell surface (Table 29-2).

The Chédiak-Higashi syndrome is an autosomal recessive disorder of dysfunctional granules. Its molecular basis is not completely understood, but giant primary granules are seen in neutrophils, and those affected suffer recurrent skin and pulmonary infections, typified by delayed *Staphylococcus* killing. Rarely, specific granule deficiencies are seen in which neutrophils are missing secondary granules, resulting in a poor inflammatory response and recurrent infections.[4,8] MPO deficiency, especially in combination with diabetes, leads to a predisposition to *Candida* infections. Chronic granulomatous disease, caused by defects in the phagocyte NADPH oxidase, results in recurrent infections with catalase-positive organisms such as *Staphylococcus aureus* and granuloma formation.[4,8]

SECRETION OF INFLAMMATORY MEDIATORS

Although for many years the primary function of neutrophils was viewed as responding to signals derived from other host cells and invading pathogens, it is now appreciated that these cells also play an active role in regulating inflammation though production and release of the cytokines IL-1, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α).[1,16] In addition, leukocyte-derived proteases participate in substrate processing that can result in the formation and release of chemotactic peptides from surface- or matrix-bound precursors.

APOPTOSIS

Although not classically considered a neutrophil antimicrobial function, apoptosis serves an important purpose. Once the

TABLE 29–2. COMPOSITION OF HUMAN NEUTROPHIL GRANULES

	Azurophil (Primary)	Specific (Secondary)	Gelatinase (Tertiary)	Secretory
Membrane Proteins	CD66c, CD63, CD68	CD11b (Mac-1), CD15, CD66a, CD66b FMLP receptor Fibronectin receptor G-protein α subunit Laminin receptor Cytochrome b_{558} NB 1 antigen Rap 1 & 2 Thrombospondin receptor TNF receptor Vitronectin receptor u-PA receptor	CD11b FMLP receptor Cytochrome b_{558} Laminin receptor Diacylglycerol deacylating enzyme	CD10, CD11b, CD13, CD16, CD35 (CR1), CD45 Alkaline phosphatase Cytochrome b_{558} FMLP receptor DAF u-PA receptor
Serine Proteases	Elastase Cathepsin G Proteinase 3 Esterase N			
Microbicidal Enzymes	Myeloperoxidase Lysozyme Azurocidin Neuraminidase (sialidase)	Lysozyme Neuraminidase	Lysozyme	
Metalloproteinases	Collagenase	Collagenase Gelatinase	Gelatinase	
Acid Hydrolyases	*N*-Acetyl-β-glucosaminidase Cathepsin B Cathepsin D β-Galactosidase β-Glucuronidase β-Glycerophosphatase α-Mannosidase			
Inhibitors	α_1-Antitrypsin Heparin binding protein	Apolactoferrin Vitamin B_{12}–binding protein Protein kinase C inhibitor Histaminase Heparinase		
Other	Defensins Bactericidal permeability increasing protein (BPI) Acid mucopolysaccharide Ubiquitin	Plasminogen activator hCAP-18 SGP28 β_2-Microglobulin Lipocalin	Acetyltransferase	Albumin Tetranectin pro-u-PA/u-PA

Adapted from Skubitz KM: Neutrophilic leukocytes. In Lee GR, Lukens J, Paraskevas F, et al (eds): Wintrobe's Clinical Hematology. Philadelphia, Lippincott Williams & Wilkins, 1999, pp 300-350; and Abramson SL, Malech HL, Gallin JI: Neutrophils. In Crystal RG, West JB (eds): The Lung: Scientific Foundations. New York, Raven, 1991, pp 553-563.

threat of microbial invasion or tissue injury is over, inflammation must be rapidly down-regulated and neutrophils eventually disposed of in a manner that will not result in release of cytotoxic products with consequent host cell injury. One noninflammatory way of disposal of effete (spent) neutrophils is through apoptosis, also known as programmed cell death.[17] There are many signals for this process involving a variety of signal transduction pathways, and this subject is beyond the scope of this chapter, but interested readers are referred to recent reviews of this important subject.[17]

NEUTROPHILS AND INFLAMMATORY TISSUE INJURY

Although neutrophils primarily serve a protective role in the body, it is apparent that as part of the exuberant inflammatory response, neutrophils and their products can contribute to the tissue injury and dysfunction seen in sepsis and ALI and ARDS. Normally, unstimulated neutrophils pass through the pulmonary vasculature and are retained in the pulmonary capillary for seconds to minutes. This transit time can be affected by hemodynamic and soluble factors but no damage to the lungs typically occurs under physiologic circumstances. However, under pathologic conditions such as in ALI and ARDS, large numbers of neutrophils are sequestered in the microvasculature of the lung and other organs. In these strategic locations, the neutrophils become activated and may release cytotoxic products outside the cell that are capable of damaging host tissues. Under such circumstances, neutrophils are no longer innocuous. In experimental models of lung injury, there is evidence that direct activation of neutrophils, for example by preincubation with agonists such as lipopolysaccharide, can cause lung injury when reinjected into animals[18] and, conversely, that depletion of neutrophils can attenuate lung injury.[16,19,20] Despite this apparent propensity for host damage, neutrophil depletion is not a practical strategy for the treatment of ARDS for two reasons. First, there is evidence that ARDS can occur in neutropenic patients,[21,22] implying that neutrophil-independent mechanisms of lung injury may still be sufficient to engender acute lung injury. Second, and perhaps most importantly, is that neutrophil depletion undoubtedly predisposes the patient to infection, which is the most common cause of death in patients with ARDS.

MICROVASCULAR SEQUESTRATION AND ADHESION OF LEUKOCYTES

One of the earliest changes in ALI is increased neutrophil sequestration in the pulmonary capillaries that is reflected clinically by a transient leukopenia preceding respiratory deterioration.[23] The reasons for this remain incompletely understood but are likely related in part to an alteration in cellular biophysical properties (cell stiffening) as a consequence of polymerization and redistribution of the actin cytoskeleton.[24] This makes the 8-μm neutrophil less deformable and more likely to be unable to negotiate the 5.5-μm-wide pulmonary capillaries. Various signals, including IL-1, IL-6, IL-8, and TNF-α, mainly from alveolar macrophages and leukocytes, and bacterial products such as formyl peptides and lipopolysaccharide, can stimulate neutrophils and contribute to microvascular sequestration.[25] Alternatively, increased sequestration may be related to marrow release of neutrophils; in a rabbit model, therapy with granulocyte colony-stimulating factor (G-CSF) caused the bone marrow to release increased numbers of neutrophils that preferentially sequestered in the lungs.[26] It is noteworthy that production of G-CSF, a potent cytokine that mobilizes bone marrow neutrophils, is stimulated by bacterial products as well as host-derived cytokines such as TNF-α and IL-1.

Stimulation of neutrophils will induce the up-regulation of the number and function of cell surface adhesion molecules, leading to enhanced adhesivity.[24,27] In addition, mechanical deformation of the neutrophil, especially once activated, as occurs with passage through the pulmonary vasculature, leads to increased integrin/ICAM-1 binding.[28] Adhesion not only prolongs neutrophil sequestration and allows for transmigration but also activates various signaling cascades and thus impacts on many aspects of neutrophil function, including phagocytosis and the respiratory burst.[29]

Strategies to reduce leukocyte microvascular sequestration and adhesion with the goal of diminishing tissue injury are not always successful. In sheep, for example, blockage of P-selectin did not protect against lung injury in a burn model.[30] By contrast, in a murine "two-hit" model of endotoxemia combined with hemorrhagic shock, aggressive fluid resuscitation combined with reduced neutrophil endothelial adherence ameliorated the subsequent development of ALI.[31]

Once the neutrophil has adhered to the endothelial cell, it can then transmigrate across the endothelial barrier and into the interstitium after a chemotactic gradient.[32] In this extravascular location, neutrophil activation can lead to tissue damage. However, it is important to bear in mind that the process of transmigration from the vascular space into the alveolus per se does not necessarily lead to alterations in endothelial or epithelial permeability or injury.[33,34] Rather, damage may be mediated by extracellular release of proteases and other cytotoxic compounds during transmigration if the neutrophil is also subject to unregulated activation.[35]

ROS AND PROTEASES

There is a substantial body of evidence implicating neutrophil proteases in the pathogenesis of ALI.[36-41] Indeed, mice that are genetically deficient in both granulocyte elastase and cathepsin G are protected from LPS-induced lung injury.[42] Elastase, cathepsin G, proteinase 3, and various matrix metalloproteinases may injure the lung directly through proteolytic action on cells. Alternatively, proteases can enhance the inflammatory response by stimulating production of cytokines[43,44] and contribute to pathology through enhanced transcription of mucin genes.[45,46] In addition, proteases can cleave proteins in the airway and lead to the production of chemotactic peptides.[43,47] Evidence for benefit of protease inhibitors is limited to controlled animal studies[48] and a few small clinical trials. However, despite the purported role of proteases in ALI, the inflammatory milieu is sufficiently complex that simply delivering antiproteases to the lung may not ameliorate lung injury (hence the failure of the body's own natural antiproteases to prevent lung injury). Antiproteases can be inactivated by oxidation or by direct proteolytic cleavage rendering them ineffective. An additional consideration is the "protected space" between the neutrophil and the adjacent target cell in which a localized area of high protease concentration can exist that is isolated from high-molecular-weight antiproteases such as α_1-antitrypsin.[49]

Oxygen and nitrogen reactive species generated by neutrophils can contribute to pulmonary cell damage and the pathology of ALI.[50] Free radical formation can be secondary to the action of NADPH oxidase resulting in the formation of superoxide. Superoxide can then reduce iron, form hydrogen peroxide, and, through the action of myeloperoxidase, form oxidized halogens, such as hypochlorous acid. Alternatively, free radicals can be generated through inducible nitric oxide synthase (iNOS), leading to the formation of peroxynitrite ($ONOO^-$). Inhibition of either of these enzymes, in specific animal models, results in attenuation of ALI.[51-53]

PHOSPHOLIPASE A_2 METABOLITES

Although still uncertain, the neutrophil is believed to be a key cellular source of phospholipase A_2 (PLA_2) in the setting of ALI. This enzyme results in the formation of arachidonic acid from plasma membrane phospholipids and has been implicated in the pathogenesis of ALI. Bronchoalveolar lavage fluid PLA_2 activity is increased in humans with ARDS.[54] In animal models, delivery of PLA_2 intravenously[55] or by direct intratracheal instillation[56] can result in lung injury. Additionally, pharmacologic inhibition of PLA_2 attenuated ALI associated with intestinal ischemia reperfusion in rats[57] and targeted gene disruption of PLA_2 can attenuate ALI associated with sepsis and acid aspiration in mice.[58] PLA_2 may influence lung injury through the production of various arachidonic acid metabolites, including platelet-activating factor, lysophosphatidylcholine, and prostaglandins.[25] Inhibition of PLA_2 has not been attempted in humans with ALI/ARDS, but selective inhibition of specific PLA_2 isoforms may represent a therapeutic approach to ALI/ARDS, especially as more specific inhibitors are developed.

APOPTOSIS

Evidence exists that neutrophil apoptosis is delayed early in the course of ARDS by the presence of various proinflammatory cytokines such as GM-CSF.[17] This may result in a prolonged inflammatory process and contribute to further lung injury. In addition, delayed clearance of apoptotic neutrophils by alveolar macrophages may result in greater inflammatory injury. Mice deficient in caspase-1, a deficiency

that resulted in delayed apoptosis, demonstrated prolonged pulmonary inflammation in response to intratracheal LPS administration.[59] However, the precise relationship between prolonged neutrophil survival in ALI remains to be defined, and given the potential untoward effects on the innate immune system of reducing neutrophil survival, further study is needed before this can be a suggested therapeutic approach.[17]

SIGNAL TRANSDUCTION PATHWAYS AS POTENTIAL THERAPEUTIC TARGETS

Research is uncovering the basic mechanisms regulating neutrophil function, and it is clear that specific cell signaling molecules fulfill important actions that allow the neutrophil to assume its role in inflammation and ALI. As our understanding of these processes increases, these molecules will become potential targets for pharmacologic modification in hopes of attenuating ALI and ARDS.

NF-κB

The transcription factor NF-κB binds to specific sequences in the promoter region of the genes for inflammatory cytokines such as IL-1β, IL-6, TNF-α, IL-8, and macrophage inflammatory protein as well as in other immunoregulatory molecules such as the endothelial adhesion molecules ICAM-1 and E-selectin that relate to the development and progression of lung injury.[60,61] NF-κB is normally composed of three components that bind to and form a complex (heterotrimer) that is retained in the cytoplasm through its association with the inhibitory molecule IκB. Phosphorylation, ubiquination, and proteolysis of IκB allows NF-κB to translocate to the nucleus and induce gene transcription.

The active form of NF-κB is a dimer composed of members of the Rel family in the active DNA-binding form. Five mammalian members of this family have been described: p50, p52, p65, c-Rel, and Rel B.[62,63] Various combinations of NF-κB have different transactivation abilities; for example, p50/p65 heterodimers are able to strongly promote transcription whereas p50/p50 homodimers produce important suppressive activities on gene activation.[60]

Hemorrhage or endotoxemia induces activation of NF-κB in lungs.[16,64] In this study, induced neutropenia significantly reduced the amount of NF-κB that accumulated in the nuclei of lung cell populations.[16] These observations indicate that neutrophils are important in modulating NF-κB activation in the lungs. Inhibition of NF-κB activation with antioxidants decreased edema, diminished neutrophil infiltration, and suppressed proinflammatory cytokine expression in the lungs.[64,65] As mentioned in the preceding section on apoptosis, apoptosis is thought to be a major mechanism for the clearance of effete neutrophils and especially important in the clearance of neutrophils from the injured lung.[66] NF-κB is considered to have both antiapoptotic and proapoptotic effects. Activation of the PI3-kinase/Akt pathway has potent antiapoptotic effects and NF-κB is a target of Akt. Activation of NF-κB results in enhanced transcription of antiapoptotic genes.[67-69] On the other hand, NF-κB may also have a proapoptotic role in p53-induced cell death.[70] Thus, NF-κB activation in the setting of acute lung injury may regulate not only the expression of proinflammatory mediators but also the numbers of activated neutrophils within the lung. Therefore, regulation of NF-κB is a logical target for potential therapeutic intervention for the prevention or minimization of ALI.

PHOSPHATIDYLINOSITOL-3-KINASE

Phosphatidylinositol-3-kinases (PI3K), a group of heterodimeric enzymes, catalyze the conversion of membrane phosphatidylinositol-3,4-biphosphate (PIP_2) to PIP_3 in response to various growth factors, hormones, chemokines, and chemoattractants.[71,72] PIP_3 can then lead to the activation of other cellular signaling pathways and thus impact on many aspects of neutrophil functioning, including chemotaxis, adhesion, and apoptosis. There are four isoforms of the catalytic subunit of PI3K, with PI3K-γ found exclusively in leukocytes. PI3K-α and PI3K-β knockout mice are not viable; however, PI3K-γ –/– mice, when exposed to LPS, have reduced lung edema, neutrophil accumulation, and pulmonary cytokine levels when compared with wild-type mice.[73] Although the precise mechanism by which PI3K inhibition modulates neutrophil-mediated lung injury is not clear, PI3K may contribute to ALI through its effects on NF-κB translocation, chemotaxis, or apoptosis.[60] There are currently no pharmacologic inhibitors specific to the γ isoform of PI3K, but with time PI3K-γ inhibition may be possible. Caution must be exercised, however, given the wide-ranging effects of PI3K.

MITOGEN-ACTIVATED PROTEIN KINASE

Three distinct mitogen-activated protein kinase (MAPK) pathways have been described in neutrophils: p38, extracellular signal-regulated kinase (ERK), and c-Jun NH_2-terminal kinase (JNK). These signaling pathways, composed of a cascade of kinases that are activated by phosphorylation, function to transmit signals from the cell surface to the cytoplasm and nucleus.

The p38 pathway is important in neutrophil adhesion, chemotaxis, respiratory burst, and apoptosis.[74-76] Selective p38 inhibition, even up to 4 hours after aerosolized administration of lipopolysaccharide to mice, resulted in reduced neutrophil accumulation in the alveolar airspaces as compared with the findings in control animals.[74] Although promising, this result contrasts with observations in endotoxemia and hemorrhage-induced ALI in which p38 inhibition had no effect on neutrophil accumulation or other markers of ALI.[77] It may be that p38 activity is specific to neutrophil migration to the airspaces or in response to airway LPS.[60]

The ERK pathway has important roles in cytokine production and chemotaxis to fMLP, LTB4, C5a, and IL-8, but because ERK inhibitors are toxic, little information exists pertaining to inhibition of this pathway in modulation of lung injury.

The JNK pathway is important in cell proliferation and apoptosis and is activated in response to cellular stress. JNK-1 knockout mice have increased susceptibility to hyperoxia-induced ALI.[78] Interestingly, BAL neutrophil counts were lower in knockout compared with wild-type mice. The reason for this is not clear but may be due to decreased adhesion and migration or to increased neutrophil apoptosis. In this model it is difficult to determine the specific effects of neutrophil JNK inhibition because all cells were affected and

increased epithelial cell apoptosis contributed significantly to the overall pathology. Inhibition of MAPK pathways in cell culture and controlled animal models may help distinguish the relative importance of these pathways in different cell types. However as a potential tool in humans, unless cell specific inhibitors are developed, generalized MAPK inhibition may prove to be an unrealistic therapeutic approach.

CONCLUSION

In this chapter, we have focused initially on the essential role of neutrophils in the innate immune response to invading microbial pathogens. The importance of this function is underscored by disease states resulting from the absence (neutropenia) or dysfunction (leukocyte adhesion deficiency and chronic granulomatous disease) where affected individuals have an enhanced susceptibility to infection. It remains a paradox that these essential antimicrobial processes can apparently turn against the host and result in tissue and organ injury. It must be emphasized that inflammation is an inherently beneficial process and that only when it becomes excessive or otherwise unregulated does host damage occur. Throughout this chapter we have indicated potential therapeutic targets that might be selected in an attempt to mitigate inflammatory injury while preserving the host defense functions of these essential phagocytes. It is clear, however, that given the complexities and redundancies of this system, successful therapeutic intervention will not be an easy task.

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Chapter 30
MACROPHAGE FUNCTION

Donna M. Paulnock • Stefanie N. Vogel

KEY POINTS

1. **Macrophages are present in blood (monocytes) and all tissues of the body.** At these sites they provide a critical first line of host defense, through recognition and elimination of entering pathogens.
2. **Macrophages throughout the body express a wide range of functional activities,** including phagocytosis, secretory activity, and microbial killing. Macrophages in individual tissues express a unique spectrum of these properties that is regulated at and characteristic of that tissue site.
3. **Macrophages are the central cells in the process of inflammation,** the classic innate immune response to microbial infection. Macrophages at the site of inflammation are activated by host and microbial factors to express enhanced functional activities.
4. In addition to their roles in innate immunity, **macrophages and dendritic cells serve a critical function in the initiation of adaptive immune responses,** through their ability to serve as antigen-presenting cells (APCs) for the activation of T lymphocytes.

MACROPHAGE DEVELOPMENT AND IDENTIFICATION

Cells of the mononuclear phagocyte system are ubiquitously distributed throughout the body, present in essentially all tissues, in peripheral blood and bone marrow, and in body cavities.[1] Immature progenitor populations begin the developmental process in the bone marrow, ultimately giving rise to monocytes that enter the circulation. Blood monocytes then migrate into the peripheral tissues, where they differentiate further into resident tissue macrophages.[1,2] The network of fixed tissue macrophage populations present throughout the body thus is ideally positioned to serve as a first line of defense at the major portals of microbial entry in the body. In addition, this system of cells serves critical roles in maintaining tissue homeostasis and regeneration.[3]

Cytokines present in the bone marrow stromal milieu, including in particular granulocyte-macrophage colony-stimulating factor (GM-CSF) and colony-stimulating factor-1 (originally termed macrophage-colony-stimulating factor), control early macrophage progenitor cell commitment and differentiation.[4,5] Additional stimuli provided in each tissue, including both endogenous factors from other cells within the tissue and microbial factors resulting from the presence of circulating or commensal organisms, subsequently shape the functional and phenotypic attributes of resident macrophages present at that site, giving rise to cells adapted to perform specific functions within this local environment.[6-8] For example, in the liver, the fixed macrophage population, the Kupffer cells, provides key detoxification functions whereas microglia, specialized brain macrophages, are believed to provide cytokines and other growth and differentiation factors essential for other brain cells. Thus, a given macrophage population will have phenotypic and functional characteristics both in common with and distinct from macrophages found at other defined locations.

These aspects of macrophage development and anatomic location have made it difficult to identify markers that unequivocally define macrophages at various developmental stages or in various tissue sites. Few, if any, of the available monoclonal antibodies against macrophage surface antigens are either fully macrophage specific or identify all macrophage subpopulations. Nonetheless, recent characterizations have provided information on some molecules expressed solely by cells within the mononuclear phagocyte lineage. The antibody F4/80, although still functionally ambiguous, detects a cell surface glycoprotein that is expressed by mature mouse macrophages and often is used to identify these cells in tissue samples and preparations of isolated cells.[9] Similarly, the MAC-1 antibody detects the C3bi receptor, a critical member of the array of surface proteins expressed by macrophages, but also is expressed by granulocytic cells in the myeloid lineage.[10] The receptor for the differentiation factor CSF-1 serves as an alternative macrophage-specific marker, reflecting the critical role of CSF-1 in macrophage differentiation, and can aid in the identification of earlier developmental stages.[11]

A number of additional functionally associated surface molecules have been used to identify these cells in tissue and blood samples, although these clearly are not macrophage specific. Such molecules include cell surface receptors for the Fc portion of immunoglobulin G, for complement-coated particles, and for acute phase response proteins normally produced during the early stages of infection.[12-14] More recently, receptors for "pathogen-associated molecular patterns" (PAMPs) have been recognized as critical components of macrophage functional activities and thus useful as markers of these and other innate immune system cells. These include the Toll-like receptors (TLR) that play a major

role in pathogen recognition and initiation of inflammatory responses and other endocytic receptors, such as type A scavenger receptors and C-type lectin family molecules.[15] However, this category of molecules again is not strictly confined to macrophages. Thus, unlike the situation for T and B lymphocytes, it has not been possible to define phenotypically distinct markers for various stages of macrophage differentiation. However, the presence of subsets of cells that belong to the mononuclear phagocyte system in mice and humans can be assessed using combinations of antibodies against sets of cell surface proteins and such reagents can be used effectively to isolate/characterize these cells.

One final issue regarding macrophage identification is the recent recognition that differentiation into mature, tissue-specific macrophages is not the only developmental option for a cell within the myeloid lineage. These cells also may give rise to dendritic cell (DC) populations. DCs and macrophages share a number of functional attributes, including internalization of pathogenic microorganisms, secretion of cytokines, and antigen presentation to T cells, although DCs clearly are recognized as the most potent professional APC for naive T cells.[16] DCs are now recognized to be descended from both lymphoid and myeloid progenitor cells, deriving from hematopoietic progenitors of those lineages as well as from blood monocytes.[17,18] The re-direction of less-mature macrophages toward DC development is driven by a variety of diverse stimuli, including multiple cytokine mediators produced during the development of immune response.[19] These observations support the idea that early in their differentiation process, macrophages retain some degree of developmental plasticity. This may contribute to the enrichment of DC populations, and therefore antigen presentation and lymphocyte activation, during immune responses but also may pose some challenges for the process of macrophage versus DC identification.

MACROPHAGE FUNCTIONAL ACTIVITIES

Functionally, macrophages are the quintessential "multitasking" cells of the immune response. Although a full review of macrophage functional activities is beyond the scope of this brief discussion, macrophages generally do express a variety of shared functional characteristics, including phagocytic capability, cytokine production, processing and presentation of antigens to lymphocytes, and killing of microbes and tumor cells.[20] These activities reflect the participation of macrophages in the process of pathogen elimination at all levels, including microbial detection, microbial engulfment and cellular destruction, and the activation of downstream immune response cellular elements. Through these activities, macrophages both act directly as antimicrobial effector cells and bridge the early innate immune response with the more antigen-specific adaptive immune response.

The ability of macrophages to phagocytose particles represents the first step in a series of events that ultimately lead to the elimination of intruding microorganisms, tumor cells, and cellular debris. Internalization of different substances is mediated through multiple distinct surface receptors. These include complement receptors, vitronectin, and other specialized receptors that recognize apoptotic cells and altered self molecules.[21] Phagocytosis can be dramatically enhanced through the use of receptors for the Fc region of immunoglobulins bound to target cells such as tumor cells and parasites.[22] Finally, as noted in the preceding section on macrophage development, a large family of pattern recognition receptors (PRR) recognize various conserved motifs (mannans, lipopolysaccharides, polyanionic molecules, formylated peptides, and others) expressed by microbes but absent in their vertebrate hosts.[23] These evolutionarily conserved receptors are critical recognition receptors for initiation of multiple innate immune functions, and aspects of their structure and function are receiving considerable attention. Although phagocytosis is not a prerequisite for PRR-mediated signaling, the uptake of organisms after sensing through PRRs couples phagocytosis and intracellular signaling in many cases.[24,25] The specific molecular events that follow PRR engagement remain to be fully characterized for each receptor; however, activation of the NF-κB pathway of signal transduction and expression of genes transcribed after activation of this transcription factor family have emerged as prominent outcomes of innate recognition.[26]

Phagocytosis of microorganisms generally is followed by two outcomes in a macrophage population: the production of biologically active secreted products and the elimination of the phagocytosed target organisms. Two independent biochemical pathways principally contribute to the ability of macrophages to eliminate intracellular pathogens and extracellular targets. Synthesis of nitric oxide (NO) appears to be responsible for much of the antimicrobial activity of macrophages against certain pathogens.[27] This simple but strikingly effective molecule, along with additional reactive nitrogen intermediates, plays an essential role in the immune response to a number of intracellular pathogens, including *Mycobacterium tuberculosis*, the protozoan parasite *Toxoplasma gondii*, and the fungus *Cryptococcus neoformans*.[28-30] Reactive oxygen metabolites also are associated with the potent antimicrobial and antitumor activity of macrophages, including, most importantly, hydrogen peroxide and superoxide anion, which are directly toxic to microorganisms.[27] Toxic oxygen-derived products are produced as a result of the action of lysosomal enzymes, including NADPH oxidases, which on fusion of the phagosome and lysosome following organism internalization act to destroy the pathogen directly.[31,32] Additional microbicidal molecules derived from macrophages, including a large class of secreted antimicrobial peptides called defensins, various enzymes such as lysozyme, and diverse competitors for essential nutrients, such as lactoferrin, provide antimicrobial action for both intracellular and extracellular microbes.[33]

A second important outcome of the interaction between pathogens and macrophages is activation of these cells to release cytokines and other soluble mediators. Macrophages produce a vast array of secreted products after antigen interaction.[34] Many of these products result from induction of new gene expression as an outcome of PRR (and other receptor) engagement and the ensuing downstream signal transduction events. Recent studies using functional genomic analyses to dissect macrophage and DC innate responses have identified three broad classes of secreted products produced by macrophages after activation: (1) cytokines and chemokines, responsible for proinflammatory and anti-inflammatory effects, cell recruitment, and cell growth; (2) non–cytokine-secretory products, including enzymes that contribute to the inflammatory response (e.g., cyclooxygenase-2), hormones, and other molecules involved in basic cellular processes; and (3) products of inducible metabolic pathways, for example, NO and H_2O_2, the downstream products of inducible enzymes.[35-37] Some molecules

within this spectrum of responses are likely to represent pathogen-specific responses, whereas others can be induced by multiple organisms or nonmicrobial activating ligands. This is, in part, regulated by the particular PRR engaged. For example, it is clear that the differential gene expression observed in response to engagement of distinct TLRs is related to differential utilization of adapter proteins on extracellular activation by microbial agonists.[38] Thus, while the ability to produce immunoregulatory factors is a defining function of activated macrophages, the diversity of cytokines or other products induced will, again, be influenced by the nature of the inducing stimulus and the local microenvironment of the cells.

CURRENT PARADIGMS OF MACROPHAGE ACTIVATION

Although newly arrived tissue macrophages constitutively display some of their characteristic functions, such as phagocytosis, essentially all macrophage functions are induced or enhanced by cellular activation. The notion of an "activated macrophage" was originally proposed by Mackaness, and extended by Russell, Hibbs, and others, to describe a cell that had developed increased microbicidal or tumoricidal capacities as a function of stepwise signaling.[39-42] This definition still is valuable in emphasizing that there are substantial changes in macrophage activity and function during the evolution of an immune response that have beneficial outcomes for the host. Within the context of modern immunology, the concept of an activated macrophage can be expanded to define a cell that has responded to cell-derived and/or environmental factors with specific molecular changes that allow an enhanced functional response specific for the inciting stimulus.

Multiple studies have confirmed that the underlying basis of the activation process is the induction of new gene expression in response to host and microbial ligands. These ligands are almost limitless in their number and include such diverse mediators as the cytokines interferon-gamma (a potent macrophage activating agent) and interleukin (IL)-12; arachidonic acid metabolites; and microbial products such as bacterial lipopolysaccharide, lipoteichoic acid, and CpG oligonucleotides, to name a few. Studies of the response of isolated mouse macrophage populations have demonstrated that each agonist has distinct effects and induces a unique pattern of induced genes.[35-37] In addition, the activation response of any macrophage will be influenced by the nature of the microenvironment of that particular population of macrophages and whether multiple stimuli are used, such as is commonly the case in the stepwise activation treatments used in in-vitro studies of macrophage function.[42] The genetic background of the mouse strain (and presumably of human cells) and the source of macrophage progenitors also influence the level of activation achieved.[43] These considerations suggest that, again, there is no single characteristic, metabolic or genetic, that can be used universally to define an activated macrophage. Instead, the nature of the activation response will be linked to the nature of the inducing stimulus/stimuli and environment.

Recent studies have proposed that two subsets of activated macrophages can be identified that preferentially promote or dampen inflammatory and antimicrobial responses, labeled classically activated versus alternatively activated macrophages, respectively. These populations are defined largely on the basis of the immunopotentiating (e.g., IL-12, IL-18) versus immunosuppressive (e.g., IL-10, transforming growth factor-beta) cytokines produced.[44,45] Given the nature of macrophage heterogeneity discussed earlier, it seems likely that these functionally based distinctions represent examples of macrophages at different points along the continuum of the activation process or as a function of specific types or combinations of stimuli. Nonetheless, the importance of identifying macrophages that display functional polarization during infection or tumor development may be important for understanding how these situations modulate innate and acquired immune responses.

CENTRAL ROLE OF MACROPHAGES IN INFLAMMATION

The inflammatory response serves as perhaps the best showcase of the array of macrophage functional activities. Innate immune recognition underlies most inflammatory responses, and this is set in motion by pathogen recognition. As noted previously, macrophages located in peripheral tissues serve as an effective surveillance system for pathogen entry or other alterations in the cellular environment, and the decision to respond or not respond to a particular ligand is largely made by phagocytic cells at these sites.

The presence of changes in the tissue environment both stimulates the macrophages already present in the tissue and induces the rapid recruitment of additional macrophages to that site. Macrophage influx into a site of injury or infection is part of the process of inflammation and is recognized as a central component of the innate immune response.[46] Macrophages active during the early stages of inflammatory responses and at the initiation of wound healing produce the soluble inflammatory mediators such as IL-1, tumor necrosis factor-alpha, and IL-6 that stimulate a systemic response to infection.[47] Similarly, production of chemokines, including IL-8 (CXCL8), is an important outcome of microbial recognition. These chemotactic mediators enhance the recruitment and entry of phagocytes and lymphocytes to the inflammatory site and mediate changes in the local expression of adhesion molecules on endothelial cells, promoting the migration of circulating cells to the inflammatory site.[48] Finally, as discussed more fully later, the APC functions of macrophages and DCs require the increased expression of co-stimulatory molecules, as well as production of cytokines such as IL-12 and IL-18, for effective T-cell activation to proceed. The exact profile of cytokines induced by microbial recognition and produced by macrophages is determined by the nature of the stimulatory agonist and the cell surface receptor(s) engaged. In turn, these molecules both promote the functional activities of neighboring phagocytic cells and influence the character of the adaptive immune response that develops in their presence.

In the final analysis, it is somewhat difficult to separate the concept of inflammation from the process of macrophage activation, because the cells participating in the initiation of an inflammatory response clearly become activated during the development of this response. Analysis of the global response of these cells to microorganisms has suggested that a large portion of the activation-specific gene products induced in macrophages following ligand recognition are involved in regulating the subsequent inflammatory process.[35,36] In many cases, the inflammatory response, and the activities of macrophages activated during that process, are

sufficient to limit and even to clear an infection, occasionally without significant systemic effects in the infected host. Thus, this early macrophage response to infection is an effective host defense mechanism.

ROLE OF MACROPHAGES IN BRIDGING INNATE AND ADAPTIVE IMMUNE RESPONSES

If the innate immune response is not sufficient to contain infection, the ability of macrophages and DC to activate CD4+ T lymphocytes provides a critical bridge to the development of the adaptive response.[49] Much information is available concerning the events of T-cell stimulation by these professional APCs, and only a brief overview of this process is presented here. The stimulation of naive CD4+ T cells, or T helper cells, is the prototypical example of APC function, because activation of these cells is the cornerstone event in the development of adaptive immune responses.

The first stage of APC function is broadly referred to as antigen presentation and consists of antigen uptake, degradation, and loading onto major histocompatibility complex (MHC) molecules.[50,51] As noted previously, the ability of macrophages to phagocytose particles via both nonspecific and receptor-mediated uptake is a critical aspect of their presentation capacity. Antigen uptake, or in the case of intracellular pathogens the accessibility of microbial antigens within the cell, leads to the processing of these antigens into proteolytic peptides and their loading onto MHC class I or class II molecules.

Once effective peptide:MHC complexes are displayed by the APC, T-cell stimulation can follow. The process of T-cell priming (or the activation of naive cells) involves physical interaction with those cells in the T-cell zones of secondary lymphoid organs.[52] Cytokines and chemokines expressed by the macrophage after antigen uptake play a critical role in attracting and retaining naive T cells that are capable of responding to specific antigens, as noted in the previous section. T cells recognizing their cognate antigen on macrophages at these peripheral sites respond by binding the antigen:MHC complex via the T-cell receptor and binding co-stimulatory molecules such as B7.1 and B7.2 (CD80, 86) via the CD28 molecule. Increased expression of such co-stimulatory molecules is one consequence of macrophage-pathogen interaction, thus creating a reciprocal relationship between microbial recognition and T-cell stimulation. Additional engagement of adhesion molecules promotes formation of the T-cell synapse, thought to be critical for effective T-cell activation.[53] T-lymphocyte signaling through the T-cell receptor and co-stimulatory molecules then leads to T-cell activation, broadly defined as the induction of the new gene expression required for T-cell proliferation and differentiation. Effective activation requires that both the antigen:MHC complex and the co-stimulatory molecule(s) be expressed on the same APC and both must be recognized within a specific time span to lead to effective activation in the T cell.[54]

The final stage of T-cell activation by APC is the polarization of the CD4+ T-cell response toward a specific functional pathway, termed *type 1 or type 2 differentiation pathways.* Differential maturation of these responses is regulated by the nature of the cytokines produced by the APC and is thought to be influenced both by the nature of the microbial pathogen or altered cell initially recognized as well as aspects of antigen processing and presentation.[55] In this way, the APC helps to shape the character of the adaptive response, through modulation of the initial T-cell response.

CONCLUSION

Since their initial description as "big eaters" more than 100 years ago, macrophages have been recognized as scavenger cells in both invertebrates and higher organisms.[56] It is now recognized that this ubiquitously distributed population of fixed and circulating mononuclear phagocytes can express tremendous functional, morphologic, and metabolic diversity that is shaped by both the anatomic location and the differentiation or activation stage of each cell. By providing both a first line of host defense against microorganisms and altered host cells and the capacity to stimulate an adaptive immune response, the macrophage plays a central role in the regulation of host immunity.

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These two manuscripts bring consideration of macrophage biology into the molecular age. Using a genomic approach for analysis of changes in gene expression after pathogen recognition, these studies provide novel information about and a new view of macrophage activation that ultimately may be useful for effective manipulation of the consequences of microbial recognition, including inflammation.

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This paper is a classic in the field of macrophage biology. It provides the first description of an activated or "angry" macrophage, a concept that remains central to our understanding of the host defense aspects of macrophage functions.

Chapter 31
ENDOTHELIAL FUNCTION

Larry W. Kraiss • Mark L. Martinez • Stephen M. Prescott • Guy A. Zimmerman

KEY POINTS

1. **Endothelial cells,** once thought to be inert vascular lining cells, **respond to signals from the environment with functional and phenotypic changes in physiologic conditions and in critical illness.** This process is termed *endothelial activation.*
2. **Endothelial activation** is induced by a variety of agonists that act via receptors of diverse classes. Endothelial receptors are linked to intracellular signaling cascades that regulate functional responses. Endothelial responses to hemodynamic and other mechanical forces and in injury also trigger intracellular signaling pathways.
3. **Endothelial responses triggered by activation or injury** influence vasoregulation, vascular permeability, hemostasis, acute and chronic inflammation, wound surveillance and repair, and other critical events, and they affect every organ.
4. **Endothelial function is dysregulated or becomes unregulated in human diseases,** including sepsis, ischemia-reperfusion syndromes, injury by oxidants or toxins, and other conditions. Endothelial cell dysfunction is a key pathophysiologic mechanism in **organ-specific syndromes** and in **systemic responses to injury.**
5. **Endothelial cell activation responses** provide molecular targets that may ultimately be useful for **therapeutic intervention** in syndromes of critical illness and other diseases. **Endothelial cell markers** may be useful in establishing the natural history of disease states and for following the course of specific syndromes.

INTRODUCTION

The vascular system of an adult human has a surface area of several square meters and is lined by 1×10^{13} or more endothelial cells,[1] which influence the function of every organ. Endothelial cells were once thought to be passive structural units with little or no capacity to respond to activating signals with changes in phenotype and function. Electron microscopic observations documenting that endothelial cells contain secretory granules and physiologic experiments suggesting that they are not passive in interactions with leukocytes, both of which were accomplished in the 1950s, indicated otherwise.[1] The studies of leukocyte–endothelial cell interactions built on earlier observations that the endothelium has particular roles in the response to injury[2] and in inflammation.[3] Multiple subsequent studies clearly demonstrated that endothelial cells respond to signals from the environment with diverse *activation* responses that are critical for vasoregulation, hemostasis, inflammation, wound repair, and organ-specific activities.[4,5] This is perhaps the most important conceptual advance in vascular biology in recent history. A corollary is that endothelial dysfunction contributes to a variety of human diseases and syndromes,[1,4] including critical illnesses.

The endothelium itself is now considered by many investigators and physicians to be an extended and complex organ with the capacity for local, regional, and systemic activation, depending on the physiologic or pathologic stimulus and concurrent modifying features.[1,6,7] In sepsis, trauma, ischemia-reperfusion, and other conditions that are common in critical illness, multiple biochemical and physical signals are generated that can be transmitted to intracellular transduction cascades in endothelial cells, mediating acute or more protracted functional changes. These activation events,[4,5] which are triggered by physical injury, microbial products, toxins, and other stimuli, were apparently conserved after a continuous endothelium appeared as part of a closed vascular system when vertebrate species emerged,[8] and they evolved to establish and preserve vascular integrity, maintain intravascular volume and oxygen and nutrient delivery, and recruit leukocytes and platelets for local defense and repair. Critical phenotypic changes of activated endothelium include rapid transformation to a vasoconstrictive, procoagulant, and proinflammatory state that can then be further modified in a time-dependent fashion.[1] Although these responses are required for homeostasis and defense, they can contribute to tissue damage if dysregulated (Fig. 31–1). In critically ill patients, endothelial cell activity varies, depending on the nature of the illness or injury. Endothelial responses have a critical influence on the complications of organ-specific or systemic illnesses such as acute respiratory distress syndrome (ARDS) and multiple organ failure (see Fig. 31–1).[9,10]

Vasculogenesis and *angiogenesis* are not reviewed in detail here but are fundamental processes with intricate molecular regulation that are important in neoplasia, chronic inflammation, responses of hypoxic tissues, and other pathologic processes, in addition to vascular and organ development.[1,11–16] Recent observations demonstrate novel mechanisms that regulate vascular guidance in developing tissues.[16,17] In critically ill patients, pro- and antiangiogenic signaling molecules are released by platelets and myeloid

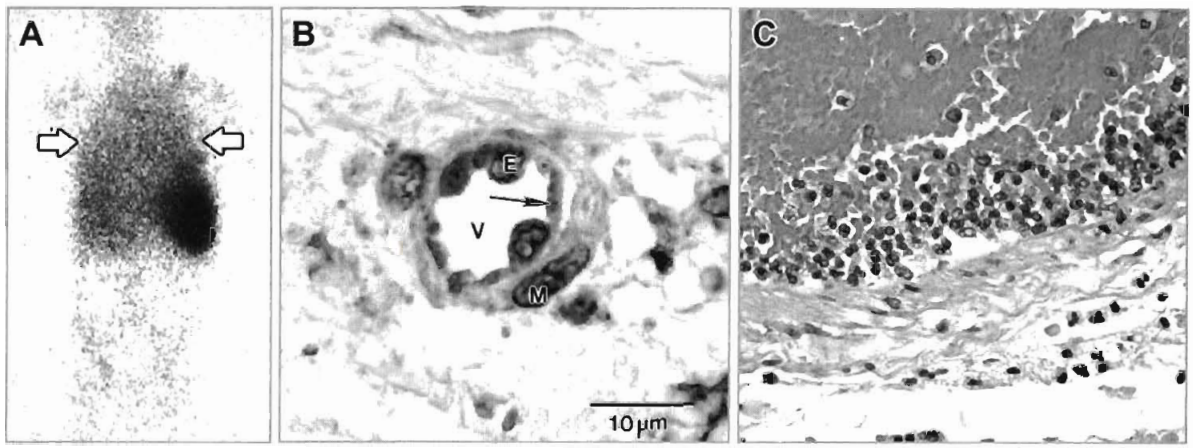

FIGURE 31–1. Endothelial cells are activated in human diseases and critical illness. *A*, Autologous radiolabeled leukocyte scanning in a patient early after the onset of acute respiratory distress syndrome secondary to Gram-negative sepsis demonstrates diffuse accumulation of polymorphonuclear leukocytes and monocytes in the lungs *(arrows)*, an event mediated in part by endothelial cell activation. There is also significant uptake of radiolabeled leukocytes in the liver and spleen. (See text for details; also reference 74.) *B*, Endothelial cells in a systemic venule in tissue removed during surgical exploration for an abdominal aortic aneurysm stain intensely for the CXC chemokine epithelial neutrophil-activating peptide-78 (ENA-78). ENA-78 is not expressed by unactivated endothelial cells at baseline. A variety of other new gene products are also expressed by activated endothelial cells. (See text for details; also references 4 and 62.) *C*, Autopsy sample from a subject dying of Gram-positive sepsis demonstrates dramatic accumulation of neutrophils, monocytes, and platelets in a systemic venule. A variety of clinical and experimental observations indicate that systemic endothelial cells are activated in septic syndromes caused by Gram-positive as well as Gram-negative bacteria, contributing to the accumulation and activation of leukocytes and platelets. V, venule; E, endothelial cell; M, macrophage. (*A*, From Zimmerman GA, Albertine KH, McIntyre TM: Pathogenesis of sepsis and septic-induced injury. In Matthay MA [ed]: Lung Biology in Health and Disease, vol 179. New York, Marcel Dekker, 2003, pp 245-287. *B*, From Imaizumi T, Albertine KH, Jicha DL, et al: Human endothelial cells synthesize ENA-78: Relationship to IL-8 and to signaling of PMN adhesion. Am J Respir Cell Mol Biol 1997;17:181-192.)

leukocytes and are generated by other mechanisms.[10,11] Certain of these mediators, such as the vascular endothelial growth factor family of polypeptides and sphingosine-1-phosphate, influence vascular permeability and other functions in addition to angiogenesis.[18–22] Angiogenic responses of endothelial cells may influence organ dysfunction and repair in specific syndromes of critical illness, but these issues are largely unexplored.

Endothelial cells at different sites in the vasculature may be more similar than dissimilar.[23] However, there is evidence of endothelial cell *heterogeneity* both between and within specific tissues and organs and between macrovascular and microvascular sources.[1,24] The genetic determinants of endothelial cell subtypes and the developmental and signaling pathways that influence their phenotypic fates after initial vasculogenic and angiogenic cues remain to be completely characterized.[1] These variables are critical to approaches that involve therapeutic delivery of stem or vascular progenitor cells to injured or terminally diseased tissues,[25] where microenvironments and selective cell-cell and cell-matrix interactions may differentially influence cell fates.[1] Endothelial cell heterogeneity and local microenvironments also are determinants of these cells' participation in gene therapy protocols and approaches.[1]

A pivotal advance in the study of endothelial cell phenotype and function occurred when methodology was developed that allows the cultivation and analysis of isolated endothelial cells from humans and experimental animals in culture and, in some models, in coculture conditions with other vascular cells.[21,26,27] Although isolated and cultured endothelial cells are not perfect replicas of the in vivo state, they have been remarkably informative (Fig. 31–2). For example, virtually all the adhesion and signaling molecules involved in endothelial interactions with leukocytes (see later) were identified using human endothelial cells in primary or early passage culture, and many additional activation events have been identified

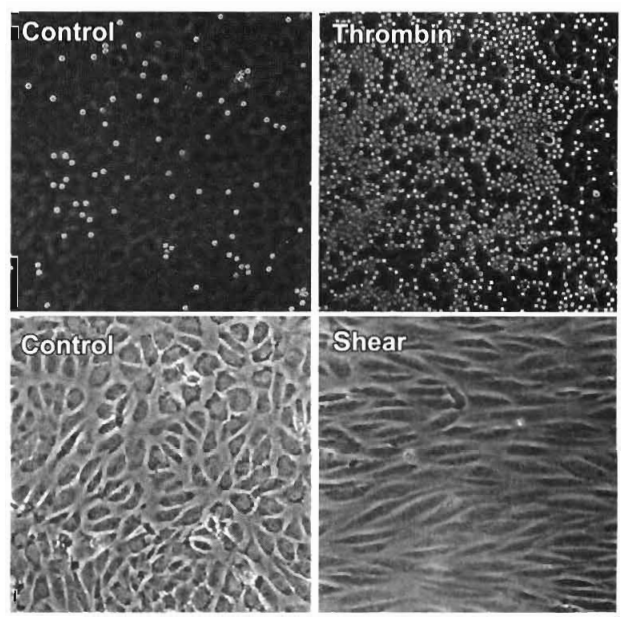

FIGURE 31–2. Cultured human endothelial cells are activated by diverse signals from the environment. *Top panels*, Human neutrophils (refractile white spheres) adhere dramatically to a monolayer of cultured human endothelial cells pretreated with nanomolar concentrations of thrombin for 5 minutes (right), compared with a control monolayer (left). Thrombin triggers endothelial cell activation, leading to neutrophil adhesion. The molecular mechanism for endothelial cell–dependent leukocyte adhesion under these conditions is shown in Figure 31–3*A*, and other relevant events are illustrated in Figure 31–4. (See text for details; also references 38, 40, and 41.) *Bottom panels*, A primary culture of human endothelial cells developed elongate morphology when subjected to shear (right), compared with a control monolayer incubated under static conditions (left) (L. W. Kraiss, unpublished experiment). As outlined in the text, cultured human endothelial cells undergo multiple additional activation events and phenotypic changes in response to clinically relevant signals from the environment. (*Top*, From Zimmerman GA, McIntyre TM, Prescott SM: Thrombin stimulates the adherence of neutrophils to human endothelial cells in vitro. J Clin Invest 1985;76:2235-2246.)

using this approach and validated in vivo (see Fig. 31–2). Strategies using isolated endothelial cells continue to be useful in defining characteristics relevant to critical illness. In addition, "in vivo cell biologic" approaches[10] are evolving and are likely to be informative in experimental models of critical illness and in clinical research involving human subjects in the intensive care unit. In animal models, endothelial-specific knockout and transgenic approaches now provide unique surrogate systems[28–30] that complement observations in in vitro and in vivo human systems and will expand our concepts of endothelial function and dysfunction.

The following sections outline specific aspects of endothelial cell function and pathobiology. Each topic is the subject of detailed discussions in vascular biology monographs and, because of space limitations, cannot be comprehensively discussed here. Therefore, the references include substantive reviews as well as illustrative archival reports.

ENDOTHELIAL RECEPTORS, INTRACELLULAR TRANSDUCTION CASCADES, AND ACTIVATION RESPONSES

Human endothelial cells display multiple surface receptors that transmit outside-in signals to intracellular transduction cascades, which then alter their functions and phenotypic characteristics. Certain endothelial adhesion molecules can also transmit outside-in signals. The diversity of endothelial signaling systems is evidence of the complexity of this cell type and its ability to mediate both physiologic responses and vascular alterations in critical illness and other pathologic conditions.

G protein–coupled pathways are major transduction mechanisms linked to surface *heptahelical receptors* and are ubiquitous in human cell signaling paradigms.[31] Human endothelial cells display heptahelical receptors (also called seven-membrane-spanning G protein–coupled receptors or serpentine receptors) that recognize thrombin, histamine, bradykinin, sphingosine-1-phosphate, and other hemostatic and inflammatory agonists. These surface receptors are differentially coupled to intracellular adapter proteins and enzymes that trigger phospholipase activation, calcium (Ca^{++}) transients, mitogen-activated protein kinase pathways, cyclic nucleotide turnover, and other intermediary events.[32] The resulting phenotypic changes and effector responses include surface translocation (degranulation) of intracellular storage granules (Weibel-Palade bodies), with von Willebrand factor release and P-selectin display on the cell surface; rapid platelet-activating factor (PAF) and prostacyclin (PGI_2) synthesis; cytoskeletal reorganization; altered permeability; altered gene expression; and others.

Human and murine endothelial cells constitutively express surface protease-activated receptors (PARs), a family of heptahelical G protein–coupled receptors that recognize thrombin and certain other proteases and transmit outside-in signals via a unique mechanism involving proteolytic release of a cryptic internal ligand.[29,33] Human endothelial cells also display PAR2, which recognizes mast cell tryptase, trypsin, and coagulation factors VIIa and Xa and is up-regulated by cytokines and lipopolysaccharide (LPS).[33–35] There is also evidence that PAR3 and PAR4 are expressed by endothelial cells and that expression of PAR4, like PAR2, is altered by inflammatory agonists.[36,37] Signaling via PARs provides regulated mechanisms by which endothelial cells respond to local thrombin generation and mast cell degranulation—two acute responses that are central in tissue injury and physiologic host defense.[33,38,39] Thrombin-induced signaling and PAR activation are also pathways for dysregulated vascular responses in syndromes of critical illness.[32,38,40] Stimulation of endothelial cell monolayers with thrombin provided the first evidence of endothelial cell–dependent adhesion of neutrophils (Figs. 31–2 and 31–3; also see later).[38,41,42] These and a variety of other studies demonstrated that thrombin induces endothelial cell activation by receptor-mediated mechanisms.[32,33,38,41] In more recent experiments, thrombin activation of cultured macro- and microvascular endothelial cells influenced intercellular gap formation by a mechanism dependent on intracellular Ca^{++} transients and a subtype of adenyl cyclase.[43] It was also reported that PAR1 and PAR2 differentially trigger exocytosis and alter permeability in human endothelial cell monolayers by influencing Rho–guanosine triphosphatase activity.[44] These and a variety of other observations document multiple thrombin-activated functional changes in endothelial cells that are relevant to endothelial behavior in critical illness. There is also evidence for thrombin signaling in vascular development and angiogenesis.[45] These findings, together with earlier observations of degranulation, endothelial cell–dependent leukocyte adhesion, and mitogenesis,[33,34,38,40,41] illustrate the diverse changes in endothelial cell phenotype triggered by PAR-mediated pathways.

Human endothelial cells display histamine H1 and bradykinin B2 receptors that mediate vasoactive and inflammatory signaling when engaged.[46,47] Histamine induces many of the same activation responses as thrombin does, including degranulation, translocation of P-selectin to the surface, rapid synthesis of PGI_2 and PAF, and endothelial cell–dependent neutrophil adhesion, and it can trigger the release of preformed chemokines in models of chronic inflammation.[46,48,49] Many of these events, which were first identified in cultured human endothelial cell systems, have been documented in vivo.[50] By using H1 and PAR2 receptors, endothelial cells respond to histamine and tryptase, which are key inflammatory agonists that are released locally in response to tissue trauma.[39] When PAR1 or other PARs that recognize thrombin are engaged in parallel with histamine stimulation, as frequently occurs in tissue injury in vivo, complex intracellular signaling responses result.[47,51,52] Although receptors for thrombin and histamine trigger many parallel and convergent signaling cascades and functional activities in endothelial cells, they also have distinct effects on gene regulation pathways in this cell type (D. Schmid, L. W. Kraiss, unpublished observations).

Receptor tyrosine kinases are expressed by human and murine endothelial cells and play critical roles in the maintenance of vascular structure and the adaptation to tissue injury and remodeling. In addition, they have developmental roles in vasculogenesis and angiogenesis. Endothelial-specific receptor tyrosine kinases include three members of the vascular endothelial growth factor receptor family and two structurally related receptors with immunoglobulin and epidermal growth factor homology domains, Tie1 and Tie2, which recognize members of the angiopoietin family and other ligands.[1,20] In development, these receptors and their ligands act in concert with other angiogenic and guidance receptors and pathways.[1,13,16,17] In addition to mediating angiogenesis and lymphangiogenesis, engagement of vascular endothelial growth factor and Tie receptors on endothelial cells transmits signals to endothelial nitric oxide synthase (eNOS), vasopermeability regulatory mechanisms, and inflammatory

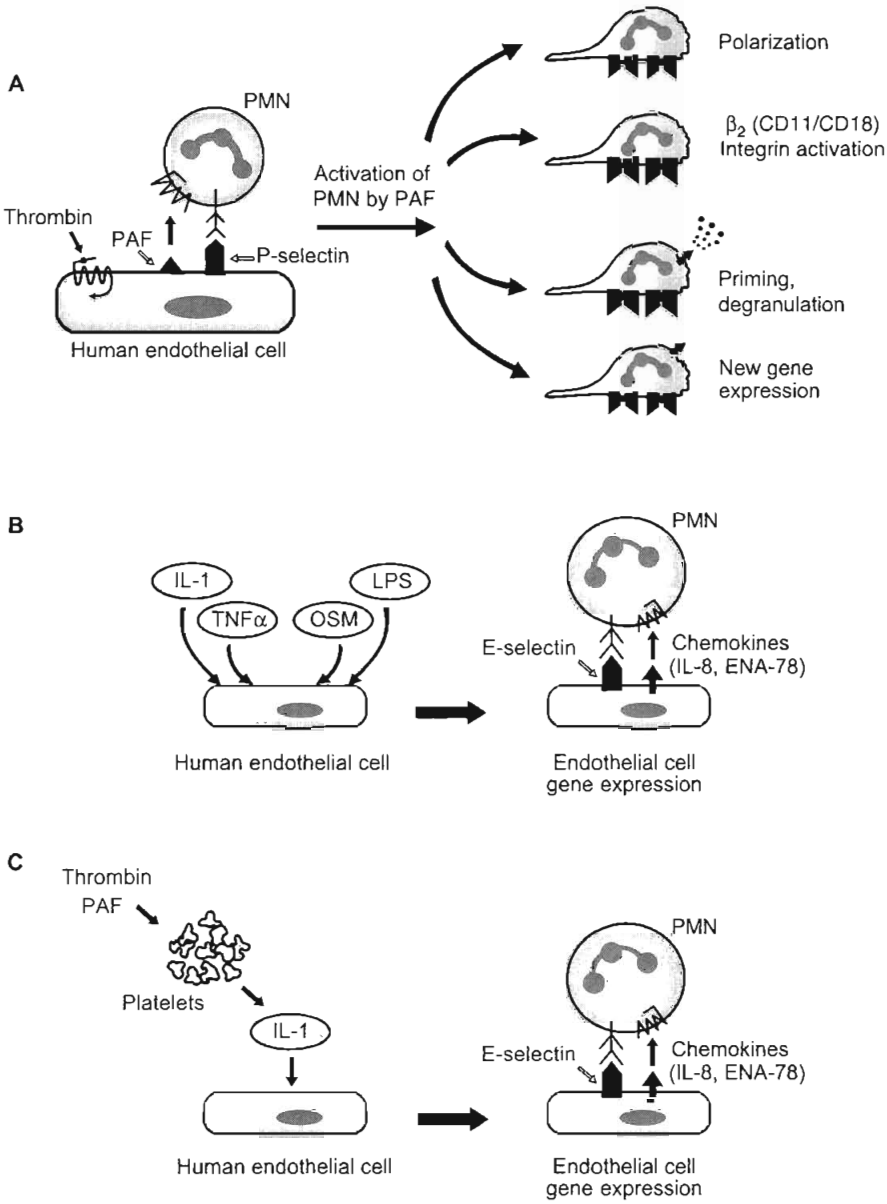

FIGURE 31–3. Human endothelial cells are activated by outside-in signals delivered by diverse inflammatory and thrombotic agonists and mechanisms. *A*, Human endothelial cells activated by thrombin via heptahelical protease-activated receptors (PARs) acutely translocate P-selectin from storage granules, rapidly synthesize platelet-activating factor (PAF), and use these factors as a juxtacrine adhesion and signaling system for neutrophils. (See text for details; also references 38, 40, and 41.) Human endothelial cells activated by thrombin via PAR pathways undergo additional changes that mediate inflammatory and thrombotic responses. *B*, Cytokines released by macrophages and other extravascular cells are recognized by receptors on endothelial cells, inducing multiple activation responses. Bacterial products, including lipopolysaccharide (LPS) and other endotoxins, bind to specific members of the Toll-like receptor family expressed by endothelial cells, also triggering activation events. *C*, Interleukin (IL)-1ß synthesized and released by stimulated platelets activates human endothelial cells, resulting in endothelial cell–dependent neutrophil adhesion. This illustrates a mechanism by which intravascular blood cells can initiate or amplify endothelial cell activation. ENA, epithelial neutrophil-activating peptide; OSM, oncostatin M; PMN, polymorphonuclear leukocyte; TNF, tumor necrosis factor. *(See also Color Figure 31–1.)* (*C*, Modified from Zimmerman GA, Albertine KH, McIntyre TM: Pathogenesis of sepsis and septic-induced injury. In Matthay MA [ed]: Lung Biology in Health and Disease, vol 179. New York, Marcel Dekker, 2003, pp 245-287.)

pathways.[20–22] Recent observations indicate that Tie2 expression is regulated by hypoxia and inflammatory cytokines in human endothelial cells.[15]

Cytokine receptors are regulators of endothelial cell phenotype and function in innate immune and acute inflammatory responses, hemostasis and thrombosis, acquired immunity and chronic inflammation, vascular remodeling, and other functions relevant to human disease (see Fig. 31–3). Endothelial cells constitutively express receptors for more than a dozen cytokines[53–55] and use them to transmit outside-in signals to mitogen-activated protein kinase cascades, ceramide turnover mechanisms, nuclear signaling pathways that involve nuclear factor kappa-B (NF-κB) and JAK/STAT activation, and other intracellular transduction circuits.[53–57] Endothelial responses to newly identified cytokines, such as high mobility group protein B1 (HMGB1), continue to be reported.[58,59] The most extensively characterized cytokine signaling events in human endothelial cells involve activation by tumor necrosis factor (TNF), interleukin-1alpha (IL-1α), and interleukin-1beta (IL-1β), which induce expression of genes that code for E-selectin and other adhesion molecules, interleukin-8 (IL-8), epithelial neutrophil-activating peptide-78 (ENA-78) and other chemokines, the inducible form of cyclooxygenase (COX-2), endothelial degranulating factors for neutrophils, and a variety of other inflammatory and thrombotic proteins and peptides.[53–56,60–64] The IL-1 signaling system, including recently identified IL-1 receptor-associated proteins, is conserved across evolutionary lines, is central to the responses of a variety of cells to infection and injury, and has both homologous features and molecular interfaces with Toll receptor signaling (see later).[65] Endothelial cells express the type I but not the type II ("decoy") IL-1 receptor—an unusual feature, because most cells display both.[53]

IL-1, TNF, IL-6, and other cytokines recognized by endothelial cell receptors are produced by macrophages and other extravascular cells in response to thrombotic or inflammatory stimuli (see Fig. 31–3).[53,54] In addition, some cytokines—for example, IL-1 and IL-6—are *endogenously*

produced by inflamed endothelial cells themselves, providing the basis for autocrine signaling loops.[53,54] Alternatively, cytokine agonists for endothelial cells can be produced by intravascular platelets or leukocytes, providing mechanisms that link thrombosis and inflammation and amplify inflammatory responses.[5,54,66,67] For example, human platelets synthesize IL-1β from constitutive messenger RNA (mRNA) transcripts in response to thrombin, PAF, and other agonists and release it in sufficient concentrations to trigger endothelial cell–dependent polymorphonuclear leukocyte (PMN) adhesion in in vitro assays (see Fig. 31–3).[67] Signal-dependent translation of IL-1β is one of many inflammatory activities of stimulated platelets[68] and provides a novel mechanism that explains earlier observations that platelets release IL-1 activity.[54,67] Activated platelets can also signal endothelium locally by releasing or displaying ligands recognized by heptahelical, growth factor, and other receptor classes, triggering key functional changes.[18,19,66] In a second example of endothelial signaling by blood cells, human neutrophils were recently found to release the alpha subunit of the IL-6 receptor (IL-6Rα), which can then associate with homodimers of glycoprotein 130 that are basally present on human endothelial cells.[54,69,70] In contrast, IL-6Rα is not constitutively expressed by endothelium.[54,69,70] The association of soluble IL-6Rα with transmembrane glycoprotein 130 homodimers constitutes a competent heterotrimeric receptor that confers to endothelial cells a new responsiveness to endogenously or exogenously synthesized IL-6, inducing the expression of inflammatory and thrombotic genes.[69,70] One consequence of new gene expression is a "switch" from neutrophil to mononuclear leukocyte accumulation, an event that is required for the resolution of acute inflammatory responses but is also a central mechanism in the transition to chronic inflammation if it is pathologically dysregulated.[71,72] This novel mechanism of retrograde or *trans*-signaling of endothelial cells by PMNs[69,70,72] may mediate a variety of pathologic activities of IL-6, together with other complex regulatory features of the system.[73]

Endothelial cells respond to local or systemic microbial invasion and to activation by LPS and other bacterial products with complex changes in inflammatory phenotype and, in some cases, by triggering apoptotic programs.[74–78] Recent characterization of the *Toll-like family of transmembrane receptors* (TLRs), which are conserved, innate immune sensors, provides insights into endothelial and leukocyte signaling by LPS and other endotoxins and microbial products.[74,79,80] The TLR system is composed of specific receptors that recognize pathogen-associated molecular patterns with ligand-dependent specificity.[79] TLRs act together with cell surface–associated modifying proteins (CD14, MD-2) and use a cytoplasmic transduction system linked to gene regulatory pathways and other effector mechanisms.[79,80] As previously noted, conserved IL-1 receptor-associated kinases are central intermediaries.[65,80,81] Human macrovascular and microvascular endothelial cells express TLR2 and TLR4 and use them to differentially recognize and respond to LPS and to bacterial endotoxic lipoproteins, including the Braun lipoprotein of *Escherichia coli* and other microbes.[82–85] Expression of TLR2 and TLR4 on cultured endothelial cells and endothelial cell lines can be modulated by LPS, interferon gamma, and reactive oxygen species.[83,85] Experimental studies in murine models demonstrate important differences in leukocyte-endothelial interactions, depending on the specific bacterial product injected, systemic versus local challenge, and the TLR and CD14 phenotype.[86,87] Previous studies in an in vitro model involving cultured human endothelial cells and whole blood demonstrated an indirect pathway of LPS-induced activation of endothelium that is mediated by monocytes and that dramatically amplifies endothelial sensitivity and response to this microbial product.[88] These and other studies indicate that in clinical sepsis and other vascular responses to pathogens, changes in endothelial phenotype and function likely involve both direct TLR signaling and indirect activation mediated by leukocyte and platelet products.[74]

Nuclear receptors recognize cell-permeant hormones, lipids, and therapeutic drugs.[89] A major nuclear hormone receptor in diverse cell types recognizes endogenous and synthetic glucocorticoids and mediates their regulatory effects on transcriptional programs.[89] The glucocorticoid receptor is present in nuclei of in situ human arterial endothelial cells, and its nuclear localization is influenced by shear stress in cultured bovine endothelial cells,[90] suggesting that nuclear receptor pathways may respond to endothelial activation or injury in a variety of conditions. Estrogen receptors, a second class of nuclear hormone receptors, are present in bovine and human endothelial cells.[91] Human endothelial cells also respond to activators of the peroxisome proliferators–activated receptor family under some conditions.[92]

In syndromes of critical illness, multiple endothelial cell surface and nuclear receptors are likely engaged in parallel and in sequence, generating complex phenotypic changes and functional responses. Sepsis is a sentinel example in which endothelial activation via several receptor pathways may be key to essential vascular and tissue responses,[74,77,78] as illustrated in this section.

ENDOTHELIAL RESPONSES TO HEMODYNAMIC FORCES

In vivo, endothelial cells are continuously subjected to hemodynamic forces. These forces include vascular wall distention induced by cyclic changes in transmural pressure and shear, which is the frictional force applied by blood flow.[93,94] Acute changes in shear induce phenotypic modulation and altered gene expression in cultured endothelial cells (see Fig. 31–2) and cellular remodeling in vessels and vascular grafts; both acute *increases* and *decreases* in shear induce phenotypic responses.[93–95] Alterations induced by shear and other hemodynamic forces are often similar to those triggered by inflammatory agonists.

Abrupt changes in shear induce rapid cytoskeletal remodeling and activation of intracellular signaling pathways in endothelial cells, including modulation of potassium channels, induction of calcium transients, alterations in inositol phosphates and diacylglycerol, generation of reactive oxygen intermediates, activation of mitogen-activated protein kinases, activation of Rho– and Rac–guanosine triphosphatases, and nuclear signaling and altered gene expression.[90,93–101] Functional consequences of shear-induced changes in endothelial cell phenotype include acute generation of nitric oxide (NO) and PGI_2, cytoskeletal and microtubular reorganization, changes in synthesis of inflammatory and thrombotic gene products, and altered DNA synthesis.[93,94,102–104] Endothelial cells also adapt to chronic changes in shear with structural alterations.[93] The mechanosensors that transmit hemodynamic outside-in signals to endothelial cells remain incompletely characterized.[93,105,106]

ENDOTHELIAL JUNCTIONS, PERMEABILITY, AND SELECTIVE BARRIER FUNCTIONS

Highly specialized junctional structures that link adjacent cells in interconnected monolayers of endothelial cells that line vascular channels regulate paracellular permeability and macromolecular transport and influence the transmigration of leukocytes from the intravascular space to the extravascular milieu.[107,108] Endothelial cell–matrix interactions mediated by basolateral integrins also influence permeability,[1,105] providing both cellular attachment and outside-in signals that modify specialized intercellular junctions. Junctional transfer of small molecules between adjacent endothelial cells occurs, potentially resulting in an additional mechanism of intercellular signaling.[109] As many as four types of junctions may mediate interactions between endothelial cells.[107] Adherens junctions and tight junctions are critical in regulating permeability and cell polarity and are modified by inflammatory and thrombotic signals,[107,110] including thrombin, sphingosine-1-phosphate, and other receptor-mediated agonists.[18,19,32,43] Thus, these multimolecular junctional structures and their interacting cytoskeletal elements are likely key sites of dysregulation in increased systemic and pulmonary vascular permeability in syndromes of critical illness.

Endothelial-specific cadherin 5, or vascular endothelial cadherin, is a central component of endothelial cell adherens junctions, contributes to the barrier function of endothelial cell monolayers, and is modified by receptor-mediated signals and leukocyte-endothelial interactions.[107,108,111] Vascular endothelial cadherin may signal through β-catenin, which influences vascular pattern and fragility in murine models,[30] and there is evidence for additional cadherin-catenin interactions.[112] Additional endothelial cell junctional molecules are involved in interactions between endothelial cells.[107] Recent observations indicate that S-ENDO 1–associated antigen (CD146), a transmembrane glycoprotein constitutively expressed by endothelial cells regardless of anatomic site or vessel size, is localized to intercellular boundaries and is coupled to a tyrosine kinase–mediated pathway that triggers intracellular Ca^{++} transients.[110,113] Cytoplasmic Ca^{++} levels regulate the activity of adenyl cyclase isoenzymes and interendothelial gap formation in cultured endothelial cell models,[43] suggesting that CD146 may have important influences on permeability via these mechanisms. These examples illustrate the concept that endothelial cell junctional molecules perform both adhesive and signaling functions and can be dysregulated in vascular injury.

The intricate mechanisms by which endothelial cell junctions are altered in leukocyte transmigration (Fig. 31–4) remain incompletely characterized and involve both adherens and tight junctions.[103,111] Vascular endothelial cadherin distribution is rapidly and dynamically modified during transmigration of PMNs and monocytes, providing a potential mechanism for interendothelial gap opening, leukocyte passage, and rapid gap closure.[111] Additional endothelial cell junctional molecules play specific roles in targeting leukocyte subclasses to intercellular sites of transmigration and stepwise emigration (see Fig. 31–4).[5] Platelet leukocyte adhesion molecule-1 is the best known of these.[5,114] Junctional adhesion molecule-1, also an immunoglobulin superfamily protein, was recently reported to be a binding partner for $\alpha_L\beta_2$ integrin on PMNs, monocytes, and T lymphocytes that is expressed predominantly at tight junctions of resting endothelial and epithelial cells.[115] CD99, a recently characterized O-glycosylated protein, is localized to endothelial cell junctions and mediates the transmigration of monocytes across cultured endothelial cell monolayers.[116] These findings indicate that endothelial cell junctional complexes and specific proteins localized to endothelial cell–endothelial cell contact domains regulate selective barrier functions involving both macromolecules and emigrating leukocytes, key functions that can be disrupted in

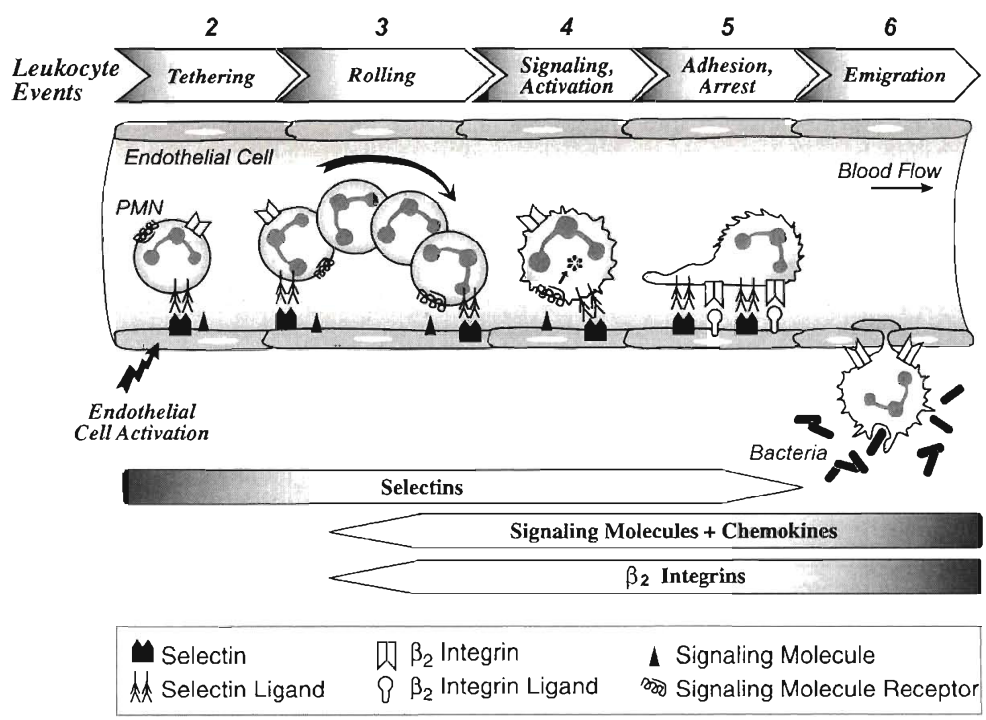

FIGURE 31–4. Activation of endothelial cells and multistep interactions control leukocyte targeting and function in inflammation. This multistep paradigm details key events in neutrophil (PMN) adhesion, localized activation, and transmigration in a postcapillary venule under conditions of flow. Each step (see text for details) is critical for PMN adhesion and emigration in dysregulated vascular injury. Initial activation of endothelial cells is key in this sequence of events. (From McIntyre TM, Prescott SM, Weyrich AS, Zimmerman GA: Cell-cell interactions: Leukocyte-endothelial interactions. Curr Opin Hematol 2003;10:150-158.)

inflammatory vascular injury involving dysregulated neutrophil accumulation and activation.[117–119]

ENDOTHELIAL CONTRIBUTIONS TO VASOREGULATION

Blood flow is partially regulated by the generation of vasoactive signaling factors by endothelium that act locally to modify vascular tone, caliber, responses to other stimuli, and hemodynamic variables.[1] NO and PGI_2 are key endothelial-derived vasodilators that also modify platelet responses and in some cases alter leukocyte-endothelial interactions.[1] Thus, they have both direct and indirect vasoactive features. In addition, endothelial cells synthesize vasoconstrictor substances, including endothelins and a number of other vasoactive factors, in response to signals delivered by surface receptors and hemodynamic forces.[1,120]

Endothelial cells generate NO in an enzymatic process catalyzed by nitric oxide synthase (NOS) in which L-arginine is converted to L-citrulline in the presence of oxygen and nicotinamide adenine dinucleotide phosphate (reduced form).[1] NO, a cell-permeant gas with a half-life of approximately 6 seconds, mediates intercellular interactions in a paracrine fashion and binds to the heme prosthetic group of guanyl cyclase in vascular smooth muscle cells, maintaining basal vascular tone and inducing vasorelaxation.[1] A parallel mechanism inhibits platelet activation responses and also leukocyte activities and smooth muscle migration and proliferation in some studies.[6,120] NO production is catalyzed by a family of NOS, including constitutive and inducible isoforms.[120] One isoform, eNOS (or NOS3), is basally active in endothelial cells, but its activity can be further increased by receptor-mediated agonists.[1] The effect of cytokines on eNOS activity and expression has species-specific characteristics, and these features may vary in individual vascular beds within a species.[1,6,54] Expression and activity of eNOS are increased in response to shear, in part secondary to transcriptional activation and a cis-acting shear response sequence in the promoter region of the gene,[1] and there is evidence for regulation by hypoxia.[121] eNOS activity can also be increased by Akt-dependent phosphorylation.[21,122] Additional features of the regulation of eNOS and inducible NOS isoforms have recently been reviewed.[120]

Activation of NOS in endothelial and other cell types influences hemodynamic events in sepsis and other syndromes of critical illness, although precise measures to modify these enzymes are not yet in general clinical practice.[123] Myeloperoxidase, a key PMN enzyme that is released by degranulation,[64] consumed NO and impaired endothelial-dependent vasodilatation in a rodent model of endotoxemia,[124] pointing to mechanisms that may contribute to pathologic hemodynamic responses in inflammatory vascular injury.

PGI_2, the first endothelial cell–derived relaxing factor to be identified, is also a major inhibitor of platelet activation and aggregation.[1,6,120] PGI_2 is synthesized by the microsomal enzyme cyclooxygenase (prostaglandin H synthase) acting on substrate arachidonic acid released from membrane phospholipids in response to cellular stimulation. The COX-1 isoform is constitutively expressed in endothelial cells, and PGI_2 generated by this enzyme is important in physiologic vasoregulation and as a local antithrombotic signal.[6,125,126] The inducible isoform, COX-2, is expressed in endothelial cells in response to stimulation with IL-1, TNF, LPS, and other inflammatory and thrombotic agonists and contributes PGI_2 and prostaglandin E_2 to the local inflammatory milieu.[6,60,61,125,126] The factors that regulate COX-2 expression in stimulated and inflamed endothelial cells are complex and continue to be dissected.[6,120,127,128]

ENDOTHELIAL REGULATION OF HEMOSTASIS

In the basal state, endothelial cells present an antithrombotic and anticoagulant surface, a critical phenotypic feature required for blood flow that acts in concert with mechanical forces and soluble factors.[1,6] In response to injury, the endothelium becomes prothrombotic and antifibrinolytic, providing a mechanism that facilitates hemostasis and wound repair and generates molecular links that couple endothelial activation to local myeloid leukocyte accumulation and other defensive inflammatory responses.[1,5,6,68,74] Endothelial procoagulant mechanisms that interface with inflammatory networks are part of an evolutionarily conserved innate defense system.[68,129,130] When dysregulated, however, this remarkable switch in endothelial phenotype initiates or amplifies pathologic thrombosis, a central mechanism of disease in critical illness.[5,74,77,129,130]

Anticoagulant and antithrombotic features of resting endothelial cells include pericellular heparin sulfate, glycosaminoglycans, and dermatan sulfate, which facilitate the activity of antithrombin III and heparin cofactor II, the expression of thrombomodulin and tissue factor pathway inhibitor (see later), and the release of PGI_2 and NO (see earlier). Each of these is dysregulated in specific syndromes of vascular injury and disease.[1,7,130]

The expression and activity of tissue factor are critical in hemostasis and in pathologic thrombosis. Tissue factor is a primary initiator of the coagulation cascade, a process that has been extensively reviewed.[130–134] Tissue factor potently accelerates factor VIIa–dependent activation of factors IX and X.[1] Thrombin generated by sequential protease-dependent steps in the tissue factor pathway subsequently cleaves fibrinogen to fibrin, the central component of the platelet-fibrin mesh that constitutes clots.[131–134] When endothelial cells that express tissue factor are exposed to plasma, thrombin is generated and fibrin is deposited on the endothelial cell surface.[1] Expression of tissue factor activity on endothelial cells is induced by a variety of pathophysiologically relevant stimuli in vitro, but factors that trigger its regional expression by endothelium in vivo remain in question.[1,6] Tissue factor is also synthesized by human monocytes and macrophages in response to LPS and other stimuli and is deposited on cell surfaces and shed into the blood in microparticles released by monocytes or neutrophils.[74,131,135] Tissue factor pathway inhibitor, a 42-kDa serine protease inhibitor with three tandem kunitz domains, is associated with endothelial granules and surfaces and is found to a lesser extent in association with platelets and in soluble form.[6,129,130,136] Tissue factor pathway inhibitor has anticoagulant effects by direct inhibition of factor Xa and by an indirect mechanism involving factor Xa–dependent inhibition of the tissue factor–factor VIIa complex.[130,137] In vivo, tissue factor pathway inhibitor expression is restricted to microvessels.[6] LPS and cytokines have only a slight effect on tissue factor pathway inhibitor expression by cultured endothelial cells in

vitro, but during infusion of LPS in rodents, its expression on pulmonary capillaries is reduced by a mechanism yet to be defined.[6]

Thrombomodulin, an integral membrane protein, is basally expressed by macro- and microvascular endothelial cells in vitro and in vivo and has profound effects on the regulation of hemostasis.[133,134] When thrombin is locally generated, it is recognized by thrombomodulin and binds to it, inhibiting the procoagulant activities of thrombin while facilitating its ability to cleave circulating protein C to activated protein C.[6,74,133,134] Activated protein C interacts with a cofactor that is synthesized by endothelial and other cell types—protein S—and this complex then inactivates factors Va and VIIa, inhibiting further thrombin generation and providing an endogenous "brake" on the procoagulant cascade that is proportional to the magnitude of the hemostatic stimulus under regulated physiologic conditions.[1,133,134] Thus, endothelial cells express key molecules that regulate coagulation. There is also evidence that activated protein C inhibits proinflammatory as well as prothrombotic cascades.[74,130,134,138] Activation of protein C by the thrombin-thrombomodulin complex is further enhanced by its high-affinity binding to an additional endothelial cell plasma membrane factor, the endothelial cell protein C receptor.[133,134,139,140] Thrombomodulin has additional regulatory effects, including enhancement of inactivation of thrombin by antithrombin III and protein C inhibitor and activation of thrombin-activatable fibrinolysis inhibitor (procarboxypeptidase B).[6]

Factors that regulate endothelial expression of thrombomodulin and endothelial cell protein C receptor continue to be defined and have regional features that may reflect endothelial cell specialization.[6,133,134] Thrombomodulin is differentially expressed by endothelial cells in specific vascular beds and is absent from brain endothelium.[6,133] It is reduced on the plasma membranes of endothelial cells in response to LPS challenge in in vitro models and in histologic analysis of biopsies from patients with meningococcemia.[74] Endothelial cell protein C receptor expression is highly specific for macrovascular endothelial cells, with the exception of hepatic sinusoids, a property influenced in part by sequence information in the promoter region of its gene.[6,140,141] LPS infusion in rodents is accompanied by an increase in endothelial cell protein C receptor mRNA but not protein,[140] indicating post-transcriptional regulation. The increased plasma levels of soluble thrombomodulin and endothelial cell protein C receptor that are reported in sepsis and other conditions appear to result from shedding of the surface proteins.[6,74]

Endothelial cells also have a major role in the regulation of fibrinolysis and synthesize a complex group of plasminogen activators, plasminogen activator inhibitors, and receptors for fibrinolytic factors.[1,6] There is evidence for differential expression of tissue plasminogen activator and other fibrinolytic regulatory molecules in specific vascular beds and for dysregulation of this system in response to pathologic stimuli.[1,6]

The balance between anticoagulant and prothrombotic features of endothelium is altered in many, and perhaps all, syndromes of critical illness. Sepsis is an intensely studied example.[74,77,129,130,137,146] Dysregulation of endothelial control of hemostasis contributed extensively to the preclinical and clinical rationales for recent trials of recombinant activated protein C and tissue factor pathway inhibitor in patients with septic syndromes.[129,130,137]

ENDOTHELIAL INTERACTIONS WITH LEUKOCYTES AND OTHER BLOOD CELLS

Endothelial cells were previously thought to be passive in interactions with leukocytes, but observations in the last 2 decades have clearly demonstrated *endothelial cell–dependent mechanisms of leukocyte adhesion and signaling* (see Figs. 31–2 to 31–4).[4,5,38,40,41] This facet of endothelial biology has been extensively reviewed.[1,4–6,53,54,64,72,142–144] Leukocyte-endothelial interactions are early and critical events in defense against infection and in wound surveillance and repair, but dysregulated adhesion and signaling of leukocytes is a central pathogenetic mechanism in vascular injury and a variety of human inflammatory diseases.[5,38,39] Similarly, dysregulated interactions between the vessel wall and circulating platelets or erythrocytes contribute to specific vascular pathologies.[1,5]

A multistep paradigm involving the tethering of leukocytes to stimulated endothelial cells, followed by rolling, localized signaling, consequent tight adhesion, arrest of activated leukocytes, and subsequent emigration between endothelial junctions (see previous section), characterizes the targeting of myeloid cells and lymphocytes in inflammation (see Fig. 31–4).[5] Fundamental aspects of this sequence of events were initially worked out in human cell models and from clinical observations of patients with leukocyte adhesion deficiency syndromes, and they have been validated and refined using animal models and further clinical observations.[5,143]

The central paradigm can be illustrated using interactions of inflamed endothelial cells and neutrophils (PMNs), although it is important to emphasize that there are cell- and context-specific variations, depending on the leukocyte subtype being considered and whether the situation involves acute or chronic inflammation or injury.[5] An overview of the multistep paradigm[5,143,144] is illustrated in Figure 31–4 and summarized here. Under basal conditions, endothelial cells and circulating PMNs are not adhesive to each other. Stimulation of endothelial cells with inflammatory agonists induces their activation and differential expression of specific selectins on their plasma membranes, which then mediates the capture, tethering, and rolling of quiescent unactivated PMNs. In the first step, endothelial cell activation by thrombin, histamine, and certain other rapidly acting agonists induces translocation of P-selectin, which is constitutively present in Weibel-Palade storage granules, to the endothelial cell plasma membrane. In contrast, LPS, IL-1, TNF, and additional cytokines signal transcriptionally regulated synthesis of a different selectin, E-selectin, which is not basally present in most endothelial cells. After synthesis, E-selectin is also displayed on the endothelial cell surface and, like P-selectin, captures and tethers PMNs (step 2). In this step, selectin ligands on the PMN are engaged by P-selectin or E-selectin displayed on the inflamed endothelial cell surface. P-selectin glycoprotein ligand-1 is the dominant selectin ligand on human and murine PMNs and has been shown in in vitro and in vivo experiments to mediate both tethering and rolling (step 3). L-selectin on the PMN surface also mediates tethering and rolling by interacting with ligands on inflamed endothelial cells and acts as an adhesion molecule for cell-cell interactions with other PMNs that accumulate locally. After tethering and rolling, endothelial cell–dependent signaling of PMNs triggers their activation (step 4). When endothelial cells are stimulated by thrombin or histamine, PAF is rapidly synthesized and is translocated

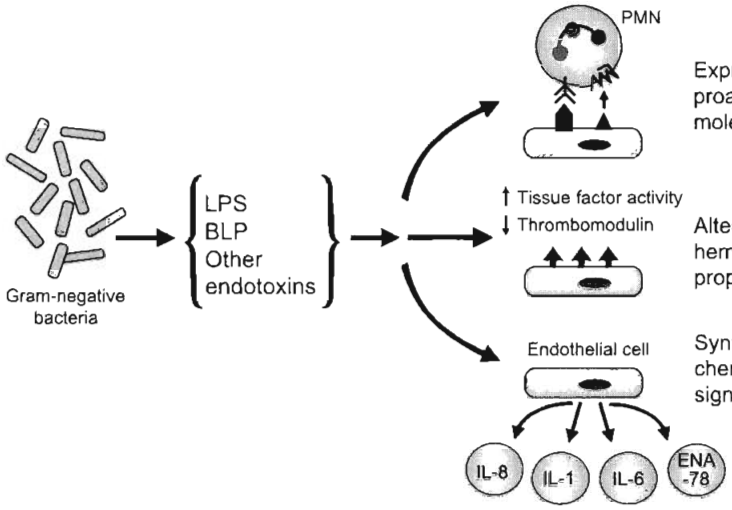

FIGURE 31–5. Endothelial cell activation and functional responses contribute to inflammatory vascular injury and thrombosis in septic syndromes. Lipopolysaccharide (LPS) and other endotoxins, such as Braun lipoprotein (BLP), activate human endothelial cells via Toll-like receptors and induce multiple phenotypic changes in experimental sepsis and clinical septic syndromes. ENA, epithelial neutrophil-activating peptide; IL, interleukin; PMN, polymorphonuclear leukocyte. (From Zimmerman GA, Albertine KH, McIntyre TM: Pathogenesis of sepsis and septic-induced injury. In Matthay MA [ed]: Lung Biology in Health and Disease, vol 179. New York, Marcel Dekker, 2003, pp 245-287.)

to the cell surface, where it acts as a signaling molecule that triggers PMN activation of PMNs tethered by P-selectin. Alternatively, in endothelial cells stimulated with LPS, IL-1, or TNF, IL-8 and ENA-78 are synthesized under transcriptional control and mediate the activation of PMNs in concert with tethering by E-selectin. Activation of PMNs by signaling molecules (e.g., PAF, IL-8, ENA-78) displayed in a juxtacrine fashion at the endothelial cell surface or when locally released induces stimulation-dependent changes in affinity and avidity of β_2 integrins on the leukocyte surface. Activated β_2 integrins then recognize intercellular adhesion molecule-1 and other ligands on the endothelial cell plasma membrane (step 5). Engagement of P-selectin glycoprotein ligand-1 enhances the activation of β_2 integrins on human PMNs signaled by PAF or IL-8. Binding of β_2 integrins to endothelial cells counterligands and then mediates tight adhesion and arrest of the PMNs (step 5), events that are essential to prevent the dislodgment of leukocytes by shear forces and for their subsequent emigration across endothelial cell junctions (step 6).

Activation of endothelial cells resulting in the display of selectins and the synthesis of PAF, IL-8, and other signaling molecules for neutrophils is critical for the sequence of events outlined in Figure 31–4 in host defense.[4,5,38,143] Similarly, constitutive and regulated expression of endothelial ligands for neutrophil β_2 integrins and expression of junctional proteins that participate in PMN emigration are essential determinants for orderly neutrophil targeting in physiologic inflammation.[5,111,115,116,143,144] Activation of endothelial cells is also central to targeting and spatially localized signaling of other classes of leukocytes in host defense.[5] In syndromes of inflammatory vascular injury, one or more of these critical steps can become disordered or unregulated, leading to pathologic accumulation and activation of leukocytes and consequent vessel and tissue damage (see Figs. 31–1 and 31–5).[5] Similarly, dysregulated accumulation and activation of platelets resulting from disruption at one or more molecular control points are central mechanisms in acute and subacute vascular injury.[5,144] These pathologic mechanisms are features of sepsis,[74] ischemia-reperfusion injury,[145,146] and other syndromes of vascular damage.

GENE EXPRESSION BY ACTIVATED ENDOTHELIAL CELLS: MECHANISTIC DIVERSITY

When appropriately stimulated, endothelial cells express or alter the expression of multiple genes. As with other responses outlined in this chapter, this was not predicted by earlier interpretations of endothelial cells as passive lining cells.[1] Patterns of transcript expression by endothelial cells may be markers of particular phenotypes in disease, such as neoplasia.[147]

Mechanisms of gene regulation in endothelial cells illustrate considerable diversity. Depending on the stimulus and time after activation, phenotypes of activated endothelial cells reflect transcriptional induction of new gene programs,[4,148–151] including genes controlled by transcription factors of the NF-κB and AP-1 families.[53,152–156] *Transcriptional regulation* is critical for new expression of E-selectin and certain other adhesion molecules by activated endothelial cells[153] and for altered expression of COX-2, chemokines, degranulating factors, and a variety of other endothelial cell gene products that are synthesized in response to injury or infection and in repair.[4,53,54,60–64,76,84,150]

In addition to transcriptional regulation, there is emerging evidence that endothelial cells have diverse *post-transcriptional mechanisms*, although these are largely uncharacterized. Individual examples that together indicate that post-transcriptional control is a key fact of gene expression in endothelial cells include shear-induced stabilization of granulocyte-macrophage colony-stimulating factor and COX-2 mRNAs,[97,128] differential expression of endothelial cell protein C receptor mRNA and protein in response to LPS,[140] and attenuation of the amount of E-selectin mRNA present in the actively translated polyribosome-associated fraction of transcripts when shear is applied to TNF-stimulated monolayers.[157] Post-transcriptional regulation provides important biologic advantages in gene regulation, including precise modulation of levels of specific proteins when acting in concert with transcriptional control.[158,159] Thus, cells with the complex functions subserved by endothelial cells would be expected to use these mechanisms.

Translational control, including signal-dependent translation of constitutive mRNAs,[5,68] is an important facet of

post-transcriptional regulation.[160] Rapid synthesis of the corresponding protein without a requirement for transcription or nuclear export of the message is one advantage of signal-dependent translation of specific transcripts that are present in the basal state.[5,68] Translational control mechanisms in stimulated endothelial cells and their phenotypic consequences are now being characterized.[102,157,161–165] Human endothelial cells have p70S6 kinase and other key components of the mammalian target of rapamycin specialized translation control pathway[163,164] and use this mechanism to regulate expression of the NF-κB family member Bcl-3 in endothelial cell monolayers subjected to shear.[164] Rapamycin, an immunosuppressant and antiangiogenic agent, inhibits Bcl-3 translation under these conditions.[164] Tumstatin, an endothelial cell–specific inhibitor of protein synthesis, inhibits mammalian target of rapamycin and angiogenesis by an integrin signaling mechanism.[165] In addition, preliminary analysis of the "translational state" of multiple mRNA transcripts in activated endothelial cells indicates differential effects by specific inflammatory and thrombotic agonists and that multiple translational control mechanisms may be used.[166] Our preliminary studies also indicate that human endothelial cells have a portfolio of RNA binding proteins and other key regulatory components in post-transcriptional regulatory and translational control pathways (M. Martinez, A. S. Weyrich, G. A. Zimmerman, unpublished studies).

ENDOTHELIAL RESPONSES IN DISEASE

As outlined throughout this chapter, changes in endothelial phenotype and function are central mechanisms in acute and subacute responses to disease, including syndromes of critical illness that are considered in detail elsewhere in this text. Endothelial cell responses in sepsis (see Figs. 31–1 and 31–5) are particularly profound and illustrative examples. Endothelial alterations in septic syndromes have recently been reviewed.[74,77,78,130,137,140] Dysregulated endothelial mechanisms are also central to systemic manifestations in ARDS, to multiple organ failure, and to localized and systemic ischemia-reperfusion syndromes, including traumatic and hemorrhagic shock and resuscitation.[10,145,146,167,168] There is evidence for quantitative and qualitative differences in endothelial responses in trauma and hemorrhagic shock compared with sepsis.[169–174] Patterns of endothelial phenotype that result from the superimposition of sepsis, trauma, ARDS, or other acute critical illnesses on the substrate of chronic endothelial dysfunction in atherosclerosis, diabetes, and other diseases of vascular dysfunction or chronic inflammation[1,175] remain to be precisely described and mechanistically characterized.

ACKNOWLEDGMENTS

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ANNOTATED REFERENCES

Aird WC: Endothelial cell dynamics and complexity theory. Crit Care Med 2002;30:S180-S185.

Aspects of endothelial activity in hemostasis, coagulation, and thrombosis are discussed, and the complexity of endothelial responses and phenotypes is underscored. These issues are outlined in the context of infectious syndromes and sepsis.

Cines DB, Pollak ES, Buck CA, et al: Endothelial cells in physiology and in the pathophysiology of vascular disorders. Blood 1998;91:3527-3561.

Physiologic and pathophysiologic characteristics of endothelial cells are reviewed in detail and discussed in the context of human vascular diseases. This review is extensively referenced.

Mantovani A, Bussolina F, Introna M: Cytokine regulation of endothelial cell function: From molecular level to the bedside. Immunol Today 1997;18:231-240.

As discussed in this article, endothelial cells both respond to and synthesize cytokines, a feature that generates multiple activation events and molecular responses in inflammation, thrombosis, and disease.

McIntyre TM, Prescott SM, Weyrich AS, Zimmerman GA: Cell-cell interactions: Leukocyte-endothelial interactions. Curr Opin Hematol 2003;10:150-158.

This review summarizes recent observations on endothelial-leukocyte interactions and endothelial activation in response to inflammatory and pathologic signals.

Zimmerman GA, Albertine KH, Carveth HJ, et al: Endothelial activation in ARDS. Chest 1999;116:18S-24S.

The concept of endothelial cell activation and its relationship to endothelial injury are discussed, particularly with respect to acute lung injury syndromes. Endothelial gene expression and rapid responses that do not require changes in gene expression are outlined.

Chapter 32
LUNG EPITHELIAL FUNCTION

Michael A. Matthay

KEY POINTS

1. The **pulmonary epithelium is morphologically diverse** from the airway epithelium to the alveolar epithelium to subserve the specific functions required at each level of the lung epithelium.
2. The **alveolar epithelium provides a tight barrier** to the passive movement of solutes and protein to keep the airspaces dry so that they can carry out the main function of the lung: to excrete carbon dioxide and absorb oxygen.
3. The **alveolar epithelium contains sodium and chloride ion channels** that are responsible for the vectorial transport of alveolar fluid from the airspaces to the lung interstitium.
4. The **active ion transporting capacity of the alveolar epithelium** is responsible for the resolution of alveolar edema.
5. The **process of alveolar fluid reabsorption** can be up-regulated by cyclic adenosine monophosphate agonists.

This chapter first considers the morphologic characteristics of the proximal, distal, and alveolar epithelium, with particular reference to the pathophysiology of acute critical illnesses. The next section considers the abnormalities of the airway epithelium in acute and chronic obstructive lung diseases and how these may contribute to acute respiratory failure in critically ill patients. The final section focuses on the role of the alveolar epithelium in lung fluid balance in patients with pulmonary edema.

MORPHOLOGY OF THE PULMONARY EPITHELIUM

There are major differences in the morphologic features of the pulmonary epithelium from the proximal airway epithelium to the alveolar epithelium. Some of these differences and their relationship to the regional function of the lung epithelium are considered here.

AIRWAY EPITHELIUM

Overall, the conducting airways form the connection between the outside world and the terminal respiratory units where gas exchange occurs. There are three major groups of intrapulmonary airways: bronchi, membranous bronchioles and respiratory bronchioles, and gas exchange ducts. Bronchi, by definition, have cartilage in their walls. Respiratory bronchi serve a dual function—as conducting airways and as part of the alveolar volume for gas exchange.[1] Overall, the conducting airways occupy the first 16 generations of airways, but ultimately they end blindly in the alveoli. Gas exchange occurs primarily in the branches that make up the last seven generations, including the respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli (Fig. 32–1). The distal airway epithelium is composed of terminal respiratory bronchial units with polarized epithelial cells that have the capacity to transport sodium and chloride, including ciliated Clara cells and nonciliated cuboidal cells.

In reference to the pathophysiology of acute and chronic obstructive airway disease, it should be emphasized that most airway resistance resides in the upper airways in the bronchi. There are glands in the submucosa in the bronchi that secrete water, electrolytes, and mucins into the lumen. Studies of the regulation of secretion in vivo and by explant cultural systems in vitro have demonstrated that release can be modulated by neurotransmitters, including cholinergic, adrenergic, and inflammatory mediators. Goblet cells, which are mucin-secreting epithelial cells, are present at most airway levels (Fig. 32–2). Several other cells are associated with the airways, including basal cells, lymphocytes, smooth muscle cells, and mast cells. Lymphocytes are frequently found between airway epithelial cells. There are also circular bands of smooth muscle around the airway epithelium as far peripherally as the respiratory bronchioles. The tone in the smooth muscles is altered by the autonomic nervous system and by local mediators released from a variety of cells. Abnormalities of several of these structural and cellular components contribute to the pathophysiology of acute and chronic obstructive lung disease.[1]

ALVEOLAR EPITHELIUM

The alveoli are composed of a thin alveolar epithelium (0.1 to 0.2 μm) that covers 99% of the airspace surface area in the lung and contains thin, squamous type I cells and cuboidal type II cells (Fig. 32–3). Alveolar type I cells cover 95% of the alveolar surface.[1,2] The close apposition between the alveolar epithelium and the vascular endothelium facilitates the efficient exchange of gases, but it also forms a tight barrier to the movement of liquids and proteins from the interstitial and vascular spaces, thus assisting in maintaining relatively dry alveoli.

At the alveolar level, the tight junctions that bind the alveolar epithelium are critical for maintaining apical and

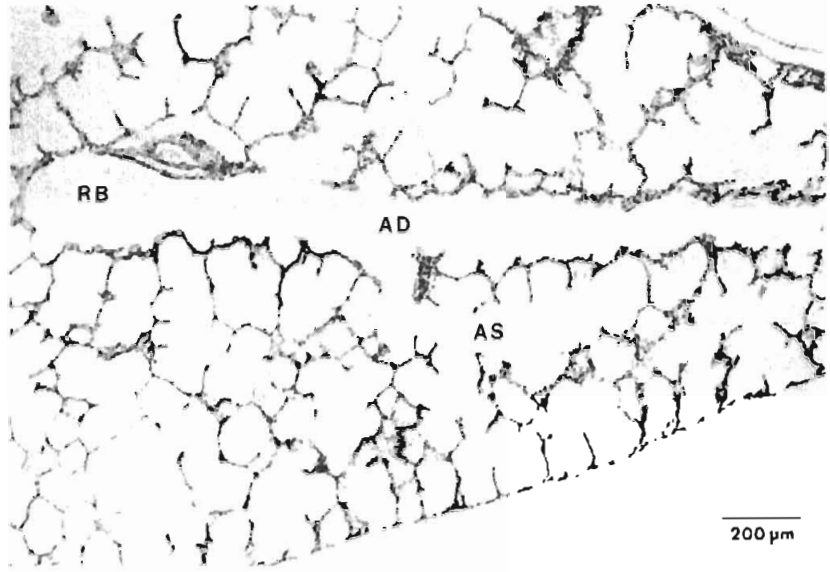

FIGURE 32–1. Longitudinal section of a gas exchange duct showing that its diameter remains relatively constant along the respiratory bronchiole (RB) and alveolar duct (AD). Alveolar sacs (AS) communicate with the gas exchange duct. (Human surgical specimen, 10-µm-thick paraffin section, light microscopy.) (From Albertine KH, Williams MC, Hyde DM: Anatomy of the lungs. In Murray JF, Nadel JA [eds]: Textbook of Respiratory Medicine, vol 1 Philadelphia, WB Saunders, 2000, pp 3-33.)

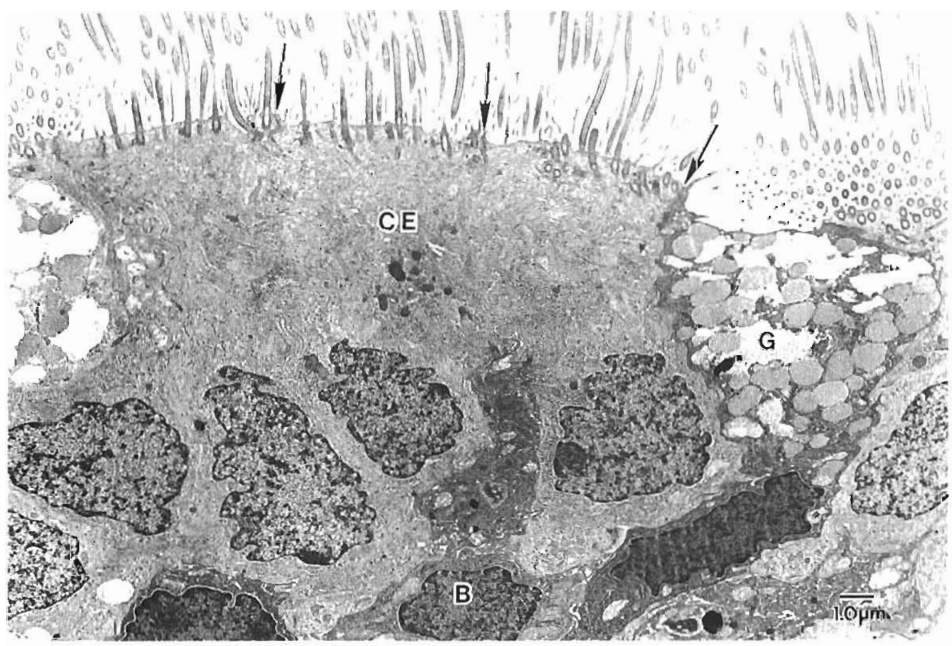

FIGURE 32–2. Cells comprising the bronchial epithelium are ciliated epithelial cells (CE), goblet cells (G), and basal cells (B). Goblet cells have abundant mucous granules in the cytoplasm, and their apical surface is devoid of cilia. Basal cells, as their name indicates, are located along the abluminal portion of the lining epithelium, adjacent to the basal lamina. The arrows at the apical surface of the airway cells indicate the location of junctional complexes between contiguous epithelial cells. (Human lung surgical specimen, transmission electron microscopy.) (From Albertine KH, Williams MC, Hyde DM: Anatomy of the lungs. In Murray JF, Nadel JA [eds]: Textbook of Respiratory Medicine, vol 1. Philadelphia, WB Saunders, 2000, pp 3-33.)

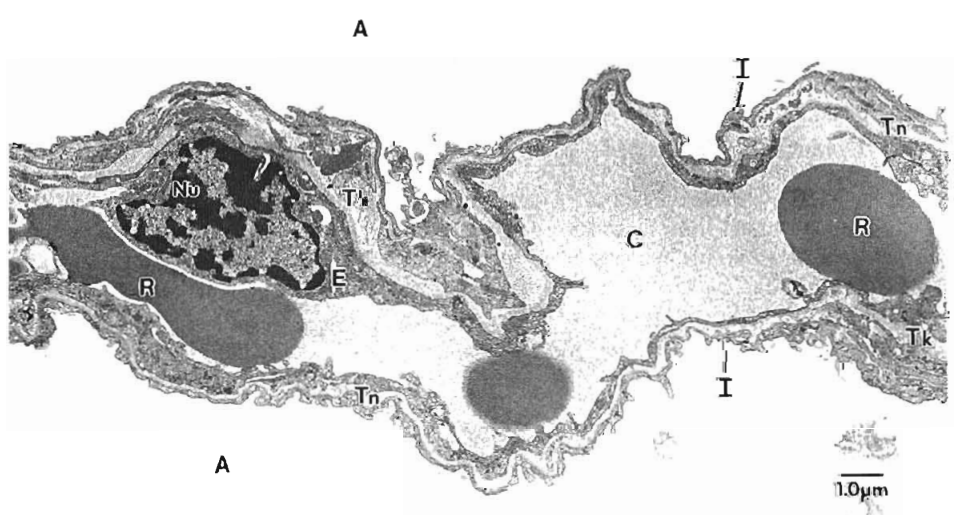

FIGURE 32–3. The thick (Tk) and thin (Tn) sides of an alveolar capillary (C) change as the capillary courses between alveoli (A). The basal laminae of the capillary endothelium and alveolar epithelium fuse in the thin regions. The nucleus (Nu) of an endothelial cell (E) is visible above a red blood cell (R). I, type I pneumonocyte. (Human lung surgical specimen, transmission electron microscopy.) (From Albertine KH, Williams MC, Hyde DM: Anatomy of the lungs. In Murray JF, Nadel JA [eds]: Textbook of Respiratory Medicine, vol 1. Philadelphia, WB Saunders, 2000, pp 3-33.)

basolateral polarity. Ion transporters and other membrane proteins are asymmetrically distributed on opposing cell surfaces, conferring vectorial transport properties to the alveolar epithelium. Based on a variety of physiologic studies, the distal alveolar epithelium is much tighter than the capillary endothelium, with an effective pore radius of 0.5 to 0.9 nm, versus 6.5 to 7.5 nm.[2]

The most extensively studied cell in the distal pulmonary epithelium is the alveolar type II cell (Fig. 32–4*A*), partly because it can be readily isolated from the lung and studied in vitro.[2-4] The alveolar type II cell is responsible for the secretion of surfactant, as well as for the vectorial transport of sodium and chloride from the apical to the basolateral surface. When the lung is injured, type II cells proliferate to provide a new alveolar epithelial barrier (see Fig. 32–4*B*). After the repair process is complete, the alveolar epithelium returns to its more normal appearance (see Fig. 32–4*C*). The active vectorial transport of ions by alveolar epithelial type II cells provides a major driving force for the removal of fluid from the alveolar space. Sodium uptake occurs on the apical surface, partly through amiloride-sensitive and amiloride-insensitive channels. Subsequently, Na^+, K^+-ATPase pumps sodium actively from the basolateral surface into the lung interstitium.[4] The epithelial sodium channel (ENaC), cloned in 1994, participates in sodium movement across the membrane. There is new evidence that cystic fibrosis transmembrane conductance regulator (CFTR), the product of the cystic fibrosis gene, plays an important role in cyclic adenosine monophosphate (cAMP) up-regulated fluid transport across alveolar type II cells and the alveolar epithelium in vivo.[5] The role of the alveolar type I cell and vectorial fluid transport in the lung is less certain, although some investigators recently found that type I cells express sodium channels.[6,7] Type I cells also express aquaporin-5 on the apical surface, although vectorial fluid transport does not seem to depend on the function of this water channel.[3]

AIRWAY EPITHELIUM IN ACUTE AND CHRONIC LUNG DISEASE

The contribution of abnormalities in the proximal and distal airway epithelium to several acute and chronic lung diseases has been explored in depth in recent years. This section focuses on abnormalities of pulmonary epithelium that occur in asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis.

ASTHMA

Asthma is a disease of the airways characterized by airway narrowing with spontaneous and pharmacologic reversibility.[1] In patients who die of acute asthma, it is recognized that the airways are edematous and the blood vessels congested, and there are usually cellular infiltrates, including neutrophils and eosinophils. Mucous plugs frequently fill the peripheral airways, and there is desquamation of epithelial cells. In patients with asthma, there is evidence of abnormalities in airway cell growth and differentiation that are similar to those of chronic inflammatory diseases such as chronic bronchitis and cystic fibrosis. These abnormalities include metaplasia of the lining epithelium from ciliated cells to squamous and goblet cells. The basement membrane is often thickened. Anatomic studies of surviving patients with asthma also demonstrate some inflammatory changes, including epithelial cell desquamation, squamous cell transformation, and neutrophil infiltration, as well as an increase in goblet cells.[1] It has generally been assumed that the airway epithelium exists as an interface between the body and the external environment; therefore, the airway epithelium must

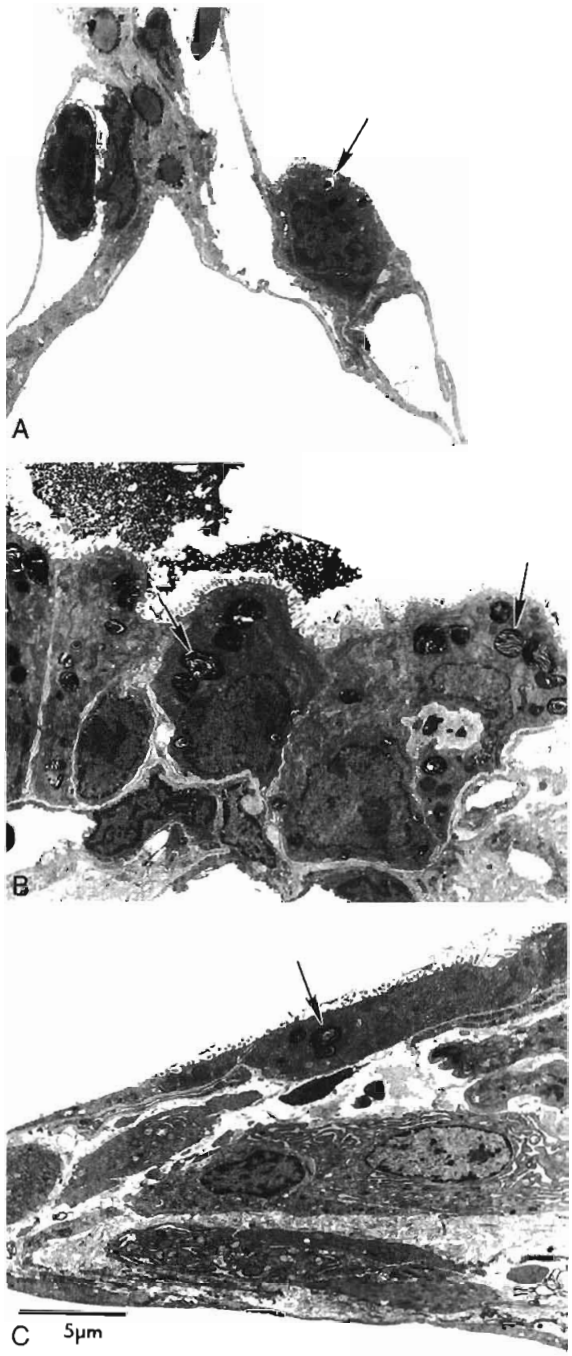

FIGURE 32–4. Ultrastructural appearance of normal rat lungs and rat lungs after the intratracheal instillation of bleomycin. *A*, Control lung (saline instilled). *B*, Ten days after instillation of bleomycin. *C*, Sixty days after instillation of bleomycin. Compared with the appearance of normal alveolar epithelial type II cells *(A, arrow)*, bleomycin-exposed alveolar type II cells *(B, arrow)* have more microvilli and larger lamellar bodies; these type II cells are hyperplastic and hypertrophied, apparently as a response to the bleomycin injury. Type II cell proliferation is the first stage of repair after injury has caused the death of type I cells, the thin cells that line most of the alveolar surface (see *A*). *C* shows recovery toward a more normal alveolar epithelial type II cell, which is flatter. (From Folkesson HG, et al: Upregulation of alveolar epithelial fluid transport after subacute lung injury in rats from bleomycin. Am J Physiol Lung Cell Mol Physiol 1998;275:L478-L490.)

have mechanisms to protect the internal environment from damaging organisms and irritants. The response of these cells has been studied in more detail recently, and their contribution to clinical asthma is still being worked out, but clearly there are specific abnormalities in the airway epithelium in patients with asthma. There is considerable evidence regarding the role of inflammation and coagulation-dependent mechanisms in the pathogenesis of asthma.[8,9]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The primary etiologic factor in the development of COPD is cigarette smoking. There is, however, individual variation in susceptibility. The mechanisms by which cigarette smoke causes emphysema, chronic bronchitis, and COPD are incompletely understood. In chronic bronchitis, there are inflammatory changes in airway epithelium. Ciliated epithelial cells undergo squamous metaplasia, and there is goblet cell proliferation, along with an increase in the volume of smooth muscle and glands. In emphysema, there is a loss of alveoli, resulting in what is commonly known as panlobular emphysema. Loss of alveoli and distal airspaces is a characteristic feature of emphysema resulting in ventilation and perfusion mismatch.[1] Recent evidence indicates that progression of COPD is associated with the accumulation of inflammatory mucous exudates in the lumen of small airways and infiltration of the airway walls with innate and adaptive immune cells that form lymphoid follicles.[10]

CYSTIC FIBROSIS

Cystic fibrosis is a genetic disorder transmitted as an autosomal recessive trait. In brief, the airway epithelium shows progressive evidence of inflammation, gland and goblet cell hypertrophy, and obstruction by secretions. The relationship between the genetic defect in cystic fibrosis and the actual clinical disease is not well understood. The abnormality in cystic fibrosis involves a failure to correctly encode CFTR, the integral protein of epithelial cells. This protein is a chloride channel that must have several other important effects, because abnormalities in transport do not explain all the abnormalities in patients with cystic fibrosis. CFTR is expressed in airway epithelium, although recent work indicates that it is also expressed highly in alveolar epithelium and has an important role in vectorial fluid transport (see next section). The mechanism by which pulmonary epithelium and airways are damaged in cystic fibrosis has been the subject of intense study. Abnormalities in ion transport, the airway surface liquid, and various innate immune responses to infection have all been implicated.[11]

ALVEOLAR EPITHELIUM

This section considers the role of the alveolar epithelial barrier in preventing alveolar flooding, as well as the role of the alveolar epithelium in resolving alveolar edema. On balance, considerable progress has been made in the last 2 decades in understanding the role of the alveolar epithelium in regulating lung fluid balance under normal and pathologic conditions.

FORMATION OF ALVEOLAR EDEMA

As described earlier, the alveolar epithelial barrier is a typical tight epithelium that resists the passive movement of macromolecules and even small solutes. This tight barrier facilitates the primary function of the alveolar epithelium—mainly, to maintain dry airspaces that can facilitate gas exchange. The epithelial barrier is also responsible for the secretion of surface-active material by alveolar epithelial type II cells.

Under normal conditions, the tight epithelial barrier prevents alveolar flooding, even in the presence of mild or moderate interstitial pulmonary edema. Several studies have demonstrated that the interstitial space of the lung can accommodate up to 500 mL of edema fluid before alveolar flooding occurs.[1] Therefore, patients may develop hydrostatic or increased permeability edema with interstitial pulmonary edema without flooding of the airspaces. From a radiographic perspective, this can be appreciated with radiographic signs of interstitial pulmonary edema and Kerley's B lines. In the presence of interstitial edema in the lung, gas exchange is minimally impaired. Once alveolar flooding occurs, pulmonary edema is associated with progressive arterial hypoxemia. The mechanisms of alveolar flooding are related primarily to a progressive rise in interstitial pressure that results in a breakdown of the epithelial barrier. The exact site of airspace flooding may be proximal to the alveolus under conditions of hydrostatic edema. In patients with acute lung injury, there may be injury to alveolar epithelial cells that facilitates the translocation of interstitial edema fluid into the distal airspaces of the lung. The active ion transport properties of the alveolar epithelium—specifically, the ability to transport fluid from the apical to the basal surface of distal lung epithelium—also helps prevent or minimize alveolar flooding. Once alveolar flooding does occur, active vectorial ion transport mechanisms are responsible for the removal of edema fluid from the distal airspaces of the lung (see next section).

RESOLUTION OF ALVEOLAR EDEMA

The distal airway and alveolar epithelium have ion transporters with the capacity to actively transport sodium and chloride, resulting in a mini-osmotic gradient that reabsorbs the water fraction of the edema fluid (Fig. 32–5). The first in vivo evidence that active ion transport in the mature lung accounted for the removal of alveolar edema fluid was obtained in studies of anesthetized, ventilated sheep.[12] In those studies, the critical discovery was that isosmolar fluid clearance of salt and water occurred in the face of a rising concentration of protein in the distal airspaces of the lung. The initial protein concentration of the instilled protein solution was the same as that of the circulating plasma. After 4 hours, the concentration of the protein increased from 6.5 to 8.4 g/100 mL, while the plasma protein concentration was unchanged. In longer-term studies in anesthetized, spontaneously breathing sheep, alveolar protein concentrations increased to even higher levels. After 12 and 24 hours, the alveolar protein concentration increased to 10.2 and 12.9 g/100 mL, respectively.[13] These data provided evidence that active ion transport must be responsible for the fluid clearance in the mature lung, especially in the face of a rising alveolar protein osmotic pressure. Additional studies in the intact lung supported the hypothesis that removal of alveolar

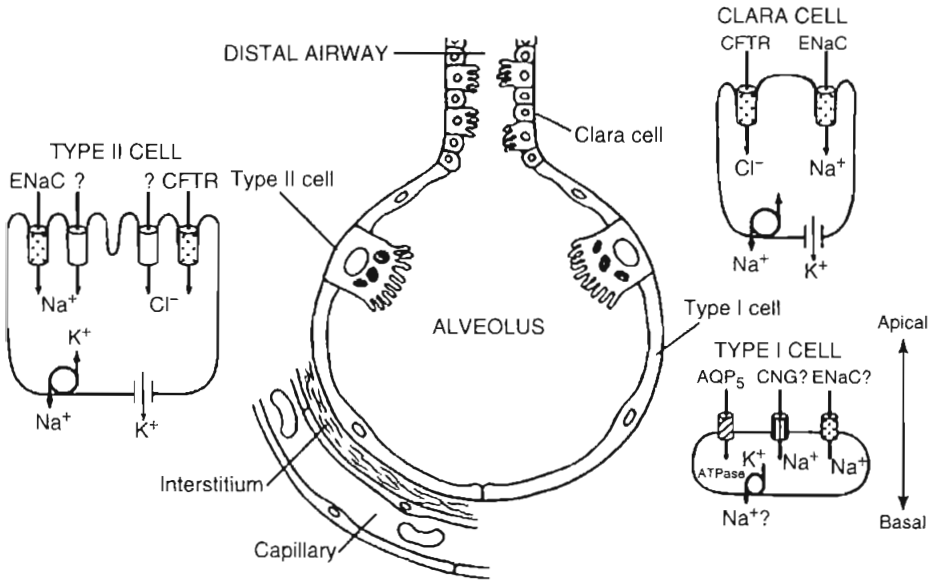

FIGURE 32–5. Schematic diagram of the distal pulmonary epithelium that is relevant for salt and water transport. AQP, aquaporin; CFTR, cystic fibrosis transmembrane conductance regulator; ENaC, epithelial sodium channel. (From Matthay MA: Lung epithelial fluid transport and the resolution of pulmonary edema. Physiol Rev 2002;82:569-600.)

fluid requires active transport processes. For example, elimination of ventilation to one lung did not alter the rate of fluid clearance in sheep, thus ruling out changes in transpulmonary airway pressure as a major determinant of fluid clearance, at least in the uninjured lung. Further, if active ion transport were responsible for fluid clearance, then fluid clearance should be temperature dependent. Studies in an in situ perfused goat lung preparation showed that the rate of fluid clearance progressively declined as temperature was lowered from 37° C to 18° C.[3] Additional evidence for active ion transport was obtained in intact animals with the use of amiloride, an inhibitor of sodium uptake by the apical membrane of alveolar epithelium and distal airway epithelium. Amiloride inhibited 40% to 70% of basal fluid clearance in most species, including the human lung. Studies were also done that used ouabain to inhibit Na^+, K^+-ATPase. The results showed that ouabain inhibited 90% of fluid clearance in isolated lung preparations.[2]

Interestingly, an early discovery from intact adult animal studies, as well as from earlier studies of fetal sheep, demonstrated that the rate of alveolar fluid clearance could be up-regulated by cAMP agonists.[3] Some species do not increase their fluid clearance with cAMP agonist therapy, but the majority of species double the rate of alveolar fluid clearance with beta-adrenergics, including the human lung.[2,3]

Several catecholamine-dependent mechanisms have the capacity to up-regulate alveolar fluid transport.[3] Both exogenous and endogenous catecholamine release can substantially up-regulate fluid clearance. For example, in the presence of hypovolemic or septic shock, the rapid rise in plasma catecholamines is sufficient to enhance alveolar epithelial fluid transport, thus preventing or limiting the formation of alveolar edema. In addition, several studies have demonstrated that aerosolized adrenergic therapy can increase the rate of fluid clearance in hydrostatic or increased permeability edema in a variety of experimental preparations.[2,3] From a clinical perspective, it is possible that administration of an aerosolized $beta_2$ agonist might be effective in up-regulating alveolar fluid transport and enhancing the resolution of pulmonary edema in patients. Clinical trials are needed to test this possibility.

There are several catecholamine-independent factors that can regulate fluid clearance as well. For example, hormonal factors, such as glucocorticoids, can up-regulate transport by transcriptional mechanisms, and thyroid hormone may work by a post-translational mechanism. Some growth factors can work by either transcriptional or direct membrane effects, or by enhancing the number of alveolar epithelial type II cells. There is also evidence that a proinflammatory cytokine, tumor necrosis factor, can up-regulate sodium uptake and fluid transport by novel mechanisms.[3]

Recent research has identified mechanisms that can impair vectorial alveolar fluid transport under pathologic conditions. For example, the halogenated anesthetics can decrease fluid clearance by inhibition of the amiloride-sensitive component. The effect is rapidly reversible after exposure to the inhaled anesthetic; the effect can also be overcome through the administration of a $beta_2$ agonist.[2] Lidocaine has been recognized as another anesthetic that can decrease alveolar fluid clearance, whether instilled directly into the lung or given intravenously in clinically relevant concentrations.[3] There is a growing body of literature demonstrating that alveolar hypoxia decreases alveolar fluid clearance by approximately 50% in the normal lung. The effect of hypoxia appears to be primarily at the membrane level, resulting in a decreased availability of ion transporters at both the apical and the basolateral membranes. Interestingly, $beta_2$ agonists can also overcome the depressant effects of hypoxia.[14]

Overall, several new insights have been obtained regarding the role of alveolar epithelium in regulating lung fluid balance. The resolution of alveolar edema depends on an intact alveolar epithelium that can transport sodium and chloride, creating an osmotic gradient for the reabsorption of water from the distal airspaces of the lung. In clinical studies, the resolution of alveolar edema is rapid in patients with resolving hydrostatic edema. In the presence of acute lung injury, there is considerable heterogeneity in the capacity of the alveolar epithelium to reabsorb pulmonary edema fluid. Patients with impaired alveolar fluid transport have a worse clinical course and a higher mortality, suggesting that alveolar epithelial injury is a major determinant of outcome

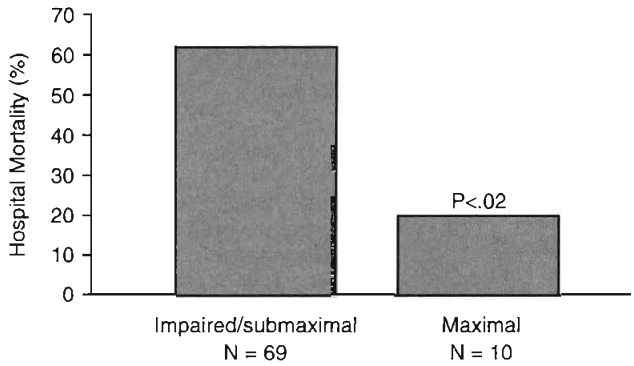

FIGURE 32–6. Hospital mortality (*y*-axis) plotted against two groups of patients with acute lung injury or acute respiratory distress syndrome—those with maximal fluid clearance (>14%/h), and those with impaired or submaximal fluid clearance (<14%/h). The columns represent present hospital mortality in each group (N = number of patients). Hospital mortality of patients with maximal fluid clearance was significantly less ($P < 0.02$). (From Ware LB, Matthay MA: Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 2001;163:1376-1383.)

in patients with acute lung injury (Fig. 32–6).[15] Conceivably, the rate of alveolar fluid transport could be up-regulated in patients with acute lung injury by the administration of aerosolized beta$_2$-adrenergic agonists, but this hypothesis requires a clinical trial to test its efficacy.

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This review summarizes 2 decades of research that has established the basic and clinical importance of active ion transport as the primary mechanism for the resolution of alveolar edema in the mature lung.

Ware LB, Matthay MA: Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 2001;163:1376-1383.

This clinical study found that alveolar fluid clearance is impaired in most patients with acute lung injury and that impaired fluid clearance is associated with a higher mortality.

Chapter 33

LYMPHOCYTE FUNCTION AFTER INJURY

John A. Mannick • James A. Lederer

KEY POINTS

1. The initial immune response to serious injury is one of inflammation.
2. Multiple organ dysfunction syndrome is clearly recognized as a major cause of mortality after serious injury and is associated with perturbations of both innate and adaptive immunity.
3. The pivotal cell in the adaptive immune system is the T-helper lymphocyte, which through cytokine production and cognate interaction sets in motion both antigen-specific cell-mediated immune responses and antibody formation.
4. Serious injury in humans and in experimental animals results in impairment of immune functions mediated by T cells. Impairments include delayed hypersensitivity responses, rejection of skin allografts, and tumor immunity.
5. A variety of agents that increase T-helper-1 function have been shown to be effective in reducing mortality from a septic challenge in various animal models of injury. These agents include IFN-γ, GM-CSF, anti-IL-6 monoclonal antibody, anti-IL-10 antibody, IL-18, and IL-12. Treatments other than cytokines and their inhibitory antibodies have also proven effective, including prolactin, melatonin, cyclooxygenase II inhibitors, and hypertonic saline.
6. Proestrus female animals are less affected immunologically than males after serious injury and a testosterone receptor antagonist can improve T-helper-1 function and resistance to sepsis in injured male animals.

Most investigators now agree that the initial immune response to serious injury is one of inflammation, usually termed the *systemic inflammatory response syndrome* (SIRS).[1-3] In patients or experimental animals with major traumatic or thermal injury, SIRS is evident shortly after initial resuscitation; and in a significant minority of patients (25% to 35%) SIRS persists without respite and may lead directly to the multiple organ dysfunction syndrome (MODS), particularly if infection supervenes.[4] MODS is clearly recognized as a major cause of mortality after serious injury and infection.[1-3] Because cells of the innate immune system are the chief source of inflammatory mediators after injury, and cellular and molecular components of innate immunity are major effectors in the early defense against invading microorganisms, it is not surprising that the majority of research on the immune consequences of injury has focused on the innate immune system.[5-9]

The T and B lymphocytes of the adaptive immune system by contrast ordinarily respond only when activated by antigen-presenting cells of the innate immune system; and although T-cell receptors and antibodies produced by B cells demonstrate remarkable diversity and exquisite precision for individual antigenic epitopes, several days of clonal expansion after initial activation are ordinarily required for a significant adaptive response to become evident.[3] Thus, at first glance, the adaptive immune system appears to be ill suited to play a role in host defense early after injury, although later participation might be anticipated. And, in fact, in the majority of injured patients the SIRS response remits after several days without progression to early MODS[4] but the patient is often left with an increased susceptibility to nosocomial infection, which is associated with production of anti-inflammatory mediators by the adaptive immune system, referred to as the compensatory anti-inflammatory response syndrome (CARS).[4,10,11] Invasive infection occurring during this period of adaptive immune depression may again induce systemic inflammation, which in turn may lead to late MODS.[4]

DECREASED T-LYMPHOCYTE FUNCTION AFTER INJURY—HISTORICAL EVIDENCE

The pivotal cell in the adaptive immune system is the T-helper lymphocyte, which through cytokine production and cognate interaction sets in motion both antigen-specific cell-mediated immune responses and antibody formation.[3] For more than 3 decades it has been evident that serious injury in humans and in experimental animals resulted in impairment of immune functions mediated by T cells. These include delayed hypersensitivity responses, rejection of skin allografts, and tumor immunity.[12-16] Moreover, a number of reports indicated that the proliferative response to T-cell mitogens by peripheral blood mononuclear cells (PBMCs) was significantly impaired in patients after traumatic or thermal injury.[17,18] These early reports were followed by studies demonstrating that diminished T-cell mitogen–induced proliferation by PBMCs was associated with decreased production of interleukin (IL)-2 and interferon-gamma (IFN-γ) by the same cells.[19,20] Decreased production of these cytokines appeared to be associated with subsequent infectious complications although a causal relationship was not established.[19,20]

T-LYMPHOCYTE PHENOTYPE CHANGES IN INJURED PATIENTS

Following the report by Mosmann and coworkers[21] that mature T-helper cells expressed at least two phenotypes, it became clear that serious injury induced decreased production of cytokines typical of T-helper-1 (Th1) cells (e.g., IL-2 and IFN-γ). It was not certain whether this represented a generalized depression of T-helper cell function or whether the synthesis of T-helper-2 (Th2) cytokines was maintained or even increased after injury. Several groups including our own studied this question in injured patients and found that the production of the Th2 cytokine IL-4 was increased several days after injury, as revealed by mitogen stimulation of circulating T cells and by direct measurement of plasma cytokines.[22,23] Our laboratory and Sherry and colleagues[24,25] reported similar findings for IL-10, although there is at least one clinical study reporting no increase in IL-10 production after injury.[26] From these studies it appeared likely that Th1 cytokine production was inhibited after injury whereas Th2 cytokine production was maintained or perhaps increased. The vigorous IL-4 production noted several days after injury offered an explanation for the previously puzzling observation that injured patients frequently had elevated levels of immunoglobulin E (IgE) in their plasma,[27] because IL-4 is the principal inducer of this immunoglobulin isotype.

ANIMAL MODELS RELEVANT TO INJURED PATIENTS

To study these and other aspects of the immune response to injury more systematically, many investigators have turned to animal models of injury and sepsis. The clinical relevance of this animal research obviously depends on how closely the animal model(s) resemble populations of injured patients. Models that appear to mimic clinical injury include full-thickness burn models (of 25% to 60% body surface area) in mice and rats, models of hemorrhage and soft tissue trauma, and models of hemorrhage and skeletal trauma in the same species. Appropriate septic challenges used in these models include direct burn wound contamination with pathogenic bacteria, intratracheal administration of pathogenic organisms, and cecal ligation and puncture (CLP), which induces a localized peritonitis with mixed gut flora. These models have allowed a number of groups of investigators to confirm and expand observations made in seriously injured patients. Rodents, especially mice, are also available with multiple genetic modifications, which allow clear-cut answers to questions concerning the importance of specific cell types or mediators in the phenomena observed.

EVIDENCE THAT NORMAL RESISTANCE TO INFECTION REQUIRES A FUNCTIONAL ADAPTIVE IMMUNE SYSTEM

For example, by using the recombinase activating gene (Rag)–deficient mouse (which lacks an adaptive immune system) Hotchkiss and coworkers[28] were able to demonstrate convincingly that adaptive immunity, more specifically adaptively transferred, syngeneic T cells are essential for survival after CLP. In these experiments the T cells were genetically altered to overexpress the antiapoptotic protein Bcl-2, thus ensuring their protracted survival in the Rag hosts. Similar experiments in our own laboratory have shown that the administration of wild-type splenocytes to the Rag animals will reconstitute T cells and B cells in the spleen and lymph nodes and will restore normal resistance to CLP.[29] Reconstitution of adaptive immune cells also reduces the excessive production of proinflammatory cytokines noted after burn injury in unmodified Rag animals.[29] The cell type responsible for the latter effect appears to be the $CD4^+$ T-helper cell and, more specifically, the $CD25^+$ $CD4^+$ T-helper cell now known to have immunoregulatory properties in a variety of experimental systems.[30]

By using animal models it was also possible, beginning nearly 15 years ago, to confirm the clinical impression that serious injury induces lowered resistance to infection at predictable time points. For example, Moss and associates[31] from our laboratory showed that in a mouse burn model mortality versus sham burn animals after CLP was similar early after injury (15% to 20%) but that there was a nearly 80% mortality at 10 days in the burn mice, which then gradually returned to control (sham burn) levels over the ensuing 10 to 15 days. Similar time dependent susceptibility to infectious challenge has also been noted in animal models of hemorrhage and trauma by Ayala and Chaudry and their coworkers[32] and by Strong and coworkers.[33]

In several animal models the loss of resistance to an infectious challenge after serious injury was coincident with decreased production of T-helper-1 cytokines and increased production of Th2 cytokines by T cells undergoing polyclonal activation in vitro.[31,32,34-38] On the other hand, in some instances, loss of resistance to infection occurred at a time when cells of the innate immune system were shown to respond with greater than normal production of inflammatory mediators on exposure to molecules associated with pathogenic organisms (e.g., endotoxin or peptidoglycan).[33,39,40] Considered together these results suggest that after serious injury, when adaptive immunity manifests a maximal anti-inflammatory response associated with decreased resistance to infection, the innate immune system is capable of supranormal and possibly destructive proinflammatory mediator production when it encounters products of the microorganisms that might be expected to be present in a supervening infection. In other words, sepsis that follows CARS in seriously injured patients may induce an exaggerated and destructive SIRS response; thus, SIRS and CARS may coexist. These findings also may begin to provide a cellular and molecular explanation for the "second hit" phenomenon,[1,4,41] which has been defined by several investigators as an exaggerated inflammatory response to a second stressful event occurring several hours to several days after an initial injury (first hit). The second-hit phenomenon is believed by many clinicians to play a significant role in the induction of MODS in a sizeable number of patients.[1,4,41]

ALTERED T-HELPER CELL PHENOTYPE AFTER INJURY, IN VIVO EFFECTS, AND POSSIBLE MECHANISMS

Thus, animal studies in the aggregate demonstrate that serious injury, both thermal and traumatic, is followed in several days by loss of Th1 function and production of cytokines stimulatory of host defenses (i.e., IL-2 and IFN-γ), whereas there is normal or increased production of Th2 cytokines, which can be inhibitory of innate and adaptive immune responses.

Using the mouse burn model, we[42] also explored the question of whether loss of Th1 cytokine production in vitro by lymphocytes from injured animals was accompanied by a loss of Th1 function in vivo as indicated by production of Th1-dependent antibody isotypes. These studies showed that when mice were immunized with a conventional antigen at the time of injury, Th1-dependent IgG2a production by B cells was markedly inhibited at 10 days while production of the Th2-dependent isotypes IgG1 and IgE was unaffected. At the same time burn but not sham-burn animals demonstrated loss of antigen specific T-cell proliferation and marked diminution in antigen specific IL-2 and IFN-γ production.

To define some of the molecular mechanisms involved in the diminished Th1 cytokine production after injury we first determined that IL-2 and IFN-γ messenger RNA (mRNA) expression in Th cells were diminished after burn as compared with sham-burn injury in the mouse whereas IL-4 mRNA was increased.[43] We further showed that decreased IL-2 mRNA expression was associated with markedly lower expression of the transcription factors activator protein-1 (AP-1) and nuclear factor-kappa B (NF-κB) heterodimer, but not nuclear factor of activated T cells (NFAT), in the nuclei of Th cells from burn versus sham-burn animals.[44] AP-1 and NF-κB are known to be essential for IL-2 gene transcription. Similar, but not identical findings have been reported by Choudhry and colleagues[45] in a rat burn model.

An important question remaining is whether the diminished production of protective Th1 cytokines several days after injury is a compensatory reaction to stimulation of Th cells early after injury or whether it simply represents a response to down-regulatory signals from the innate immune system. Monocytes/macrophages of the innate immune system are known to express lower levels of antigen-presenting major histocompatibility complex class II molecules by several days after injury[46] and to be primed for increased production of potentially inhibitory mediators, including prostaglandin E_2 (PGE_2),[6,47-49] transforming growth factor-beta (TGF-β),[50] and perhaps IL-10.[51] At the same time these cells have diminished capacity to produce IL-12, the cytokine ordinarily required for induction of the Th1 phenotype.[49,51]

To shed further light on this issue, we have explored the possibility that T cells early after injury may be activated to make a vigorous Th1-type response. We[52] initially used two strains of T-cell–receptor transgenic mice for this purpose. Seventy-five percent of the Th cells in these animals respond only to a specific peptide antigen, which they would not be expected to encounter at the time of injury. In these animals it was found that the Th cells responded to the cognate antigen in vitro with increased rather than decreased IFN-γ production for as long as 7 days after injury when compared with sham-burn controls. The injection of the relevant antigen in vivo at the time of injury produced death in 100% of the burn animals and in none of the sham animals. These studies suggested that burn injury initially induced a state of increased and potentially harmful Th1 activity in these two transgenic strains.

To confirm these findings in wild-type animals, we turned to a bacterial superantigen, staphylococcal enterotoxin B (SEB), which activates approximately 20% of the Th cell population expressing the Vβ chain of the T-cell receptor to which the superantigen binds.[53] Thus, immediate evidence of T-cell reactivity could be obtained at the time of injury without the necessity for clonal expansion, which is a prerequisite for a detectable response to a conventional antigen. These studies again showed that superantigen administration at the time of burn injury caused death of burn, but not sham-burn, animals in a dose-dependent manner and that mortality could be prevented by anti–IFN-γ antibody and soluble TNF-α receptor (thus confirming the importance of these cytokines in the fatal response) and by blockade of T-cell co-stimulation through the use of cytotoxic lymphocyte–associated protein-4 bound to immunoglobulin (CTLA4-Ig), which binds to co-stimulatory molecules on antigen presenting cells. Abrogation of mortality by CTLA4-Ig further established that death by superantigen administration at the time of injury was, indeed, a T cell–mediated phenomenon.

The two experiments just described strongly suggested that the loss of Th1 function and cytokine production with the dominance of Th2-type cytokine production, noted at about a week after injury in several human and animal studies described earlier, represented a regulatory response to activation of T cells at the time of serious injury.

This proposition could be tested most easily in the T cell–receptor transgenic mouse model. As noted previously, when burn, but not sham-burn, animals were immunized with cognate antigen at the time of injury, 100% mortality ensued. However, we found that the administration of small amounts of the same cognate antigen at the time of injury permitted survival of the majority of the immunized T cell–transgenic animals. Splenic and lymph node T cells harvested from un-immunized burn animals 7 days after injury produced large quantities of IFN-γ in comparison with sham-burn controls when cultured with the cognate antigen. In contrast, the same cell population harvested at day 7 after injury from immunized burn, but not sham-burn, animals produced large quantities of IL-4 and IL-10 on antigen stimulation in vitro.[54] In wild-type animals there is an early spontaneous proliferation of Th cells but not T cytotoxic or B cells in vivo within the first 12 hours after burn, but not sham-burn, injury. The proliferative response ceases by 24 hours. There is evidence of selective Vβ chain expression by the proliferating T-helper cell population, thus suggesting, but certainly not proving, that endogenous superantigen may be involved in this process.[55]

THERAPEUTIC RESTORATION OF T-HELPER CELL FUNCTION AFTER INJURY

Can restoration of Th1 function restore normal resistance to infection after serious injury? A variety of agents have been shown to be effective in reducing mortality from a septic challenge in various animal models of injury. These include IFN-γ,[56] GM-CSF,[57] anti–IL-6 monoclonal antibody,[58] anti–IL-10 antibody,[59] IL-18,[60] and IL-12.[43,51] Agents other than cytokines and their inhibitory antibodies have also proven effective. These include prolactin,[61] melatonin,[62] cyclooxygenase II inhibitors,[6,33] and hypertonic saline.[63] Of considerable interest recently has been the demonstration that sex differences play a role in the loss of Th1 function after injury.[64-66] Female proestrus mice are far less affected than male mice, and the use of the testosterone receptor antagonist, flutamide, after hemorrhage or trauma/hemorrhage restored Th1 cytokine production and proliferative capacity in injured as compared with sham-injured male mice and also increased survival after CLP.

Among the therapeutic agents mentioned earlier, one which is known to affect Th1 function directly is IL-12, which induces the Th1 phenotype. The administration of low doses of recombinant IL-12 beginning shortly after injury in the mouse model of burn injury in our laboratory reduced mortality from subsequent CLP to that of sham-injured controls.[51] Whereas the effect of IL-12 was dependent on IFN-γ production, the results obtained with IL-12 were superior to those achieved with IFN-γ itself in the same model.[43] IL-12 therapy was similarly shown to be protective against death from infection in burn mice by Kobayashi and colleagues.[36] IL-12 therapy was further shown to restore production of Th1-dependent antibody isotypes.[42] However, the clinical use of IL-12 to attempt to reduce the incidence of infection and septic death after serious injury is not particularly attractive because of IL-12 toxicity as demonstrated in clinical cancer trials.[67]

In summary, it appears likely that T-helper cells are programmed for a proinflammatory Th1-like response early after serious injury, which is followed in several days by the emergence of a Th2-like regulatory phenotype. The appearance of the latter phenotype is associated with diminished resistance to infection in a number of animal models and some clinical studies. B cells of the adaptive immune system are deficient in production of certain complement fixing antibodies, notably those of the IgG2 family, which appears to result from loss of effective Th1 function. Increased production of the Th2-dependent antibody IgE has been commonly observed in both injured humans and in animal models.

The fact that restoration of Th1 function by a variety of interventions is associated with improved resistance to infection in the postinjury period in animal models suggests that one or more of these approaches could prove useful clinically in preventing the onset of nosocomial infection with its attendant risk of death from MODS in seriously injured patients.

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Faist E, Kupper TS, Baker CC, et al: Depression of cellular immunity after major injury. Its association with posttraumatic complications and its reversal with immunomodulation. Arch Surg 1986;121:1000-1005.

The data presented in this manuscript indicate that major injury can lead to depression of the T cell responses, which correlates with the subsequent development of infectious complications. Inhibition of cyclooxygenase pathways was able to reverse or decrease this immunologic defect.

Goebel A, Kavanagh EG, Lyons A, et al: Injury induces deficient interleukin-12 (IL-12) production while IL-12 therapy after injury restores resistance to infection. Ann Surg 2000;231:253-261.

Serious injury is associated with loss of function of the Th1 lymphocyte phenotype and decreased IL-12 production. In this manuscript, IL-12 production was shown to be reduced in peripheral blood mononuclear cells from severely injured patients. In humans, there is a reciprocal relation between diminished IL-12 production and increased IL-10 production at approximately 1 week after injury. Low-dose IL-12 therapy in the mouse burn model markedly increased survival after a septic challenge, even when treatment was carried beyond the onset of sepsis. Low-dose IL-12 treatment in the mouse increased production of proinflammatory mediators important in host defense and at the same time maintained or increased production of IL-10, an important antiinflammatory cytokine.

Hotchkiss RS, Chang KC, Swanson PE, et al: Caspase inhibitors improve survival in sepsis: A crucial role of the lymphocyte. Nat Immunol 2000;1:496-501.

Sepsis induces lymphocyte apoptosis, and prevention of lymphocyte death may improve the chances of surviving this disorder. This study demonstrated that inhibition of caspase 3 in mice resulted in decreased lymphocyte apoptosis and improved resistance to infection. Such results indicate that caspase inhibitors enhance immunity by preventing lymphocyte apoptosis and also that lymphocyte apoptosis is involved in the control of infection during sepsis.

O'Sullivan ST, Lederer JA, Horgan AF, et al: Major injury leads to predominance of the T-helper-2 lymphocyte phenotype and diminished interleukin-12 production associated with decreased resistance to infection. Ann Surg 1995;222:482-492.

This paper shows that major burn and traumatic injury led to increased Th2 cell responses, and decreased IL-12 production. Such changes in T lymphocyte functions were associated with decreased resistance to infection.

Wichmann MW, Zellweger R, DeMaso CM, et al: Mechanism of immunosuppression in males following trauma-hemorrhage: Critical role of testosterone. Arch Surg 1996;131:1186-1192.

Male sex hormones appear to be associated with worsened outcome from sepsis and hemorrhage. In these experiments, castration of male mice before soft tissue trauma and hemorrhagic shock maintains normal immune function, whereas sham-castrated male mice show significant immunodepression. The maintenance of immune function by androgen deficiency was not related to changes in the release of corticosterone. Such results suggest that the use of testosterone-blocking agents after trauma/hemorrhage could prevent the depression of immune functions and decrease the susceptibility to sepsis under those conditions.

Chapter 34
COAGULATION

Charles T. Esmon

KEY POINTS

1. Inflammation promotes blood coagulation.
2. Blood clotting enzymes promote inflammation.
3. Proteolytic products of clotting factors (fragment 1-2) can be used to assess intravascular coagulation and fibrin formation or degradation (D-dimer).
4. Natural anticoagulants inhibit coagulation and dampen inflammation.
5. Natural anticoagulant mechanisms are impaired by inflammatory mediators.
6. Microparticles released from cells by potent agonists contribute to thrombosis.
7. Platelet activation promotes inflammation.

OVERVIEW OF BLOOD COAGULATION

Thrombosis and disseminated intravascular coagulation are relatively common complications in critically ill patients. Recent studies have shown that inflammation is a major driving force in initiating and amplifying the blood clotting process. Under normal circumstances, blood clotting is limited to the site of injury. This regulation is due in large part to natural anticoagulant pathways. Inflammation can down-regulate these pathways, leading to a tilt in the hemostatic balance favoring clot formation. Further, the blood clotting enzymes can amplify the inflammatory response, and several of the natural anticoagulant pathways exhibit anti-inflammatory activity. Thus, the change in the hemostatic balance impacts inflammation as well as favoring clot formation. Finally, normal circulation of the blood is important in preventing thrombosis. In large part, this is due to the presence of potent anticoagulant mechanisms that are concentrated in the microcirculation. Thus, when blood has little or no flow in the large blood vessels, the clotting process proceeds in the absence of adequate negative regulatory mechanisms.

The goal of this chapter is to provide a framework for understanding the regulation of the blood coagulation process. Biochemical details are presented only when they are deemed to be important for understanding the process. For a more complete biochemical description of the blood clotting process, see reference 1.

Triggering the innate immune system has long been recognized to result in potential stimulation of the blood coagulation system. More recently, the highly integrated interactions of these two systems have become apparent. Inflammation triggered by the innate immune system initiates not only the blood clotting process but also the natural anticoagulant pathways, components of which are consumed or down-regulated by the inflammatory mediators. The anticoagulant components play an important role in limiting the inflammatory response. This chapter summarizes current information on the linkage between the regulation of the coagulation and inflammatory responses to infection.

BLOOD COAGULATION PATHWAYS

The main pathways of blood coagulation are shown in Figure 34-1. All the reactions involved in generating thrombin, the enzyme responsible for blood clotting, require negatively charged phospholipid membranes to proceed at physiologically relevant rates. Functional membrane phospholipid expression (phosphatidylserine, phosphatidylethanolamine) requires exposure of the cells to potent activators such as collagen together with thrombin (for platelets) or the membrane attack complex (C5b9) of the complement system to achieve full activity.[2]

Tissue factor triggers the blood clotting process. Under normal circumstances, tissue factor is found primarily on cells lining the outside of the blood vessel,[3] where it is strategically placed to trigger hemostasis when the blood vessels are injured or severed. Once an inflammatory challenge occurs, tissue factor expression is induced on macrophage-monocytes.[4,5] Recently, it has been shown that circulating tissue factor is present in blood, albeit at low levels, where it appears to augment hemostasis and the growth of thrombi.[6] When tissue factor is exposed to blood, it binds factor VII. Factor VII is converted to the active serine protease, factor VIIa, by thrombin, factor Xa, or factor VIIa, processes that are accelerated by factor VII and factor VIIa binding to tissue factor.[7] The tissue factor–factor VIIa complex can convert either factor IX or factor X to their proteolytically active forms, factors IXa and Xa.[8] Factors V and VIII circulate as inactive high-molecular-weight proteins. They must be proteolytically activated by thrombin or factor Xa to participate effectively in the coagulation cascade. In the case of factor VIII, it circulates in complex with another very high molecular weight protein, von Willebrand's factor, a protein involved in platelet adherence to the vessel wall at wound sites. The von Willebrand's factor–factor VIII interaction helps stabilize factor VIII, a protein that is normally relatively unstable. Upon activation of factor VIII, von Willebrand's factor dissociates, leaving a relatively unstable factor VIIIa molecule. Factors Va and VIIIa are not proteases

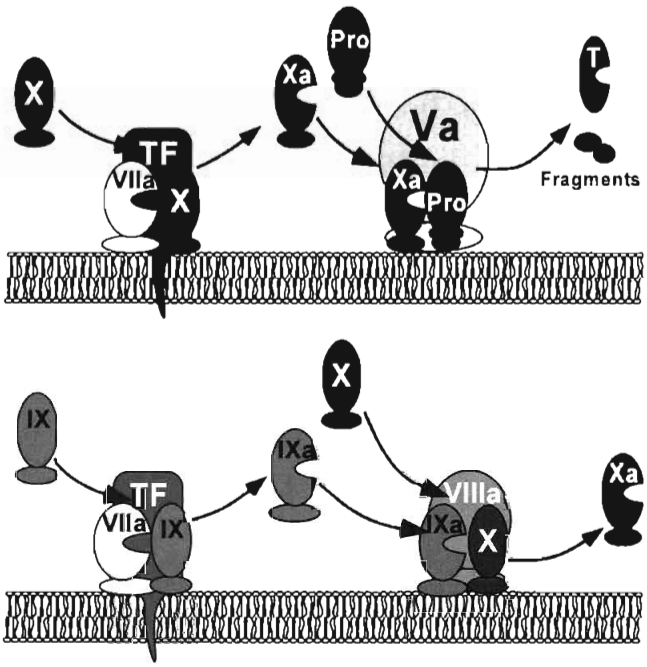

FIGURE 34–1. Initiation of the coagulation cascade. Tissue factor (TF) on extravascular cells is exposed to blood at a wound site. Factor VII (not shown) is activated by thrombin (T), factor Xa, or factor VIIa (when bound to tissue factor). The tissue factor–factor VIIa complex then cleaves factor X to generate the serine protease factor Xa. This binds to factor Va, and the complex converts prothrombin (Pro) to thrombin. Roughly half of the prothrombin molecule is released as activation fragment 1-2 (Fragments). Circulating levels of this fragment are used to determine the degree of intravascular coagulation. Alternatively, the tissue factor–factor VIIa complex can activate factor IX. Factor IXa binds to factor VIIIa to activate factor X. At this point, the different pathways converge. Factors VII, IX, and X and prothrombin need vitamin K for their synthesis. The vitamin generates γ-carboxyglutamic acid from glutamic acid residues located toward the amino terminus. These residues are required for calcium-dependent binding to negatively charged phospholipids.

but serve as cofactors that bind to both the substrates and the enzymes to accelerate the coagulation process. Factor IXa binds to factor VIIIa, and this complex also converts factor X to factor Xa. Factor Xa in complex with factor Va converts prothrombin to thrombin.[9] Nearly half the prothrombin, including the domain responsible for binding to negatively charged phospholipids, is released during activation. This activation fragment (fragment 1-2) can be detected in the circulation using immunoassays and is a monitor of intravascular coagulation (Table 34-1).

In addition to clotting blood, thrombin activates many cells, altering their phenotype by leading to tissue factor, leukocyte adhesion molecule, and cytokine expression.[10] Therefore, thrombin generation has the potential to amplify the inflammatory pathways.

TABLE 34–1. ASSAYS USED TO DETECT INTRAVASCULAR COAGULATION

Assay	Activity Measured
Fibrinopeptide A	Fibrin formation
Thrombin-antithrombin complex	Thrombin formation
D-dimer	Fibrin degradation
Prothrombin fragment 1-2	Prothrombin activation

Traditionally, blood coagulation was thought to occur via one of two pathways: the extrinsic pathway (described earlier), and the intrinsic pathway triggered by the activation of factor XII. Factor XII is activated on surfaces such as glass or collagen. Factor XIIa activates factor XI in vitro, and factor XIa in turn activates factor IX. From that point on, the pathways converge. The physiologic importance of the intrinsic pathway to coagulation is questionable, however, because patients with factor XII deficiency do not have bleeding problems. In contrast, patients with factor IX deficiency exhibit a variable and usually mild bleeding diathesis. Why factor XI deficiency, but not factor XII deficiency, is associated with increased bleeding risk remained unclear until it was shown that thrombin could feed back to activate factor XI, thereby bypassing the factor XII requirement.[11,12] Subsequently, it was shown that binding of factor XI to activated platelet receptors further enhanced this thrombin activation of factor XI.[13] This pathway is involved in bradykinin formation and has weak profibrinolytic activity (Fig. 34-2).

Once thrombin is formed, it clots fibrinogen, a process that requires the release of small peptides from fibrinogen, allowing the newly revealed N-termini to participate in fibrin formation. Fibrinogen is a complex molecule with two copies of three independently coded chains: α, β, and γ. These small fragments, referred to as fibrinopeptides A and B, are derived from the N-termini of the α and β chains (Fig. 34-3). Immunoassays designed to detect fibrinopeptides have been used to monitor intravascular coagulation (see Table 34-1).

The fibrin formed initially is somewhat fragile. Very rapidly during clot formation, factor XIII is activated by thrombin and crosslinks the clot (Fig. 34-3). Six transamidation reactions occur between the fibrin chains, each involving crosslinking between glutamine and lysine residues. The new amide bond is very stable. The resultant clot is more resistant to clot lysis and mechanical forces.[1,14]

FIBRINOLYSIS

Once the thrombus forms, it can be removed by the fibrinolytic system. The primary mechanism is initiated when tissue plasminogen activator (t-PA) binds to fibrin. The fibrin–t-PA complex rapidly converts plasminogen into the fibrinolytic enzyme plasmin. The process is facilitated by plasminogen binding to the fibrin clot and concentrating the enzyme and substrate in close proximity.[14] Fibrin is then degraded into fibrin degradation products, including D-dimer (see Fig. 34-3). D-dimer levels in the circulation are often used as a measure of intravascular coagulation (see Table 34-1). This is somewhat indirect, however, because it is a simultaneous measure of clot formation and lysis. If the fibrinolytic system is severely impaired, intravascular clot formation could be occurring without a concomitant increase in fibrinolysis and a subsequent increase in D-dimer levels.

Plasmin and t-PA are rapidly inactivated by α_2-antiplasmin and plasminogen activator inhibitor-1 (PAI-1). PAI-1 levels are elevated in inflammatory diseases and can result in impaired fibrinolysis.[15]

A weaker fibrinolytic system is initiated by another protease, urokinase. Urokinase can activate plasminogen without strong requirements for binding to fibrin. It is generally believed that the primary function of urokinase involves binding to a urokinase receptor, at which time it is involved

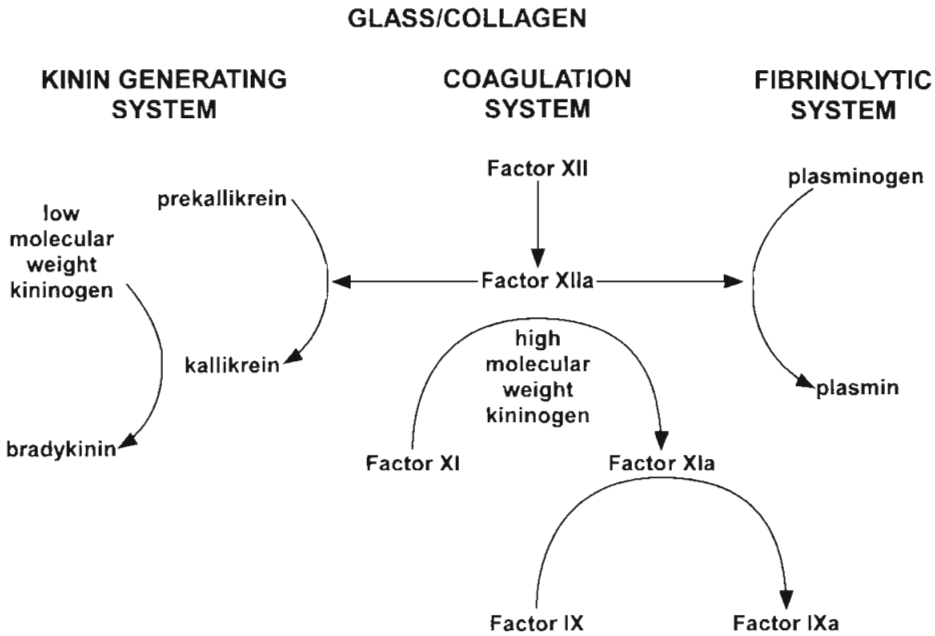

FIGURE 34–2. Intrinsic coagulation system. When blood contacts foreign surfaces such as glass, certain soils, or collagen, factor XII is activated. In the presence of high-molecular-weight kininogen, factor XIIa activates factor XI, which in turn activates factor IX. The pathway can also generate bradykinin. Factor XIIa activation of prekallikrein leads to the formation of bradykinin. Alternatively, factor XIIa can activate plasminogen, stimulating fibrinolysis.

in cellular migration, tumor growth, and development, in part mediated through cell surface activation of plasminogen.[14,16]

An obvious question is why there is so much complexity. In part, this seems to be due to the vast array of insults to which the coagulation system must respond—everything from minor nicks to severe trauma. A simple system could easily seal the wound, regardless of magnitude, but it would most likely lack the control mechanisms required to generate a hemostatic response without occlusive thrombosis. The potential thrombin that can be generated from prothrombin is more than 100 times enough to clot blood. Unchecked, these pathways would make more than enough thrombin to clot all the blood within seconds, making it essential to have potent negative regulatory mechanisms in place. This is the function of the natural anticoagulant pathways described later in this chapter.

NATURAL ANTICOAGULANT PATHWAYS

INHIBITION OF TISSUE FACTOR–FACTOR VIIa COMPLEX

Two major mechanisms regulate tissue factor–factor VIIa activity: tissue factor pathway inhibitor (TFPI) and antithrombin-heparin. Both function by inhibiting the protease factor VIIa bound to tissue factor. TFPI has an unusual

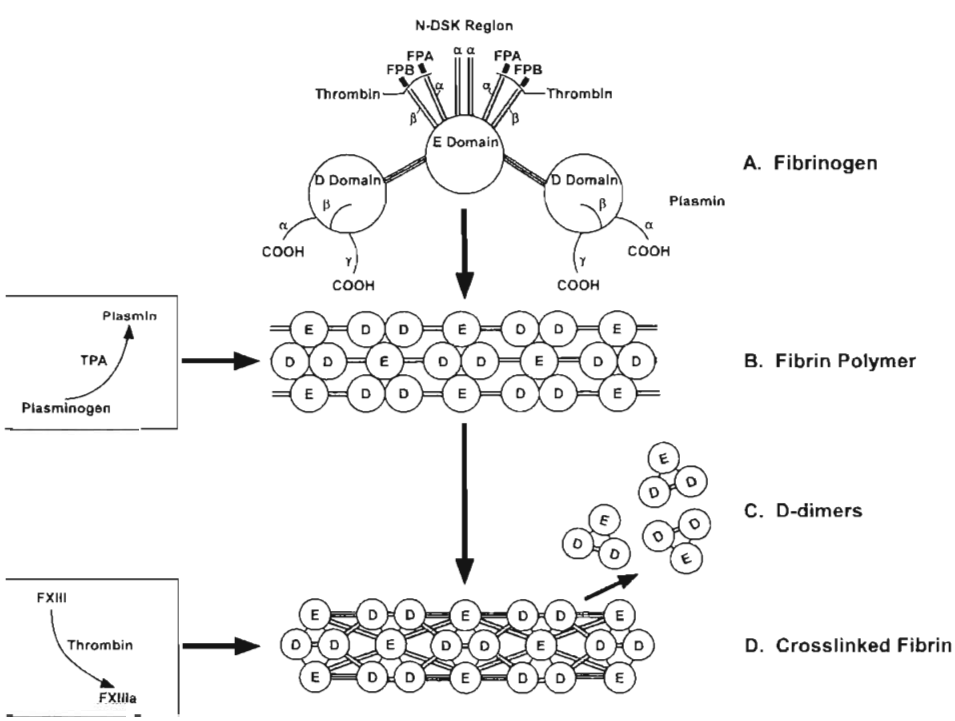

FIGURE 34–3. Formation and lysis of fibrin. Fibrinogen *(A)* has three globular domains. When thrombin releases small peptides from fibrinogen, a polymer forms *(B)*. Plasmin cleaves the polymer to release fibrin degradation products, including D-dimers *(C)*. Thrombin also activates factor XIII to cause fibrin crosslinking *(D)*. This helps stabilize the clot. FPA, fibrinopeptide A; FPB, fibrinopeptide B; N-DSK, amino-terminal disulfide knot; TPA, tissue plasminogen activator.

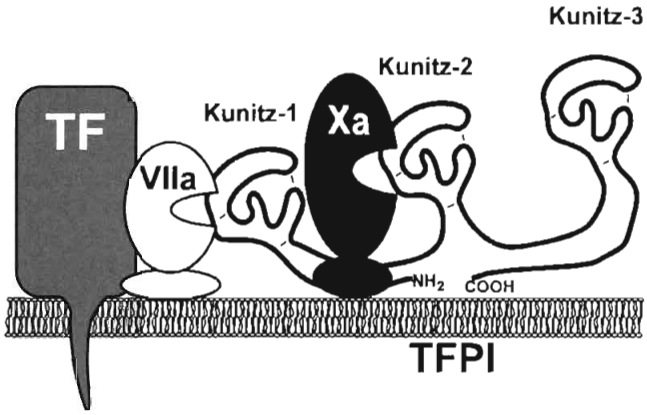

FIGURE 34–4. Proposed mechanism for tissue factor pathway inhibitor (TFPI) inhibition of the factor VIIa–tissue factor (TF) complex. Factor Xa first binds to the second Kunitz domain of the inhibitor. The complex then binds to the membrane surface. This concentrates the first Kunitz domain near factor VIIa and leads to factor VIIa inhibition. The process is reversed by removing calcium.

mechanism of action (Fig. 34-4).[17] Structurally, TFPI is composed of three Kunitz inhibitory domains. TFPI binds to factor Xa through the Kunitz 2 protease inhibitory domain. The factor Xa–TFPI complex then binds to negatively charged membrane surfaces in the presence of calcium, increasing the local concentration and favoring relatively stable, reversible inhibition of factor VIIa bound to tissue factor by the Kunitz 1 domain of TFPI.[17] Gene deletion of TFPI in mice results in an embryonic consumptive coagulopathy leading to embryonic lethality.[18] It is difficult to assess the impact of inflammation on TFPI function because the majority of TFPI is vessel associated,[17] and much of this is stored in agonist releasable endothelial cell granules.[19] Heparin also causes the release of TFPI from the vessel.[17]

Antithrombin can also inhibit the tissue factor–factor VIIa complex (see later). Although the relative importance of antithrombin versus TFPI inhibition of tissue factor–factor VIIa is uncertain, it is clear that antithrombin activity decreases markedly during severe sepsis, often dropping below 50%.[20] This decreased level of antithrombin is associated with thrombosis in thrombophilic patients.[21] Because the rate of inhibition is strongly dependent on the inhibitor concentration, a decrease in antithrombin would contribute to increased stability of the tissue factor–factor VIIa complex and hence favor intravascular coagulation.

ANTITHROMBIN REGULATION OF AMPLIFICATION REACTIONS

Antithrombin inhibition of the factor VIIa–tissue factor complex, factor IXa, factor Xa, and thrombin are all thought to be accelerated by vascular heparin-like proteoglycans. Antithrombin forms a tight, apparently covalent 1:1 complex with these enzymes (Fig. 34-5). Heparin is a highly sulfated sugar polymer that varies in size, sugar composition, and degree of sulfation. There is a relatively specific sugar sequence that determines high-affinity interaction with antithrombin.[22] Low-molecular-weight heparins are often used therapeutically. These have reduced activity toward thrombin because they cannot effectively form the bridge that is shown in Figure 34-5, but they retain a high activity toward factor Xa. Once the enzyme complex forms, heparin dissociates

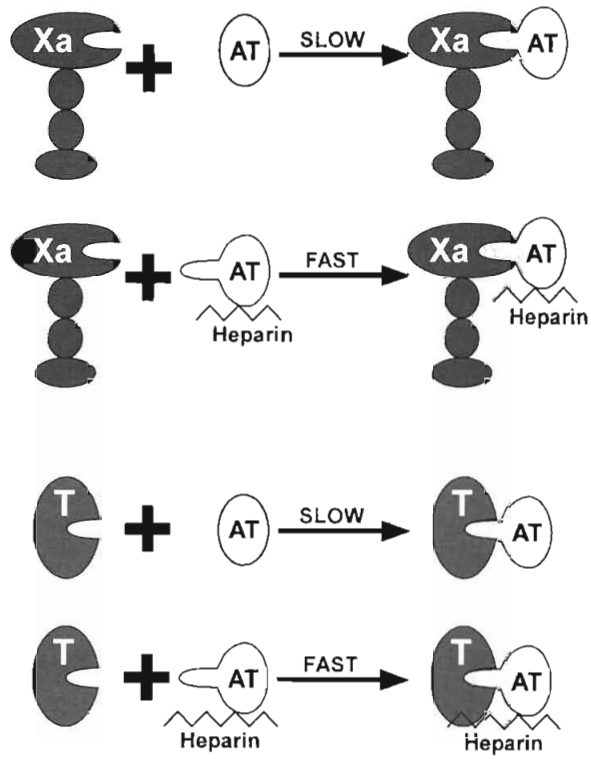

FIGURE 34–5. Heparin involvement in antithrombin function. Antithrombin (AT) undergoes a conformational change when bound to heparin, making the "bait" site more accessible. In the case of factor Xa, this is sufficient to stimulate inactivation. In the case of thrombin (T), longer heparin molecules are needed. This is the basis for some of the differences between low- and high-molecular-weight (unfractionated) heparin.

due to major conformational changes in both the enzyme and the antithrombin or related inhibitors.[23] The vascular heparin-like molecules may be inactivated during severe sepsis,[24] further reducing the effectiveness of the natural anticoagulants. This is likely to be even more important when the antithrombin level has been reduced by consumption.

PROTEIN Z–PROTEIN Z PROTEASE INHIBITOR COMPLEX REGULATION OF FACTOR Xa

Protein Z, a vitamin K–dependent anticoagulant protein, plays a significant role in the inhibition of factor Xa. Protein Z binds tightly to protein Z protease inhibitor. The protein Z protease inhibitor–protein Z complex binds to negatively charged membrane surfaces due to direct protein Z interaction with the membrane. This complex then inactivates factor Xa.[25] Deletion of the protein Z gene in mice exacerbates the thrombotic response caused by other coagulation abnormalities,[26] but alone, it is not sufficient to cause thrombosis. Low protein Z levels in humans appear to be associated with an increased risk of stroke.[27] Because protein Z appears to be a negative acute-phase reactant,[28] inflammation may reduce the effectiveness of this system also.

INHIBITION OF FACTOR Va AND VIIIa BY ACTIVATED PROTEIN C: THE PROTEIN C ANTICOAGULANT PATHWAY

The protein C anticoagulant pathway is the most complex of the natural anticoagulant mechanisms and is also the most sensitive to down-regulation by acute inflammatory responses.

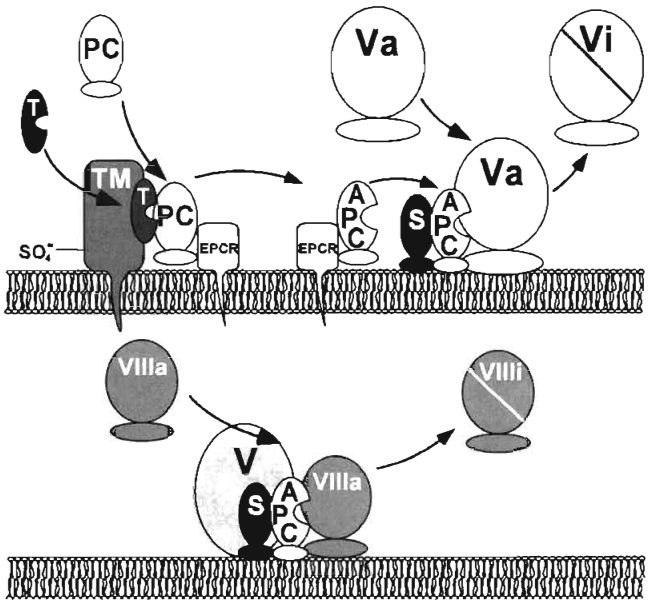

FIGURE 34–6. Protein C anticoagulant pathway. Thrombin (T) binds to thrombomodulin (TM) and activates protein C (PC). The activation is augmented by protein C binding to the endothelial cell protein C receptor (EPCR). Both protein C and activated protein C (APC) bind reversibly to EPCR. When APC dissociates from EPCR, it binds to protein S (S), and this complex inactivates factors Va (Va and Vi) and VIIIa (VIIIa and VIIIi). In the case of factor VIIIa, factor V (V) also increases the inactivation rate.

The pathway is illustrated in Figure 34-6. Protein C circulates as an inactive vitamin K–dependent zymogen at about 4 μg/mL in plasma. It is activated proteolytically on the surface of the endothelium by a complex between thrombin and thrombomodulin. Protein C activation rates are increased when protein C is bound to the endothelial cell protein C receptor (EPCR).[29] EPCR may be particularly important in preventing large vessel thrombosis[30] because it is most abundant on large blood vessels. Protein C and activated protein C (APC) bind to EPCR with comparable affinity (30 nM). The APC-EPCR complex does not appear to inactivate factor Va.[31] It is likely that this complex cleaves an alternative substrate or receptor.[32,33] This would be consistent with in vivo observations that APC infusion dampens cellular responses to inflammatory agents and decreases the generation of inflammatory cytokines.[34,35] When APC dissociates from EPCR, it can bind to protein S and catalyze the selective proteolytic inactivation of factors Va and VIIIa.[36] A common dimorphism exists in factor V in which the Arg residue at residue 506 is replaced by Gln, resulting in a factor Va that is more resistant to inactivation by APC. This condition, referred to as factor V Leiden or APC resistance, is associated with an increased risk of thrombosis.[21,37] It is found in approximately 5% of whites but is rare in other races.

APC also enhances fibrinolysis by forming a tight 1:1 complex with PAI-1 and thereby inactivating this major inhibitor of fibrinolysis. APC normally reacts slowly with PAI-1, but recently it has been shown that the reaction becomes quite rapid in the presence of vitronectin,[38] suggesting a dominant role for this reaction around platelets that release vitronectin.

Compared with other serine proteases or clotting factors, APC has a relatively long half-life in the blood of about 15 minutes before it becomes inactivated by α_1-antitrypsin (sometimes called α_1-proteinase inhibitor), protein C inhibitor or α_2-macroglobulin.[39] The APC-inhibitor complex is then cleared relatively rapidly from the circulation. Because of the relatively slow inactivation of APC, it is possible to detect circulating levels of it. This allows direct evaluation of APC levels in patients,[40,41] which in turn allows evaluation of the functionality of the protein C activation complex in vivo.

Thrombin binding to thrombomodulin not only augments protein C activation but also results in inhibition of fibrinogen clotting, platelet and endothelial cell activation, and factor V activation.[36] In addition, thrombin bound to thrombomodulin is inactivated much more rapidly than free thrombin is. Antithrombin and protein C inhibitor contribute similarly to the rapid inactivation of thrombin bound to thrombomodulin, resulting in an estimated half-life of 1 to 2 seconds for thrombomodulin bound to thrombin.[42] In severe sepsis, down-regulation of thrombomodulin would result in both decreased protein C activation and decreased thrombin clearance. It is apparent from studies of APC levels in septic patients that protein C activation can be severely impaired in a subset of patients with severe sepsis.[41,43] The modulation of thrombin functions, and the regulation resulting from thrombin-thrombomodulin interaction, allows thrombomodulin to serve as a molecular switch in the control of hemostasis and thrombosis.

IMPACT OF INFLAMMATION ON COAGULATION

Some of the changes in the vessel wall and the hemostatic balance that are caused by inflammation are illustrated in Figure 34-7. Bacteria and other pathogens can lead to the formation of inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 beta (IL-1β). These mediators, or endotoxin itself, induce synthesis and expression of tissue factor, primarily on monocytes and macrophages.[4,5] Because the monocytes and macrophages are in contact with the blood, they initiate intravascular coagulation when stimulated by these inflammatory mediators.

Complement activation as a result of inflammation can also augment the coagulant response. As mentioned previously, complement C5b9 (the membrane attack complex of complement) is a very effective cell agonist, leading to expression of negatively charged phospholipids on the surface of cells that can propagate the coagulation reaction.[44] During bacterial infections, complement activation occurs not only due to recognition of the infectious agent but also due to the increase in the acute-phase protein, C-reactive protein, which appears to augment complement activation during sepsis.[45] Cell surface expression of negatively charged lipids is a major regulatory event controlling physiologic and pathologic clotting. For instance, infusion of factor Xa at relatively high concentrations has little thrombotic effect unless coinfused with negatively charged phospholipids. These lipids are a surrogate for the activated cell surface or cellular microparticles released following treatment with potent cell agonists.[46] Further, when only an inflammatory cytokine such as TNF is infused into experimental animals, there is little fibrin formation unless appropriate lipids are also infused (and blood flow is impaired).[47] Thus, available evidence suggests that inflammation can contribute directly to two critical events in intravascular coagulation: the synthesis and expression of intravascular tissue factor and the generation

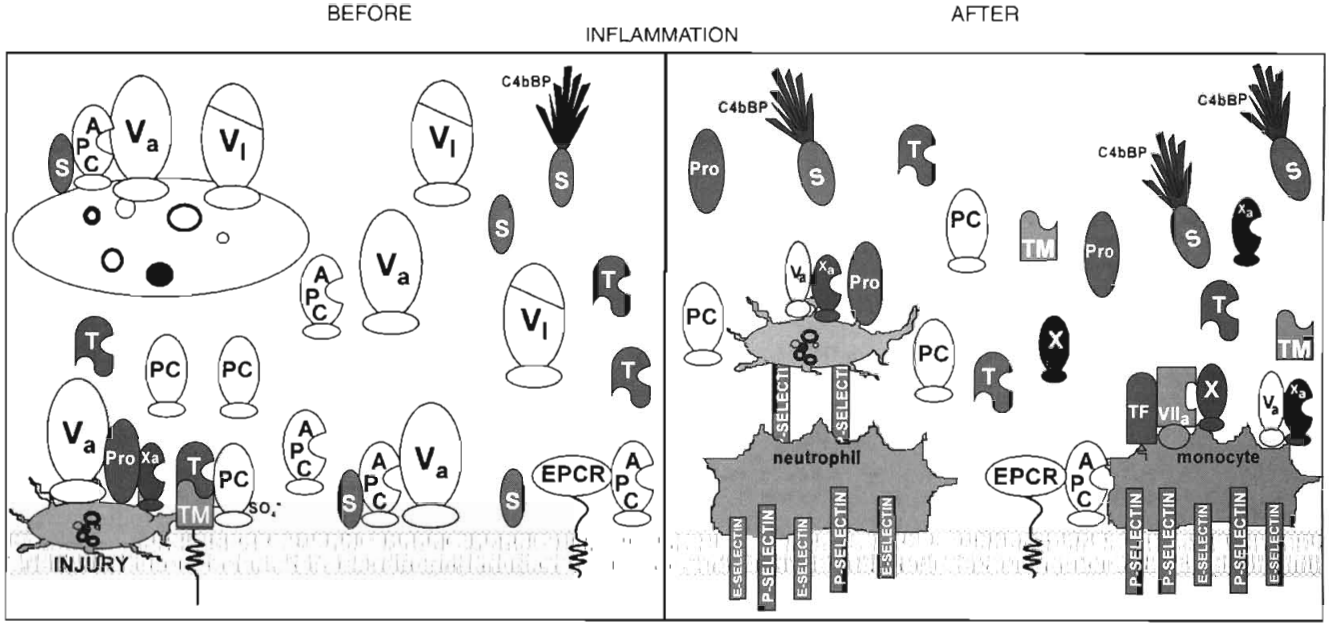

FIGURE 34–7. Impact of inflammation on the regulation of coagulation. Under normal circumstances, strong anticoagulant properties are associated with the endothelium. Inflammation causes leukocytes to adhere, thrombomodulin (TM) to be shed, and the endothelial cell protein C receptor (EPCR) to be down-regulated. Tissue factor (TF) is induced on leukocytes. Protein C (PC) is consumed, and free (active) protein S (S) decreases. Active lipid surface becomes exposed, propagating the coagulant response. APC, activated protein C; Pro, prothrombin; T, thrombin.

of membrane surfaces capable of augmenting the initiation and propagation of the coagulant response.

Thrombin impacts both its own generation and the inflammatory response. In addition to clotting fibrinogen and activating platelets, thrombin plays a major role in leukocyte activation by causing the expression of the leukocyte adhesion molecule P-selectin on platelets and endothelial cells.[48] Thrombin is a potent agonist for endothelial cell platelet-activating factor formation, a potent neutrophil agonist.[49] Neutrophil activation is potentiated by adhesion to P-selectin, further augmenting the inflammatory response. P-selectin appears to play an important role in thrombus formation. Blocking P-selectin binding to its ligand, the P-selectin glycoprotein ligand-1, decreases thrombus formation under both flow[50] and stasis conditions.[51]

Inflammatory mediators can also impact platelet function. For instance, interleukin-6 (IL-6) not only increases platelet production but also creates a population of platelets that are more thrombogenic. IL-6–induced platelets are more readily activated by platelet agonists such as thrombin.[52] Activated platelets are a rich source of the proinflammatory mediator CD40 ligand. CD40 ligand induces tissue factor formation[53,54] and increases inflammatory cytokines such as IL-6 and interleukin-8 (IL-8).[55,56]

IMPACT OF INFLAMMATION ON NATURAL ANTICOAGULANT PATHWAYS

Natural anticoagulant pathways play key roles in preventing excessive inflammation induced by augmentation of the coagulation response. In addition to preventing excess clotting, these pathways feed back to dampen the inflammatory response. However, in severe acute inflammatory diseases, some of the key negative regulatory pathways are down-regulated.

Both thrombomodulin and EPCR are down-regulated by inflammatory cytokines such as TNF at the transcriptional level.[57,58] In cell culture, about half the activity disappears in 8 hours. A single exposure of the endothelium to the cytokine reduces the protein and messenger RNA levels more than 90%, and these low levels are maintained for at least 24 hours. Neutrophil adhesion and activation on the endothelium can reduce thrombomodulin activity further, both through oxidation of a sensitive methionine residue[59] and by elastase-mediated release of soluble thrombomodulin,[60] a form with reduced activity. Decreased protein C activation is particularly important, because factors Xa and IXa are resistant to inactivation by antithrombin when they are complexed with factors Va and VIIIa, respectively.[61,62]

The protein C pathway seems to be particularly important in the prevention of microvascular thrombosis, as demonstrated by the purpura fulminans that develops in neonates with protein C deficiency.[63] Down-regulation of thrombomodulin, with the loss of thrombin clearance and decreased protein C activation, would therefore be expected to have a major effect on clotting in the microcirculation, a major site of thrombotic complications in sepsis.

ANTI-INFLAMMATORY ACTIVITIES OF NATURAL ANTICOAGULANT PATHWAYS

Natural anticoagulants have anti-inflammatory activities as well as anticoagulant functions. Antithrombin, TFPI, and APC have all been shown to protect baboons from *Escherichia coli* sepsis when given before the challenge.[64] In the baboon and several rodent models,[65] neither synthetic factor Xa inhibitors[65] nor active site-blocked factor Xa, an effective, high-affinity, competitive inhibitor of prothrombin activation in vivo,[66] protected the animals from death or

organ failure and failed to diminish cytokine elaboration. In contrast to ineffective synthetic coagulation inhibitors, the ability of natural anticoagulants to both protect from sepsis and minimize inflammation-mediated injury suggests that cellular and anti-inflammatory activities of the natural anticoagulants may be important aspects of their physiologic functions.

ANTITHROMBIN

Antithrombin can protect experimental animals from endotoxin-mediated septic shock.[67] Heparin prevents this protection, despite increasing the antithrombotic activity. A negative effect of heparin and antithrombin coadministration was observed in clinical trials.[68] High levels of antithrombin in vitro have been shown to inhibit endotoxin-induced IL-6 formation by mononuclear cells and endothelium.[67,69] Antithrombin stimulates prostacyclin release from endothelial cells in culture,[70] a process that appears to be protective in lung injury models.[71] Antithrombin-mediated signaling probably occurs through syndecan-4.[69] Antithrombin binding to cell surface receptors has also been shown to block nuclear factor kappa-B (NF-κB) translocation.[72] This prevents the subsequent release of cytokines and the induction of adhesion molecules.

TISSUE FACTOR PATHWAY INHIBITOR

TFPI infusion can reduce leukocyte activation and decrease TNF in vivo.[65] Although inhibition of cytokine elaboration appears to be independent of blood coagulation, the mechanism responsible for TFPI-mediated cellular effects remains unknown.

PROTEIN C PATHWAY

APC has been shown to protect nonhuman primates from *E. coli*–induced sepsis whether given before or after the *E. coli* challenge.[73] Recently, this observation was confirmed and extended in clinical studies demonstrating that APC infusion can reduce the relative risk of all-cause 28-day mortality from severe sepsis by 19.4%.[74] One feature of critically ill patients is the relatively high frequency of antiphospholipid antibodies.[75] Some antiphospholipid antibodies inhibit APC anticoagulant activity extremely effectively,[36] but whether this is the case in critical care patients remains to be examined.

The protective effects of APC appear to be receptor mediated. APC binding to monocytic cells can block agonist-induced calcium transients[76] and inhibit NF-κB–mediated signaling.[34,77-79] In cultured endothelium, APC reduces NF-κB messenger RNA levels, reduces the expression of cell surface adhesion molecules and cytokine formation, and elevates molecules involved in preventing apoptosis.[35] On the monocytic cell line U937, APC has been shown to dampen both basal levels and the phorbol-induced expression of tissue factor in an EPCR-dependent fashion.[32] Under appropriate conditions, APC can also cleave protease-activated receptors,[33] which are normally cleaved by coagulation enzymes, particularly thrombin.[10] The role of cleavage of the protease-activated receptors in APC function remains to be fully elucidated. Most of the downstream events following activation of these receptors enhance inflammation.[80] It is possible that activation of the protease-activated receptors is a negative side reaction occurring under in vitro conditions.

Conway and coworkers[81] recently revealed a novel anti-inflammatory activity of thrombomodulin. The N-terminal lectin-like domain[82,83] dampened activation of the mitogen-activated protein kinase and NF-κB signaling systems in endothelium. This anti-inflammatory activity was imparted by either cellular thrombomodulin or the soluble lectin-like domain. Infusion of the lectin-like domain, which does not participate in protein C activation, resulted in decreased leukocyte adhesion to the endothelium. These observations have important implications. Thrombomodulin is down-regulated on endothelium overlying atherosclerotic plaques, on vein bypass grafts, in diabetes, and by acute inflammatory insults such as bacterial infection.[84] Loss of thrombomodulin would not only reduce protein C activation but also increase the endothelium's sensitivity to leukocyte-mediated injury. Important roles for thrombomodulin in vascular protection were demonstrated earlier when its overexpression was found to reduce thrombosis, restenosis, and leukocyte infiltration in rabbits with deep arterial injury.[85,86]

Thrombomodulin also accelerates thrombin activation of a plasma procarboxypeptidase B called thrombin-activatable fibrinolysis inhibitor (TAFI).[87] TAFI removes terminal lysine residues in fibrin. Lysine residues facilitate binding of plasminogen or plasmin and t-PA. Removal of these lysine residues decreases the rate of clot lysis about fourfold.[87] Initially, TAFI was considered a prothrombotic molecule. More recently, it was found that TAFI can remove terminal Arg residues very effectively from vasoactive substances such as the anaphylotoxin C5a, generated during complement activation; this inactivates C5a. Recent studies found that TAFI is the major enzyme responsible for the inactivation of C5a.[88,89] Activation of TAFI by the thrombin-thrombomodulin complex appears to be important in preventing vascular toxicity due to C5a in conditions in which complement activation is intense. Thus, thrombomodulin may play multiple roles in the regulation of clotting, inflammation, and complement-mediated cell injury.

EPCR was recently found to be important in controlling the inflammatory response to bacterial infusion. Specifically, when protein C binding to EPCR was blocked and the animals were challenged with a low dose of *E. coli*, both the coagulant and cytokine responses were elevated dramatically, and more leukocytes migrated into the tissues compared with controls.[90] A possible mechanism involved in diminishing leukocyte migration was suggested by the recent finding that soluble EPCR, released by a metalloproteinase in endothelium,[91] binds to activated neutrophils. Soluble EPCR binds to proteinase 3, a cytosolic protein of the neutrophil that is released upon activation. Proteinase 3 binds to neutrophil integrins, particularly Mac-1 (CD11b/CD18),[92] whether or not it is bound to EPCR. In vivo data suggest that this interaction reduces tight binding of neutrophils to activated endothelium.

EPCR is also a candidate for immune modulatory functions. The crystal structure of EPCR[93] reveals that it is closely related to the major histocompatibility complex (MHC) class 1/CD1 family of proteins, most of which are involved in inflammation. The crystal structure demonstrated that EPCR has a tightly bound phospholipid in the "antigen presenting groove."[93] CD1 family members serve as glycolipid antigen-presenting molecules. For instance, CD1c seems to present a lipid antigen derived from tuberculosis.[94] The CD1

family of proteins then instructs T cells to modulate the cellular and humoral response to inflammation.[95] Further, these proteins appear likely candidates for involvement in autoimmunity.[95] Whether EPCR plays similar roles should become clear through the analysis of genetically modified mice.[96]

STRUCTURES LINKING THE COAGULATION PATHWAY AND INFLAMMATION

Coagulation and inflammatory pathways share many conserved structures, suggesting parallel evolution. In addition to the EPCR–MHC class 1 similarities, tissue factor and the cytokine receptors share structural similarities,[97] and the selectins involved in leukocyte adhesion and the lectin domain of thrombomodulin are homologous.[98] The complement and coagulation systems also have functional interactions. Protein S and a complement regulatory protein, C4 binding protein, bind tightly. When binding occurs, protein S anticoagulant activity is lost, but this allows C4 binding protein to interact with membrane surfaces, probably protecting mammalian cells from complement activation–mediated damage.[99] These findings suggest that the coagulation and inflammatory pathways evolved in parallel.

SUMMARY

It is clear that coagulation and inflammation are involved in mutual regulation. Considering these interactions, it is apparent that inflammation can contribute to a hypercoagulable state by many discrete mechanisms. Likewise, natural anticoagulants can decrease the inflammatory process. The ability of natural anticoagulants to down-regulate the inflammatory process may provide new therapeutic strategies for the treatment of acute inflammatory disease.

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Chapter 35
COMPLEMENT

Niels C. Riedemann • Peter A. Ward

KEY POINTS

PATHWAYS OF ACTIVATION

1. The **complement system can be activated** by one of three separate pathways: the classic, lectin, and alternative pathways.
2. Typically, the **classic pathway is activated by immunoglobulin G immune complexes or C-reactive protein.** The lectin pathway is activated by mannose residues on surfaces of bacteria. The alternative pathway is activated by lipopolysaccharide from Gram-negative bacteria.
3. Regardless of the activation pathway, **the most important products of activation are the anaphylatoxins C3a and C5a and the membrane attack complex C5b-9,** which cause lysis of Gram-negative bacteria. C3a induces histamine release from mast cells and causes smooth muscle contraction. C5a reacts with receptors (C5aR) on neutrophils and macrophages to cause cell signaling, chemotactic movement, enzyme release, and generation of superoxide anion ($O_2^{\bullet}$) and H_2O_2, which are involved in the myeloperoxidase-dependent killing of bacteria.

COMPLEMENT RECEPTORS AND THEIR FUNCTIONS

1. **Complement receptors exist on a variety** of myeloid and nonmyeloid cells and induce signaling responses in the presence of the ligand (complement activation product).
2. **Receptors of C1q (C1qR)** exist on a variety of cell types and often work synergistically with Fc receptors to enhance the inflammatory response.
3. **Receptors for C3a (C3aR) and C5a (C5aR)** are abundant on myeloid cells. In mast cells, the presence of C3a induces granule secretion and histamine release. Engagement of C3aR on smooth muscle cells results in smooth muscle contraction, especially in the airways. Engagement of C5aR on phagocytic cells causes mitogen-activated protein kinase signaling cascades, resulting in chemotaxis, enzyme release, and generation of superoxide anion ($O_2^{\bullet}$) and H_2O_2. Engagement of C5aR on endothelial cells causes P-selectin and tissue factor expression on the endothelium and release of von Willebrand's factor, a procoagulant protein.

GENETICALLY BASED COMPLEMENT DEFICIENCIES

1. **Deficiencies of early complement components (C1q, C1r, C1s, C2, C4)** are associated with manifestations of systemic lupus erythematosus (SLE), glomerulonephritis, and susceptibility to streptococcal pneumonia. Deficiencies of C3 are often life-threatening owing to loss of innate immune defenses to bacteria. Deficiencies of C5, C6, C7, C8, or C9 cause increased susceptibility to infection by *Neisseria* species.
2. **Deficiency of C1 inhibitor** causes hereditary angioedema, and **deficiency of a glycoprotein I–anchored protein** prevents the functioning of complement regulatory proteins, resulting in paroxysmal nocturnal hemoglobinuria.

IN VIVO BIOLOGIC FUNCTIONS OF COMPLEMENT

1. **Ischemia-reperfusion injury in animals** undergoing gut or myocardial ischemia has been shown to be complement and neutrophil dependent.[1] Infusion of C1 inhibitor can ameliorate the injury. Complement activation products also play an important role in hyperacute rejection following organ transplantation.
2. **In the setting of sepsis in animals and humans,** there is clear evidence of complement activation. In animals with sepsis, blockade of C5a or its receptor (C5aR) is protective. There are also suggestions that complement activation occurs in acute respiratory distress syndrome and that C5a can also be generated by activated phagocytic cells.[2]
3. **In SLE, rheumatoid arthritis (RA), and many cases of glomerulonephritis,** there is evidence of complement activation in synovial tissues and in the kidney, as demonstrated by deposition of C3 or its activation products in these locations.
4. **In acute thermal injury and acute trauma,** including cases of closed head injury, there is evidence that complement activation has occurred.

COMPLEMENT INHIBITORS

Several mechanisms exist to prevent uncontrolled activation of the complement system (Fig. 35-1). Such inhibitors of complement activation either exist in plasma or are bound to the cell membrane. As explained later, genetic deficiency of such inhibitors is often associated with human disease.

The natural fluid phase inhibitors occur accordingly: C1 inhibitor inhibits activation of C1s and C1r and, thereby, the classic pathway, but it has also been shown to inhibit activation of the mannose-binding lectin (MBL) pathway. Heterozygous deficiency of C1 inhibitor manifests clinically as life-threatening angioedema. Factor H and C4 binding protein are large plasma proteins that inhibit C3 and C4 activation (in part, as cofactors for other inhibitors), thus inhibiting all pathways of complement activation. Factor I is a serum protease that inactivates C3b and C4b and, therefore, C3 and C5 convertases. It needs cofactors to elicit its effect. Carboxypeptidase N is another serum protein that greatly reduces the biologic activities of C3a and C5a. S protein, fibronectin, and clusterin are present in the plasma and disable the insertion of C5b-9 into the cell membrane.

The membrane-bound inhibitors elicit their effects at different points of the complement system as well. CD59 is a glycoprotein I (GPI)–linked protein that blocks the insertion of C9 into the membrane-bound C5b-9 and also prevents the polymerization of C9, which effectively inhibits the ability of C5b-9 to cause cell lysis.[3] Membrane cofactor protein and

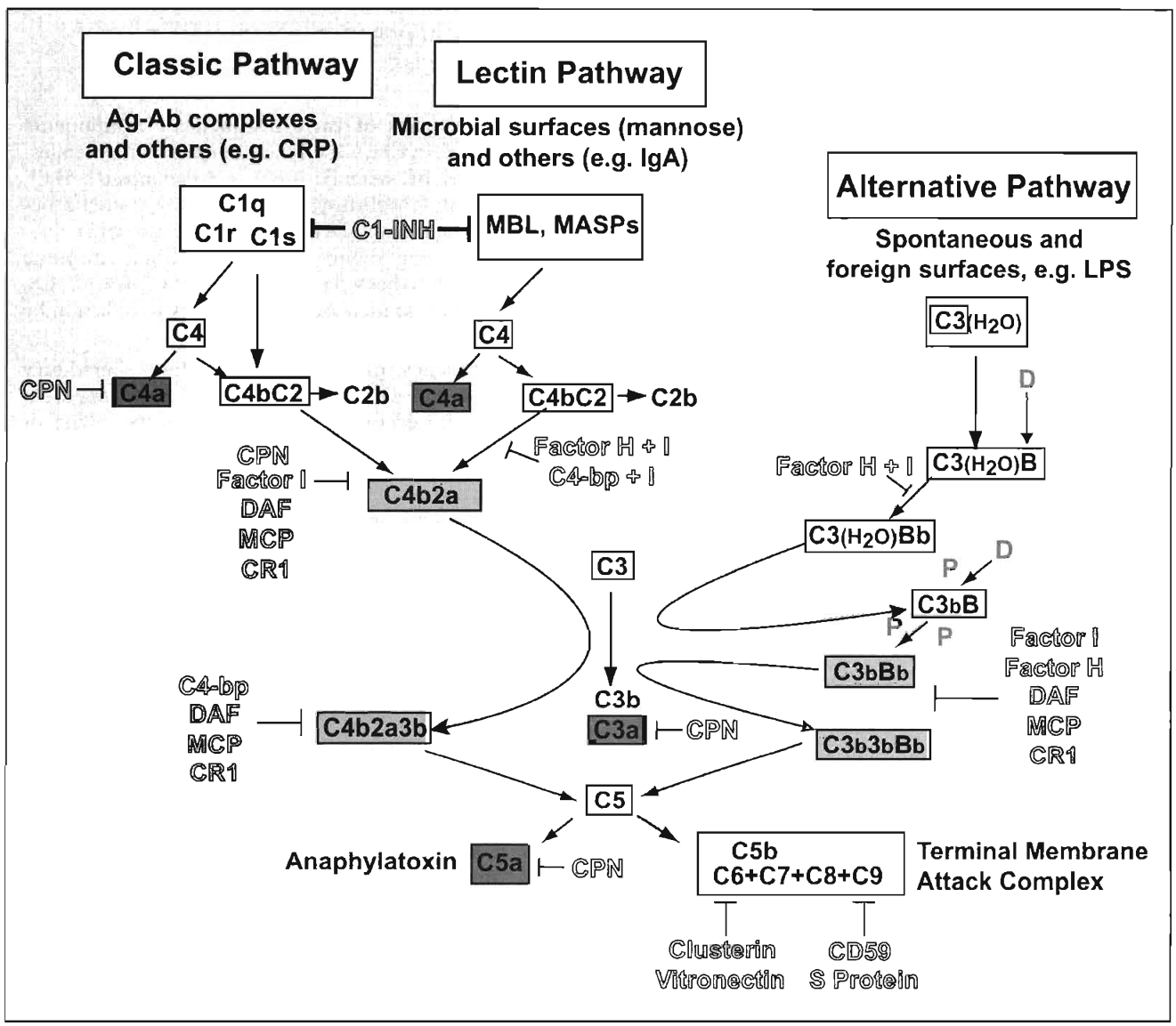

FIGURE 35–1. Activation pathways of the complement system. Complement components C1 to C9 are depicted in square boxes, as well as mannose-binding lectin (MBL) and the MBL-associated serine proteases (MASP). C3 and C5 convertases (classic and alternative) are depicted. The complement split products and anaphylatoxins C3a, C4a, and C5a are depicted. Cofactors of activation are factor D (D) and properdin (P). Inhibitor function is depicted with the symbol (⊥). Membrane-bound inhibitors are CD59, decay-accelerating factor (DAF), complement receptor 1 (CR1), and membrane cofactor protein (MCP). Fluid phase inhibitors are C1 esterase inhibitor (C1-INH), factor H, factor I, clusterin, vitronectin, S protein, and carboxypeptidase N (CPN). IgA, immunoglobulin A; LPS, lipopolysaccharide.

decay-accelerating factor act, either directly or as cofactors for factor I, to deactivate C3 and C5 convertases of all pathways, as well as to cleave C3b and C4b.

COMPLEMENT RECEPTORS

Many of the effects associated with complement activation are achieved by the binding of activated complement products (the anaphylatoxins and opsonic factors such as C3b) to specific receptors. A broad variety of complement receptors exists, although the function of some of them is not yet well established. Often, complement receptors bind various complement activation products with different affinities and thereby elicit a wide range of effects on different cell types (Table 35-1). In general, complement receptors may function as signaling units (transmembrane receptors) for various cell types or as inhibitors of complement activation, especially in their soluble form.

The C1q receptor is present on myeloid cells, endothelial cells, and platelets and can bind C1q as well as MBL. C1qR enhances the phagocytic activity of neutrophils, especially when initiated by Fc receptor activation (binding of immunoglobulin G [IgG] to the cell surface) or by complement receptor 1 (CR1) activation (see later). C1qR may be involved in the up-regulation of cell adhesion molecules on endothelial cells (see Table 35-1). CR1 exists on most blood cell types, as well as on dendritic cells, podocytes in renal glomeruli, and liver Kupffer cells, and also exists in a soluble form. CR1 binds C3b (and the derivative iC3b), as well as C4b and C1q, with high affinity. Many functions have been assigned to CR1.[4] CR1 elicits complement regulatory functions by facilitating, in concert with cofactor I (similar to decay-accelerating factor or membrane cofactor protein), cleavage of C3b and C4b, thereby inactivating C3 and C5 convertases. CR1 is believed to be involved in the clearance of C3b-bound immune complexes in the serum to promote phagocytosis activity and to activate T cells (see Table 35-1).

Complement receptor 2 (CR2) binds iC3b and C3d (cleavage products of C3b) and interacts less effectively with C3b. CR2 is also the receptor that binds Epstein-Barr virus. CR2 is present on B cells, some subtypes of T cells, thymocytes, and a variety of epithelial cells. CR2 is believed to be responsible for a variety of effects, especially activation of B cells and T cells and their adherence when bound to immune complexes.[5]

Complement receptors 3 and 4 (CR3, CR4) are members of the integrin family and are expressed on most myeloid cells. Both receptors bind iC3b and C3b but have affinities to many other ligands (e.g., fibrinogen, intercellular adhesion molecule-1). Besides many other effects elicited by these receptors, they are believed to enhance the phagocytic activity of neutrophils and macrophages.[6]

Whereas some complement receptors interact with a variety of C3 and C3b cleavage products (CR1–4), as well as with C1q (C1qR), other complement receptors specifically recognize the cleavage products C3a (C3aR) and C5a (C5aR). Both receptors are widely expressed on almost all cell types and operate through G-protein activation, leading to phosphorylation of various intracellular signaling pathways, such as the mitogen-activated protein kinase pathways. Most of the known biologic effects of complement ligation are associated with activation of C3aR or C5aR. Recent work suggests that C5aR plays a role in the onset of experimental sepsis and the development of multiorgan failure[7] and that it may be induced in various organs during sepsis by interleukin-6 (IL-6).[8] Similarly, it has been suggested that C3aR plays an important role in the lung during endotoxic shock.[9,10] Blockade of C5aR in experimental sepsis greatly improves survival.[7,11]

BIOLOGIC FUNCTIONS OF THE COMPLEMENT SYSTEM

Obviously, an important and already mentioned biologic effect of the complement system is its opsonic function (C3b), which marks invading microorganisms as "foreign," leading to a targeted host defense response. Ultimately, the formation of C5b-9 leads to the lysis of Gram-negative bacteria, another important defense mechanism of innate immunity. But besides these prominent functions, there are numerous other biologic effects elicited by activation of the complement system (Table 35-2). An important function with broad implications is the regulation of immune complex processing and solubility. Immune complexes often activate complement and bind C3b, resulting in clearance from the circulation via binding with CR1.[12] In addition, complement factors (especially C3b) are responsible for inducing the solubility of immune complexes, and thereby their size.[13] Similarly, the clearance of circulating necrotic or apoptotic

TABLE 35–1. COMPLEMENT RECEPTORS

Receptor	Molecular Weight	Biologic Functions
C1qR	126,000	Enhances Fc-receptor and CR1-mediated phagocytosis, induces adhesion molecule expression on endothelial cells
C5aR (CD88)	50,000	Induces C5a-dependent chemotactic responses of neutrophils, release of granular enzymes and production of superoxide anions in phagocytic cells, vasodilatation, increases in vascular permeability, increases in adhesion molecule expression on endothelial cells, procoagulatory and antifibrinolytic effects, increased expression of various cytokines in different cell types
C3aR	60,000	Similar to C5aR
CR1 (CD35)	190,000-250,000	Binds C3b (and iC3b), C4b, and C1q and facilitates, together with factor I, cleavage of C3 and C5 convertases, clearance of C3b-bound immune complexes in serum; promotes phagocytosis, activation of T cells
CR2 (CD21)	145,000	Binds iC3b and C3d and stimulates B cells (antibody production), Epstein-Barr virus receptor, maintenance of self-tolerance
CR3 (CD11b/CD18)	170,000	Binds iC3b and C3b as well as other molecules (e.g., fibrinogen, intercellular adhesion molecule), integrin-adhesion function, enhances phagocytosis activity of neutrophils, facilitates antibody-mediated phagocytosis
CR4 (CD11c/CD18)	150,000	Similar to CR3

TABLE 35–2. BIOLOGIC ACTIVITIES OF COMPLEMENT ACTIVATION PRODUCTS

Product	Biologic Functions
C1q	Clearance of immune complexes, enhancement of antibody-dependent cellular cytotoxicity, enhancement of phagocytosis in monocytic cells, increase in reactive oxygen species production in neutrophils, adhesive function in fibroblasts
C5a > C3a (>C4a) Anaphylatoxins	Chemotaxis of neutrophils, release of granular enzymes and superoxide anion production in phagocytic cells, increased vascular permeability and vascular dilatation, regulation of cytokine and chemokine production during sepsis, procoagulative and antifibrinolytic effects, pro- and antiapoptotic effects dependent on cell type
C3b	Opsonizing function for bacteria and other invading microorganisms leading to targeted phagocytosis, clearance of immune complexes and circulating apoptotic cells or cell debris, enhancement of antibody production by B cells, regulation of immune tolerance
C5b-9 (MAC)	Permeation of membranes and lysis of bacteria and other invading microorganisms, enhancement of cytokine and adhesion molecule production in various cell types, mediation of tissue injury during ischemia-reperfusion, regulation of cell apoptosis and cell cycle activity, increase in prothrombinase activity on platelets

MAC, membrane attack complex.

cells is believed to be strongly dependent on complement activation and interaction with C1q.[14,15] If, in the presence of complement deficiencies, such clearance becomes inefficient, circulating debris (including immune complexes and dead cells) could act as an autoantigen and possibly initiate the development of autoantibodies, resulting in autoimmune disease.[16] This may explain why most of the deficiencies in the classic complement pathway are associated with the development of SLE.

C5b-9 (membrane attack complex) in sublytic concentrations is involved in the regulation of apoptosis and cell cycle activity.[17] Besides this, membrane attack complex plays a role in the activation of various immune cells via signaling-induced gene transcription, leading to the generation of proinflammatory mediators in nucleated cells and to the generation of reactive oxygen species.[18] C5b-9 has also been demonstrated to make a major contribution to complement-mediated tissue injury after ischemia-reperfusion,[19,20] and it causes relaxation of coronary arteries.[21]

More recently, the biologic effects elicited by the anaphylatoxins C5a and C3a have generated a lot of attention because of their numerous, mostly proinflammatory effects. C5a facilitates a strong chemotactic effect on neutrophils,[22] the release of granular enzymes from phagocytic cells,[23] the production of superoxide anion in neutrophils,[24] and vasodilatation and increases in vascular permeability,[25] as well as expression of adhesion molecules, in endothelial cells.

Recent studies provide evidence of "cross-talk" between the complement system and the coagulation system, suggesting that C5a may be involved in procoagulant effects and antifibrinolytic effects during the onset of sepsis.[26] C5a and C5b-9 have been shown to increase the expression of tissue factor on endothelial cells and monocytes, and C5b-9 has been demonstrated to increase prothrombinase activity on endothelial cells. These observations provide a possible explanation for the described cross-talk.

Even though the complement system is regarded as one of the most powerful defense functions of innate immunity, it also plays an important role in the activation of the adaptive immune system in terms of antigen presentation and antibody production.[27,28] Complement activation (especially C3b deposition) is believed to enhance the antibody production of B cells[29] and to increase the survival time of B cells in various settings of inflammatory disease.

In addition to its affiliation with inflammatory responses, recent studies provide evidence that the complement system plays a role in modulating cellular responses and cell-cell interactions that are crucial to early development and cell differentiation.[30]

GENETIC DEFICIENCIES IN THE COMPLEMENT SYSTEM

Genetically based deficiencies in complement proteins or cofactors of complement activation are rare and, in many cases, are compatible with human life only in the heterozygous state,[31] because most of these defects are inherited in an autosomal recessive manner. Clinically, most patients with deficiencies in complement proteins or cofactors of complement activation have an increased risk of infection (Table 35-3), with meningococcus being the predominant bacterial infection in the case of complete deficiency of C5.[32,33] Generally, there is a distinction among deficiencies of the classic and MBL pathways (C1q, C1r, C1s, C2, C4, MBL), deficiencies of the alternative pathway (factors D and B, properdin), deficiencies of factor C3 together with factors H and I (all resulting in low C3 concentrations), and deficiencies of late-acting complement components (C5, C6, C7, C8, C9). Each of these groups of deficiencies presents with a distinctive pattern of bacterial infection, as described in detail elsewhere.[34] Deficiencies in the classic pathway group are all associated with an increased occurrence of SLE. Infections that occur in the presence of deficiencies involving classic pathway proteins, as well as in deficiencies in C3 and in alternative pathway proteins, are often severe and life threatening (see Table 35-3). Deficiencies in the terminal, late-acting complement components are associated with meningococcal meningitis, but individuals with one of the distal pathway deficiencies are often asymptomatic during their lifetimes. In general, the treatment for complement deficiencies is linked to prophylactic immunization, especially with tetravalent meningococcal vaccine and *Haemophilus influenzae* vaccine. Assessment for complement deficiencies usually is not done during routine screenings.

Deficiencies for the receptors CR1 and CR2 have not been reported, but defective CR3 or CR4 (heterodimeric β_2 integrins) due to mutations in the CD18 β chain results in so-called leukocyte adhesion deficiency, which is linked to frequent and severe bacterial infections.

In contrast to the rarity of deficiencies in complement components, deficiencies in inhibitory proteins of the

TABLE 35–3. GENETICALLY DETERMINED DEFICIENCIES IN THE COMPLEMENT SYSTEM AND RELATED CLINICAL SYMPTOMS

Deficient Component	Clinical Manifestations
Classic pathway (C1q, C1r, C1s, C2, C4)	SLE, glomerulonephritis, recurrent severe infections starting in early childhood (streptococcal pneumonia predominant)
Alternative pathway (factors B, D, P)	Reduced complement activation ability; infection (predominantly meningococcal) starting in adolescence—for factor D especially, often life-threatening
C3, factors H and I	Life-threatening recurrent bacterial infections (especially oropharynx, pulmonary, meninges), often leading to sepsis starting in early childhood; reduced clearance of immune complexes
C5-C9	Predominantly meningococcal infections or gonococcal sepsis, usually in adolescence; approximately 50% recurrent infections; rarely life-threatening. SLE associated in some cases
CR4, CR3 (integrins)	Leukocyte adhesion deficiency syndrome, bacterial infections rarely recurrent
C1-INH	Hereditary or acquired angioedema; also associated with SLE and autoimmune glomerulonephritis
GPI-anchoring protein (affecting CD59 and DAF function)	Paroxysmal nocturnal hemoglobinuria accompanied by thrombosis, iron deficiency anemia (manifestation in young adulthood)

DAF, decay-accelerating factor; GPI, glycoprotein I; INH, inhibitor; SLE, systemic lupus erythematosus.

complement system are more common. C1-esterase inhibitor deficiency can be either inherited (by autosomal dominant mutations) or acquired (formation of autoantibodies).[35] Both forms lead to the clinical picture of angioedema, which is associated with recurrent episodes of edema of the subcutaneous tissue and gastrointestinal tract and often life-threatening edema of the upper airways.[34] Experimental evidence suggests that both complement activation and kallikrein activation (generating bradykinin) are linked to edema in patients with hereditary or acquired angioedema.[36]

Another well-known clinical symptom associated with defects in the inhibitory part of the complement system is paroxysmal nocturnal hemoglobinuria.[37,38] Patients with this disorder develop recurrent hemolytic episodes involving all types of bone marrow–derived blood cells. The defect is a genetic deficiency in a GPI anchoring protein, which is necessary for the proper function of the GPI-linked membrane-bound complement inhibitors CD59 and decay-accelerating factor.[39] This defect results in a high rate of membrane buildup of C5b-9, which is usually controlled by CD59 and decay-accelerating factor. This results in a high rate of lysis of red blood cells especially, as well as other cell types such as granulocytes, lymphocytes, and monocytes. Patients with paroxysmal nocturnal hemoglobinuria often experience an increased incidence of thrombosis and related complications.

SEPSIS

The complement system has been demonstrated to play a key and harmful role in the onset of sepsis in rodents. Microorganisms in the bloodstream or their products, such as lipopolysaccharide, can cause complement activation. Given the well-known variety of proinflammatory effects of complement activation, it is not surprising that sudden "overactivation" of this powerful system can result in serious, harmful consequences in the host. Conversely, experimental data involving C3 and C4 knockout animals suggest that an intact complement system (at least involving C3 and C4) may be required to a certain extent to clear endotoxin and bacteria.[40,41] The harmful effects of complement activation in the context of sepsis have been ascribed to excessive generation of the potent anaphylatoxin C5a. Various clinical studies indicate that complement activation occurs during human sepsis, as exemplified by elevated serum levels of C3a and C5a. In some studies, these levels were significantly higher in nonsurviving septic patients and in those with multiorgan failure than in those with less severe sepsis and survivors.[42–44] Experimental studies in primates suggested some time ago that blockade of C5a by antibodies could significantly attenuate *Escherichia coli*–induced septic shock and acute respiratory distress syndrome (ARDS) in monkeys.[45,46] Studies in rats suggested that lipopolysaccharide-induced shock could be mimicked by the injection of C5a, whereas blockade of C5a with antibody attenuated lipopolysaccharide-induced responses.[47] Blockade of C5a during experimental sepsis was found to be protective in rats,[48] and in another study, the protective effects of C5a blockade during sepsis were associated with the prevention of multiorgan failure.[49] In these studies, C5a generation had to be inhibited early in the course of sepsis to protect against multiorgan failure and death. The exact role of C5a at the onset of sepsis has yet to be determined, but experimental evidence suggests that when C5a is generated in excessive amounts, it may be involved in the shutdown of crucial innate immune functions of neutrophils (generation of reactive oxygen species, release of granular enzymes, phagocytosis, chemotaxis), increasing the susceptibility for infection in the later stages of sepsis. Production of IL-6 and adhesion molecules is also linked to C5a. C5a can interact directly with endothelial cells and myeloid cells. C5aR has been shown to be up-regulated in an IL-6–dependent manner on various cell types (endothelial, epithelial) during experimental sepsis, potentially intensifying the effects of circulating C5a.[7] It remains to be determined whether such findings can be extrapolated to humans with sepsis and whether potential therapeutic targets can be derived from such findings.

The naturally occurring inhibitor of the classic complement and lectin pathways, C1-esterase inhibitor, also inhibits clotting factor XIIa–mediated contact activation of the coagulation system. It has been shown to be decreased in humans with sepsis.[50] Initial pilot clinical trials involved the infusion of C1 inhibitor into septic patients, with some suggestion of benefit in these patients.[51,52] A randomized, double-blind trial suggested that the administration of C1 inhibitor attenuated renal impairment in patients with severe sepsis or septic shock.[53] Larger phase II and III clinical trials will have to be conducted to confirm such findings.

ACUTE RESPIRATORY DISTRESS SYNDROME

A role for the complement system in ARDS has been suggested, based on elevated plasma levels of C3a and C5a in patients with ARDS. These levels were correlated with neutrophil aggregation and lung dysfunction.[54,55] Treatment with anti-C5a antibodies in an animal (primate) model of ARDS resulted in improved oxygenation and circulatory parameters.[45] Serum levels of C5a and C3a in humans with ARDS may reflect the severity of lung injury and might be useful for predicting clinical outcome.[56] Based on these and other findings, a phase I clinical trial used recombinant soluble CR1 in patients with ARDS,[57] but phase II trials will be necessary to determine the potential benefits of such treatment.

ISCHEMIA-REPERFUSION AND ORGAN TRANSPLANTATION

Clinical settings of ischemia-reperfusion, such as myocardial infarction, artery stenosis, thrombosis, and dissecting aortic aneurysm, as well as solid organ transplantation and heart surgery, are accompanied by rapid changes in cell homeostasis, leading to perturbations in signaling pathways and surface molecule expression. Depending on the time and severity of ischemia-reperfusion, toxic products accumulate intracellularly, leading to apoptosis and necrosis, causing loss of organ function. Depending on the duration and severity of ischemia-reperfusion, the injury may be completely or partially reversible. After the reestablishment of blood flow to the organ, oxygenation occurs, and repair mechanisms may be set into motion. During reperfusion, activation of the complement system and incoming neutrophils contribute to further cell injury; such injury appears to be dependent on the amount of complement and neutrophil activation. Experimental data suggest that complement products of the classic pathway are associated with ischemia-reperfusion cardiac injury in rats,[58] rabbits,[59] and humans,[60] and that complement depletion reduces infarct size.[61] Different strategies to block complement activation in experimental settings of ischemia-reperfusion have been successful in terms of reducing organ damage and impairing function. In experimental models of acute myocardial ischemia-reperfusion, successful strategies include the application of soluble CR1 (sCR1),[62] C1 inhibitor,[63-65] blocking antibodies to C5[66] or C5a,[67,68] a small molecular inhibitor of C1s,[69] and antibodies to MBL.[70] These and other findings led to the first successful use of C1 inhibitors in patients receiving emergency surgery for failed percutaneous transluminal coronary angioplasty in 1998. In another study, C1 inhibitor was administered to neonates undergoing transposition of the large arteries, with the beneficial effect of less inflammatory response in the treated group.[71] These preliminary data have not been confirmed in larger clinical trials. Another promising strategy is the use of monoclonal antibodies to C5, which may benefit patients undergoing cardiopulmonary bypass procedures.[72] In these studies, patients treated with anti-C5 showed significantly reduced postoperative myocardial injury, fewer cognitive defects, and less blood loss, suggesting a range of benefits. These findings need to be replicated in large phase II clinical trials.

It has also been suggested that complement activation is a major mediator of hyperacute organ rejection after transplantation. In an experimental model of lung allotransplantation, the administration of sCR1 significantly limited the amount of acute and subacute rejection.[73] No clinical data exist demonstrating the potential benefits of such a strategy in organ transplantation in humans, however. It is not clear to what extent the different complement pathways contribute to ischemia-reperfusion–related injury (reviewed in reference 74).

AUTOIMMUNE DISEASES

Various autoimmune diseases are associated with circulating immune complexes and evidence of complement activation. A possible role of complement activation in the development and progression of autoimmune diseases has been suggested. C1q, C4, C3, and C5b-9 have been found in association with tissue damage in SLE, RA, Sjögren's syndrome, Behçet's syndrome, bullous pemphigoid, dermatomyositis, myasthenia gravis, Alzheimer's disease, multiple sclerosis, and other neurologic diseases. Tissues often affected by complement activation in these autoimmune diseases are skin, kidney, choroid plexus, blood vessels (endothelial cells), and skeletal muscle. A strategy to target complement activation in these diseases in a clinical setting has not yet been developed. A few prominent examples are discussed here.

SYSTEMIC LUPUS ERYTHEMATOSUS

As mentioned earlier, complement deficiencies, especially in the classic pathway, are often associated with SLE. Indeed, C4 serum levels in SLE patients are often reduced (consumptive hypocomplementemia) and may be a useful monitor of disease progression.[34] About one third of SLE patients also have autoantibodies to C1q. In addition, in SLE nephritis, C3 deposition often occurs in kidney glomerular mesangial cells and is strongly associated with the severity of the nephritis. Blockade of C5 in a rodent model of SLE resulted in improved survival and reduced proteinuria and glomerular damage.[75] SLE mice that were deficient in factor B (alternative complement pathway) also showed less renal disease progression.[76]

RHEUMATOID ARTHRITIS

In the synovial fluid of RA patients, elevated levels of C5b-9 are frequent.[77,78] Interaction of C5b-9 with synovial fibroblasts in RA has been demonstrated.[79] In an experimental model of RA in rodents, blockade of the late complement components with monoclonal antibodies to C5 resulted in amelioration of disease activity and partial reversal of joint destruction.[80] Similar results were found in rodents treated with recombinant sCR1.[81] Genetic deficiency of C3, C5, or factor B significantly decreased joint destruction in RA models in rodents.[82-84] Accordingly, it has been suggested that the alternative complement pathway plays a critical role, in contrast to the classic pathway.[84] Recent studies demonstrated that C5a and its receptor, C5aR, are important mediators in experimental RA settings; blockade of C5aR with an oral antagonist or C5aR gene knockout resulted in greatly reduced joint destruction in such studies.[85,86] The complement system, therefore, appears to play a major role in the induction and progression of RA. The occurrence of C-reactive

protein may be important for complement activation in RA in humans.[87]

IMMUNE COMPLEX GLOMERULONEPHRITIS

Circulating immune complex (deposited in a subepithelial location) and locally formed immune complex (deposited subendothelially or mesangially) are the cause of various types of glomerular diseases (reviewed in detail elsewhere).[34] A pathogenetic role for complement activation in immune complex–induced glomerulonephritis can be assumed from experimental Heymann glomerulonephritis models in which inhibition of complement activation resulted in attenuated acute and chronic renal injury. Genetic knockout of C3 as well as C4 in mice also resulted in beneficial effects in a glomerulonephritis model.[88,89] Similar results were obtained when various C3 inhibitors were overexpressed.[90,91]

ALZHEIMER'S DISEASE

This degenerative disease is characterized by "senile plaques," consisting of neurofibrillary tangles and interstitial deposition of β-amyloid in the brain tissue and cerebral blood vessels. In Alzheimer's disease, the presence of C1q, C3, C4, and C5b-9 has been demonstrated in senile plaques, suggesting a pathogenetic role for the complement system.[92,93] Other studies demonstrated that β-amyloid (peptides 39-43) effectively activates the classic complement pathway via C1q.[94] In addition, it was demonstrated that the production of C1 inhibitor in brain cells is reduced in senile plaques from Alzheimer's patients.[95] A recent study suggested a prominent role for C5aR in Alzheimer's disease progression,[96] and activation of the complement system may also be a key factor.[97] Recent studies provide evidence of the potential beneficial role of the complement product C3 in a mouse model of Alzheimer's disease; overexpression of a soluble complement receptor-related protein y (sCrry), which initiates C3 activation, caused increased deposition of β-amyloid, suggesting a possible regulatory role for C3.[98] Even though the complement system appears to be involved in the progression of Alzheimer's disease, it is not clear to what extent therapeutic strategies targeting activation of the complement system might be beneficial.

ACUTE BURN INJURY

Evidence of activation of the complement system in patients with acute burn injuries was found in the 1970s.[99] Subsequent studies demonstrated early consumptive depletion of C1q, C3, C4, and C5 after burn injury[100,101] and the generation of C3a.[102] Neutrophil activation is related to increased expression of CR1 and CR3 on neutrophils in burn patients.[103] In rodent models of burn injury, complement activation and deposition at the site of tissue injury were also noted,[104,105] and the generation of hydroxyl radicals was suggested as an initiating mechanism.[106] Additional activation of the alternative complement pathway in a murine model of burn injury worsened the outcome.[107] The vascular injury in the lungs of mice following thermal skin injury revealed a strict dependency on the generation of C5a, suggesting that this anaphylatoxin is a major player in burn-associated tissue injury.[108] In subsequent studies, complement inhibition with sCR1 in a rodent model of thermal injury demonstrated significant reduction in associated lung injury (reduced vascular lack of albumin and reduced hemorrhage).[109] In a thermal injury model in pigs, complement inhibition with C1 inhibitor was also reported to be beneficial,[110] perhaps related to reduced bacterial translocation in the gut barrier after skin burn injury[111] and significant reduction in vascular leak.[112] Clinical trials to confirm these findings have yet to be done.

ACUTE TRAUMA

Trauma patients often show elevated levels of inflammatory mediators in the blood. Tissue injury is believed to trigger an acute inflammatory response, especially by activation of the complement system. Although the exact mechanisms of such activation are not yet understood, it has been reported that patients with traumatic brain injury show elevated levels of the complement components C3 and factor B in cerebrospinal fluid.[113] An important role of the complement system has also been suggested in patients with multiple trauma, in whom elevated levels of complement activation products have been found. Elevated C3a levels reportedly correlate with outcome.[114,115] The complement system's role in organ dysfunction has been suggested in animal models of closed head injury.[116] One study reported that C5aR was induced on neurons after closed head injury in mice, mediated by tumor necrosis factor and lymphotoxin-α.[117] Recent studies suggest that in patients with head injury, elevated levels of C3b and C5b-9 are present,[113,118] the latter correlating with blood-brain barrier dysfunction.[119] Despite the strong evidence for the role of complement activation in trauma-related tissue injury, only one study exists demonstrating the beneficial effects of complement inhibition (using C1 inhibitor) in a murine model of acute trauma.[120] Whether therapeutic intervention (complement inhibition) in patients with acute trauma would be beneficial remains speculative. If so, the timing of drug administration would be crucial for achieving maximal clinical success.

CONCLUSION

Activation of the complement system appears to be a double-edged sword. Although complement activation is a crucial defensive function of the innate immune system in combating invading microorganisms, it also appears to be responsible for a variety of harmful effects. A broad spectrum of stimuli can activate the complement system, leading to the production of powerful proinflammatory and potentially harmful mediators such as the anaphylatoxin C5a and C5b-9. The complement system is clearly involved in the progression of autoimmune diseases and plays a role in acute inflammatory conditions such as sepsis, burn injury, trauma, and ischemia-reperfusion–related injury (e.g., myocardial ischemia and organ transplantation). In all these disorders, inhibition of complement activation has been demonstrated to have beneficial effects in experimental settings. Only preliminary data from clinical studies of complement inhibition in acute inflammatory disorders are available. In these studies, C1 inhibitor (in sepsis trials) and sCR1 and monoclonal antibodies against C5 (in trials of cardiopulmonary bypass) have been used and suggest potential benefits. However, larger clinical trials employing these interventions are needed.

Because the complement system is involved in so many different physiologic systems and defense mechanisms, each acute inflammatory disorder likely requires a specific target in the complement system for optimal beneficial effects. More research is needed to understand the precise contribution of the various complement activation pathways and the specific complement activation products involved in clinical disorders. General problems of drug discovery (half-life, side effects, safety, costs) and the potential problem of increased susceptibility to infection are important considerations if complement activation is to be inhibited (discussed in detail in reference 121).

Recent experimental data suggest the benefits of inhibiting C5a or C5aR with antibodies or with small molecular chemical inhibitors (especially for ischemia-reperfusion injury, sepsis, and RA). Because this approach does not target complement activation in general (as does C1 inhibitor or sCR1) but rather targets a more specific activation product downstream, this strategy appears to be promising and needs to be evaluated in a clinical setting.

Given the impressive experimental evidence of the beneficial effects of complement inhibition in various acute inflammatory (and other) disorders, it seems likely that successful therapeutic strategies will be developed in clinical settings in humans in the near future.

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Chapter 36

CYTOPATHIC HYPOXIA: MITOCHONDRIAL DYSFUNCTION IN SEPSIS

Mitchell P. Fink

KEY POINTS

1. Adenosine triphosphate (ATP) is the **energy currency of the cell.**
2. **Aerobic generation of ATP** by a process termed oxidative phosphorylation is carried out in cells by specialized organelles, the mitochondria.
3. Data from studies using animal models of sepsis or biopsies of human skeletal muscle support the view that **severe sepsis is associated with derangements in cellular respiration and mitochondrial dysfunction**; this phenomenon has been termed cytopathic hypoxia.
4. Although it is now well established that mitochondrial function is impaired in sepsis, **it remains to be determined whether cytopathic hypoxia is an epiphenomenon or one that actually contributes to organ dysfunction and mortality.**

According to the first law of thermodynamics, the total amount of energy in a system remains constant before and after any sort of transforming event. The second law of thermodynamics holds that even though the total amount of energy does not change after a transforming event, the total amount of usable energy—the Gibbs free energy (G)—always decreases. In accordance with the second law, all reversible chemical reactions proceed in a direction that results in a net decrease in the Gibbs free energy for the system; in other words, the change in G (ΔG) is always less than zero. When cells in living systems need to carry out a reaction for which ΔG is positive, they couple the reaction to another reaction that is energetically favorable (i.e., characterized by $\Delta G < 0$). If the algebraic sum of the ΔGs for the two coupled reactions is negative, formation of the desired product can proceed. Within cells, the exergonic reaction that drives the formation of the desired product is almost always the hydrolysis of the terminal pyrophosphate ester linkage of adenosine triphosphate (ATP) to yield adenosine diphosphate (ADP) and inorganic phosphate anion (Pi). The hydrolysis of ATP also drives other energy-requiring processes in cells, such as the active pumping of solutes against a concentration gradient across a membrane barrier. Thus, for proper functioning, all cells need a steady supply of ATP. Stated another way, ATP is the energy currency of the cell.

ATP can be generated in cells as a result of both aerobic and anaerobic processes. Anaerobic generation of ATP, or of the energetically equivalent compound guanosine triphosphate (GTP), occurs in both the cytosol and the mitochondria as a result of the phosphorylation reactions that are catalyzed by the enzymes phosphoglycerate kinase, pyruvate kinase, and succinyl coenzyme A synthase. Aerobic generation of ATP occurs in the mitochondria as a result of a carefully orchestrated series of reactions that effectively couple the oxidation of substrates by molecular oxygen (O_2) to the phosphorylation of ADP to form ATP.

Good "reducing agents" are elements or compounds that have a strong propensity to donate electrons to another element or compound. Conversely, good "oxidizing agents" are elements or compounds that avidly accept electrons. Molecular oxygen is a very potent oxidizing agent. Two strong reducing agents—the reduced forms of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$)—are produced in cells during certain enzymatic reactions that occur during glycolysis and the citric acid cycle. In mitochondria, these two reducing agents are oxidized by O_2, and the energy released during this process is used to drive the formation of ATP.

The reaction of a strong reducing agent, such as NADH, with a powerful oxidizing agent, such as O_2, releases a large amount of energy (i.e., ΔG is very negative). To take optimal advantage of this highly exergonic redox reaction and capture as much of the energy released as possible in a usable form (i.e., the high-energy terminal pyrophosphate bond of ATP), mitochondria "step down" the reducing potential of NADH (and $FADH_2$) in stages. Thus, the electrons are not transferred from NADH to O_2 all at once; rather, they are transferred through a series of intermediate compounds, called electron carriers, that have progressively lower reducing potentials. Several of the electron carriers involved in the mitochondrial respiratory chain are organized as complexes (called complexes I to IV) located within the inner mitochondrial membrane (Fig. 36-1). These complexes use the energy released during electron transfer to actively pump hydrogen ions from the mitochondrial matrix into the intermembrane space, thereby generating an electrochemical gradient across the inner mitochondrial membrane. The presence of this gradient drives hydrogen ions through a mitochondrial enzyme, F_oF_1-ATPase, that catalyzes the formation of ATP from ADP and Pi.

For each mole of glucose metabolized to carbon dioxide and water, the net yield of ATP from substrate-level (anaerobic) phosphorylation reactions is 4 moles of ATP, whereas

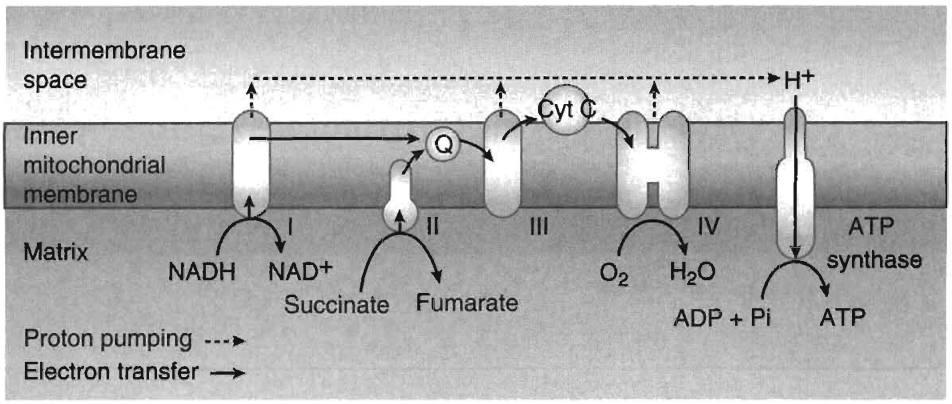

FIGURE 36–1. Diagrammatic representation of mitochondrial electron transport and proton pumping across the inner mitochondrial membrane. Oxidation or conversion of succinate to fumarate requires reducing equivalents supplied by flavin adenine dinucleotide ($FADH_2$). ADP, adenosine diphosphate; ATP, adenosine triphosphate; Cyt C, cytochrome *c*; NAD, nicotinamide adenine dinucleotide; NADH, reduced form of NAD; Pi, inorganic phosphate; Q, ubiquinone. (Adapted from Brealey D, Singer M: Mitochondrial dysfunction in sepsis. Curr Inf Dis Rpt 2003;5:365-371.)

the net yield of ATP from oxidative phosphorylation reactions is 32 moles of ATP. Thus, oxidative metabolism in normally functioning mitochondria is far more efficient at producing ATP than is anaerobic metabolism, and many cell types, such as hepatocytes, neurons, and cardiac myocytes, are dependent on a steady supply of O_2.

EVIDENCE FOR IMPAIRED MITOCHONDRIAL RESPIRATION IN SEPSIS

Convincing data support the view that early, aggressive efforts to improve systemic O_2 delivery by administering intravenous fluids, packed red blood cells, and inotropic agents can improve outcome for patients with septic shock.[1] By the same token, however, efforts to improve systemic O_2 delivery later in the course of sepsis are at best ineffective[2,3] and at worst deleterious.[4] If improving perfusion and O_2 delivery in patients with established sepsis fails to improve survival or prevent organ system dysfunction, one might wonder whether alterations in energy metabolism are important at all in the pathogenesis of the syndrome.[5] Alternatively, one could hypothesize that cellular energetics are deranged in sepsis not just because O_2 delivery is impaired but also because the cells' ability to use available O_2 is compromised. The term *cytopathic hypoxia* has been used to describe such an acquired intrinsic derangement in cellular respiration.[6,7] Although the clinical significance of this phenomenon has not been established with certainty, accumulated evidence supports the notion that cytopathic hypoxia occurs when certain cell types are exposed to proinflammatory cytokines or sera from septic patients in vitro.[8-10] Further, it is fairly clear that mitochondrial function is impaired in experimental animals with sepsis or endotoxemia.[11-15]

Measurements of Tissue Oxygen Partial Pressure and Cytochrome a,a_3 Redox State. Tissue hypoxia is an expected correlate of any of the three classic causes of impaired cellular aerobic metabolism identified by Barcroft more than 80 years ago.[16] Thus, when the delivery of O_2 decreases on the basis of low arterial oxygen tension (PO_2), anemia, or hypoperfusion, cells extract a greater fraction of the available O_2 in an effort to defend aerobic ATP production. As a consequence, the distribution of tissue PO_2 values shifts to the left (i.e., closer to 0). In contrast, when ATP production is impaired as a result of an intrinsic derangement in cellular respiration, cells extract less O_2 per unit time from the available supply. The expected consequence of this change in O_2 extraction is a rightward shift in the tissue PO_2 distribution (i.e., toward higher values).

One line of evidence that supports the concept of cytopathic hypoxia comes from studies measuring tissue PO_2 in patients or experimental animals. If tissue hypoperfusion is a major factor contributing to cellular dysfunction in sepsis, septic shock, or endotoxemia, one would predict the detection of abnormally low tissue PO_2 values in these conditions. However, if classic tissue hypoxia is not important, or if the main problem is an intrinsic derangement in cellular O_2 use, one would predict normal or even supranormal tissue PO_2 values in animals or patients with sepsis. Indeed, observations of this sort have been reported.

Astiz and colleagues used cecal ligation and puncture (CLP) in a rat model of sepsis and showed that mean skeletal muscle PO_2 was similar in septic animals and normal controls, provided that the rats with peritonitis were infused with albumin solution to expand intravascular volume.[17] In a conceptually similar study, Hotchkiss and coworkers used a novel approach to determine whether tissue hypoxia occurs after the induction of sepsis in rats.[18] Tissue PO_2 was not measured directly but was estimated by measuring the retention of [^{18}F]-fluoroisonidazole, a lipophilic 2-nitroimidazole derivative that is irreversibly bound to intracellular macromolecules under hypoxic, but not normoxic, conditions. Retention of [^{18}F]-fluoroisonidazole in a variety of tissues, such as skeletal muscle and liver, was similar in septic rats and nonseptic controls. These data provide very strong evidence that sepsis in rats is not associated with tissue hypoxia.

Some data support the even more remarkable conclusion that tissue PO_2 actually increases in sepsis relative to normal values. For example, VanderMeer and colleagues used a porcine model to investigate the effects of endotoxemia on intestinal mucosal PO_2.[19] When anesthetized pigs were infused with lipopolysaccharide (LPS) and simultaneously resuscitated to maintain normal cardiac output, mean mucosal PO_2 increased significantly. Similarly, Rosser and coworkers reported that bladder mucosal PO_2 increased in rats challenged with LPS.[12] The same pattern has been observed in humans. Boekstegers and colleagues showed that the distribution of PO_2 values in skeletal muscle was shifted to the left in patients with cardiogenic shock, as expected, but was shifted to the right (i.e., to supranormal values) in patients with septic shock.[20] Similar findings were reported by Sair and associates.[21] These data are consistent with the view that cellular utilization of O_2 is impaired in patients with sepsis and septic shock.

This same idea is supported by another related study. Simonsen and colleagues used near-infrared spectroscopy to monitor the redox state of the terminal element of the mitochondrial respiratory chain, cytochrome oxidase, in skeletal

muscle cells of baboons rendered septic by an infusion of viable *Escherichia coli*.[22] The functional status of cytochrome oxidase was monitored by periodically causing temporary skeletal muscle ischemia using a proximally placed tourniquet. Inflating the tourniquet caused a decrease in the spectroscopic signal from oxidized cytochrome oxidase, whereas deflating the tourniquet resulted in an increase in the signal from the oxidized enzyme. Early in the sepsis protocol (i.e., at 6 hours), the rate of cytochrome oxidase reduction following tourniquet ischemia was the same as at baseline, although the rate of reoxidation following the release of ischemia was slowed. These data are consistent with the notion that delivery of O_2 to the tissue is decreased early in sepsis. Later in the sepsis protocol (e.g., at 18 hours), the rate of cytochrome oxidase reduction during tourniquet ischemia was markedly slowed, a finding that was thought to be consistent with either a defect in the enzyme's ability to accept electrons from O_2 or a limitation in the availability of reducing equivalents (i.e., NADH, $FADH_2$, or both). These data are particularly interesting because they suggest that cytopathic hypoxia is not present early in sepsis but develops after the septic process has evolved for many hours. These temporal considerations might explain the positive results obtained in a clinical trial of early, goal-directed hemodynamic support by Rivers and associates[1] and the negative results obtained in similar trials that included patients with more established critical illnesses.[3,4]

Not all studies of sepsis have obtained data showing that tissue PO_2 values are normal or increased. Indeed, contrary findings have been reported by a number of investigators. For example, two studies showed that intestinal mucosal PO_2 decreased when experimental animals were infused with LPS to a sepsis-like state.[23,24] Similarly, Sair and colleagues reported that skeletal muscle PO_2 decreased markedly in a rat model of endotoxemia.[25] Differences in the timing of the measurements (i.e., early versus late sepsis) or in the adequacy of resuscitation might explain the discordant findings regarding tissue PO_2 levels in different studies.

Measurements of Mitochondrial Respiration. The colorless compound 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) is reduced by functioning mitochondria to a blue dye (MTT-formazan). Concentration of the blue product can be determined spectrophotometrically. Thus, reduction of MTT is a convenient, albeit indirect, way to assess mitochondrial function. In 1974, Bankey and coworkers used this approach to assess mitochondrial function in cocultures of rat hepatoctyes and rat liver macrophages.[26] Sequential stimulation of the cultures with a proinflammatory cytokine, interleukin-6 (IL-6), and then LPS decreased MTT reduction by about 50%. Similar results were reported more recently by Zingarelli and colleagues, who showed that MTT reduction is decreased in cultured macrophages and vascular smooth muscle cells after incubation with a proinflammatory cytokine, interferon gamma (IFN-γ), plus LPS.[27]

Unno and coworkers used the reduction of MTT to MTT-formazan to assess mitochondrial function in vivo.[28] In this study, rats were injected with saline or a low dose of LPS that caused neither hypotension nor mortality. Twenty-four hours later, the lumen of the intestine was loaded with a solution of MTT. After a 30-minute incubation period, the epithelial layer was scraped off the intestine, and the concentration of MTT-formazan in enterocytes was determined spectrophotometrically. MTT reduction was significantly lower in enterocytes from endotoxemic rats than in those from normal controls. When the endotoxemic rats were treated with aminoguanidine, a drug that blocks inducible nitric oxide synthase (iNOS), MTT reduction was restored to normal levels. This latter finding suggests that impaired mitochondrial respiration in sepsis is mediated, at least in part, by a mechanism that depends on increased production of the mediator, nitric oxide (NO), due to up-regulated expression of the enzyme, iNOS.

The MTT assay reflects the activity of a number of different dehydrogenases, particularly succinate dehydrogenase,[29] and is not a direct measure of mitochondrial O_2 consumption per se. Several studies have obtained more direct evidence that cellular or mitochondrial respiration is impaired in animals with sepsis or endotoxemia. For example, Kantrow and associates showed that hepatocytes isolated from septic rats consumed significantly less O_2 than did hepatocytes from nonseptic control rats.[30] Later, King and colleagues showed that ileal mucosal O_2 consumption is impaired in endotoxemic rats.[11] In these studies, rats were injected with either LPS or a similar volume of the saline vehicle. Eight hours later, a strip of ileal mucosa was obtained from the animals and mounted in a polarographic chamber to determine the rate of O_2 consumption (Fig. 36-2). The decrease in the rate of ileal mucosal O_2 consumption induced by LPS injection was not due to decreased delivery, because the measurements were made ex vivo with the tissue suspended in a well-oxygenated buffer. If the endotoxemic rats were treated with aminoguanidine to block iNOS activity, normal ileal mucosal O_2 consumption was preserved. Thus, these findings support the notion that the development of cytopathic hypoxia in LPS-challenged rats requires iNOS-dependent NO production.

Chen and coworkers evaluated cardiac muscle mitochondrial function in rats with sepsis induced by CLP.[31] As in some previous studies, these investigators evaluated mitochondrial function both early after the onset of sepsis (9 hours after CLP) and later (18 hours after CLP). Rather than measuring cellular or mitochondrial O_2 consumption, these investigators used standard enzymatic assays to determine the activities of

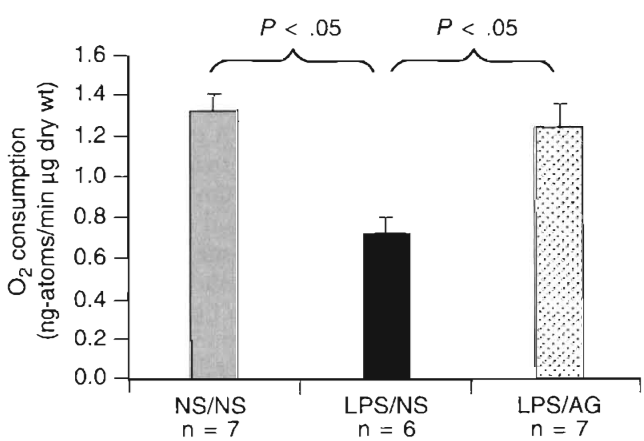

FIGURE 36–2. Effect of lipopolysaccharide (LPS) on ileal mucosal oxygen (O_2) consumption. Rats in the NS/NS group were injected at 0 hours with normal saline (NS) and treated with NS. Rats in the LPS/NS group were injected with LPS (5 mg/kg) at 0 hours and treated with NS. Rats in the LPS/AG group were challenged with the same dose of LPS and treated with aminoguanidine (AG; 30 mg/kg per dose at 1, 3, and 6 hours). Ex vivo O_2 consumption was measured at 8 hours. (Adapted from King CJ, Tytgat S, Delude RL, Fink MP: Ileal mucosal oxygen consumption is decreased in endotoxemic rats but is restored toward normal by treatment with aminoguanidine. Crit Care Med 1999;27:2518-2524.)

key mitochondrial enzymes (NADH cytochrome *c* reductase, succinate cytochrome *c* reductase, cytochrome *c* oxidase). Early after the induction of sepsis, these enzymatic activities were normal, as was expression of the four mitochondrial enzyme complexes involved in electron transport and respiration (complexes I to IV), as assessed by Western blotting. In contrast, in samples of cardiac tissue obtained 18 hours after the onset of sepsis, the function of all three mitochondrial enzymes was significantly decreased, as was the expression of complexes II and IV.

In addition to the results from animal studies, there are now data from clinical studies that support the idea that mitochondrial function is impaired in human sepsis as well. Brealey and coworkers assessed mitochondrial function in skeletal muscle biopsies obtained from 28 critically ill septic patients within 24 hours of admission to an ICU, as well as in biopsies obtained from 9 control patients undergoing elective hip surgery.[32] Using standard polarographic methods, these investigators assessed the activity of the four mitochondrial enzyme complexes responsible for electron transport and respiration (complexes I to IV). The biopsy specimens were also analyzed with respect to several other relevant biochemical parameters, including ATP concentration and nitrite-nitrate concentration (an index of NO production). Of the 28 patients with sepsis, 16 survived and 12 died. Complex I activity was significantly lower in septic nonsurvivors than controls. Skeletal muscle ATP concentrations were significantly lower in the 12 patients with sepsis who died than in the 16 septic patients who survived ($P = 0.0003$) and in controls ($P = 0.05$). Complex I activity was inversely correlated with tissue nitrite-nitrate concentration ($P = 0.0004$), suggesting that increased NO production and sepsis-induced cytopathic hypoxia are linked phenomena.

POTENTIAL MECHANISMS OF CYTOPATHIC HYPOXIA IN SEPSIS

INHIBITION OF PYRUVATE DEHYDROGENASE

The end product of glycolysis is pyruvic acid, a three-carbon alpha-keto acid. Pyruvic acid can either be reduced to lactic acid or enter the tricarboxylic acid (TCA) cycle, ultimately to be oxidized to water and carbon dioxide. The rate-limiting step for entry of pyruvate into the TCA cycle is the reaction catalyzed by the enzyme complex pyruvate dehydrogenase (PDH). In the presence of NAD^+ (the oxidized form of nicotinamide adenine dinucleotide) and coenzyme A, PDH converts pyruvate into acetyl coenzyme A. Because of its pivotal role in the regulation of intermediary metabolism, the activity of PDH is tightly regulated by both end-product inhibition and reversible phosphorylation. A group of isoenzymes, the PDH kinase family, catalyzes the phosphorylation of PDH to its inactive form (PDH_i). A PDH phosphatase catalyzes the dephosphorylation of PDH_i to the active form of the enzyme complex (PDH_a). Vary and coworkers showed that the PDH_i/PDH_a ratio in skeletal muscle tissue increases during chronic sepsis in rats.[33,34] The mechanism responsible for this effect is increased PDH kinase activity rather than decreased PDH phosphatase activity.[35,36] Because inactivation of PDH limits the flux of substrate through the TCA cycle, excess pyruvate accumulates in cells, leading to increased production of lactate. Thus, according to the data obtained by Vary and coworkers, hyperlactatemia in sepsis is not necessarily evidence of impaired O_2 delivery but may be the result of the combined effects of PDH inhibition and accelerated glucose transport into cells.[34] Some clinical data support this notion.[37]

NITRIC OXIDE–MEDIATED INHIBITION OF CYTOCHROME OXIDASE

Sepsis is associated with iNOS induction and increased production of the pluripotent signaling and effector molecule NO.[38] At physiologically relevant concentrations (~1 μM), NO rapidly, but reversibly, inhibits the activity of cytochrome oxidase, the terminal enzyme complex of the mitochondrial electron transport chain.[39-42] NO-mediated inhibition of mitochondrial O_2 consumption is the result of competition by the two gases (O_2 and NO) for the same binding site on the enzyme complex.[43,44] Accordingly, the inhibitory effect of NO tends to be more pronounced when PO_2 is relatively low.[40-42] Although much of the work related to this mechanism has been done using NO derived from an exogenous source (i.e., authentic NO gas or a chemical compound that releases NO in solution), it is clear that endogenously produced NO is also capable of causing reversible inhibition of cytochrome oxidase, leading to reduced cellular respiration.[45]

PEROXYNITRITE-MEDIATED INHIBITION OF MITOCHONDRIAL ENZYMES

Under the right conditions, NO reacts rapidly with a partially reduced form of O_2, superoxide radical anion (O_2^-), to form peroxynitrite ($ONOO^-$), a molecular species that is a potent oxidizing, nitrosating, and nitrating agent.[46-49] Appropriate conditions for the production of $ONOO^-$, namely, biosynthesis of approximately equimolar levels of NO and O_2^- in close proximity, are present in many cell types during sepsis. In addition, small quantities of O_2^- are continually being produced by mitochondria. Under certain conditions, such as when O_2 availability is limited[50] or cytochrome oxidase is inhibited by NO,[51] mitochondria generate increased quantities of O_2^- by this mechanism. Moreover, a calcium-dependent NOS isoform that is either identical or very similar to neuronal NOS is present in mitochondria.[52-56] Thus, within the confines of the organelle itself, mitochondria are capable of generating both NO and O_2^- and, under appropriate conditions, large quantities of the potentially toxic moiety $ONOO^-$.[54,57]

Incubating mitochondria with authentic $ONOO^-$ causes irreversible inhibition of mitochondrial respiration. The deleterious effects of $ONOO^-$ on mitochondrial function are potentiated by increases in the concentration of ionized calcium (Ca^{++}).[58,59] The synergistic effects of $ONOO^-$ and Ca^{++} are likely important in a number of pathophysiologic conditions relevant to critical care medicine (e.g., inflammation, tissue ischemia followed by reperfusion), because these conditions are known to increase intramitochondrial concentrations of both species.

Several mechanisms have been implicated as being important in this phenomenon. Specifically, $ONOO^-$ has been shown to inhibit the mitochondrial F_oF_1-ATPase that phosphorylates ADP to form ATP.[60] In addition, $ONOO^-$ inhibits two of the mitochondrial enzyme complexes (I and II) that are involved in electron transport.[60] Finally, $ONOO^-$ inhibits the activity of aconitase, the TCA cycle enzyme that converts citrate into isocitrate.[61] Endogenous production of

$ONOO^-$ secondary to iNOS induction plus O_2^- generation has been implicated as the major factor in impaired mitochondrial respiration in some tissues, such as rat diaphragm, following in vivo challenge with LPS.[15] Data obtained by Brealey and colleagues support the view that complex I activity is impaired in skeletal muscle biopsy samples from patients with lethal septic shock, probably as a result of increased production of NO or a related compound, such as $ONOO^-$.[32]

THE PARP HYPOTHESIS

PARP-1 is a nuclear enzyme that participates in a variety of cellular functions, including the repair of single-strand breaks in nuclear DNA,[62,63] DNA replication,[64] and apoptosis.[64] PARP-1 is activated by single-strand breaks in nuclear DNA and then catalyzes the cleavage of NAD^+ into ADP-ribose and nicotinamide and the polymerization of the resultant ADP-ribose units into branching poly(ADP-ribose) homopolymers.[65,66] The poly(ADP ribose) generated by this process is degraded by various nuclear enzymes, most notably poly(ADP-ribose) glycohydrolase.[66,67] The concurrent actions of PARP-1 and poly(ADP-ribose) glycohydrolase constitute the functional equivalent of an NADase. In states of acute inflammation, reactive oxygen species, including $ONOO^-$ (and related oxidants), cause single-strand breaks in nuclear DNA and thereby activate PARP-1. Activation of PARP-1 has also been identified within mitochondria following oxidant stress,[68] suggesting that damage to mitochondrial DNA induced by reactive oxygen species might be another mechanism leading to activation of the PARP pathway. Activation of PARP-1 leads to intracellular depletion of NAD^+ and its reduced form, NADH. Because NADH is the main reducing equivalent used to support oxidative phosphorylation, activation of PARP-1 can lead to a marked impairment in the cells' ability to use O_2 to support ATP synthesis—in other words, cytopathic hypoxia.

The notion that redox stress can lead to PARP-1 activation and hence metabolic inhibition was first proposed by Schraufstatter and associates.[69,70] More recently, Szabó and coworkers showed that exposure of cultured cells to physiologically relevant concentrations of $ONOO^-$ activates PARP-1 and thereby impairs mitochondrial respiration.[71] They further showed that endogenously generated $ONOO^-$ was capable of activating PARP-1 and thereby inhibiting mitochondrial respiration in cultured immunostimulated macrophages[72] and vascular smooth muscle cells.[73]

Recent in vitro studies by Khan and colleagues support the importance of PARP-1–dependent NAD^+/NADH depletion as a mechanism for cytopathic hypoxia caused by inflammatory mediators.[8] The consumption of O_2 by human Caco-2 enterocyte-like cells was measured using an O_2-sensitive optode. Incubation of the cells with cytomix—a cocktail of three proinflammatory cytokines (tumor necrosis factor, IL-1β, and IFN-γ)—decreased cellular O_2 consumption by more than 50%. This phenomenon was entirely reversible; if the cells were washed free of the cytokine cocktail and then incubated for a short period in normal culture medium, the normal rate of O_2 consumption was restored. Thus, the cytokine-induced decrease in O_2 consumption was caused not by cell death but by a sublethal process that impaired normal cellular respiration. The decrease in O_2 consumption induced by incubation with cytomix was significantly ameliorated by pharmacologically blocking NO or $ONOO^-$ production, providing further support for the role of NO and related compounds in the pathogenesis of cytopathic hypoxia. Moreover, pharmacologic inhibition of PARP-1 also ameliorated the development of cytopathic hypoxia, providing support for the PARP hypothesis. The decrease in O_2 uptake induced by cytomix was associated with significantly decreased cellular levels of NAD^+/NADH. Interestingly, incubating the cytomix-stimulated Caco-2 cells with NAD^+ encapsulated in liposomes partially restored cellular NAD^+/NADH levels and prevented the development of cytopathic hypoxia.

In addition to the findings just described, other data support the view that PARP-1 activation is a major factor in the pathogenesis of sepsis. For example, using pharmacologic agents to block PARP-1 activity can prevent LPS-induced vascular contractile dysfunction in rodents.[74,75] Moreover, in comparison to wild-type controls, mice with a genetic defect in the PARP-1 enzyme (i.e., PARP-1 knockout mice) are relatively resistant to the lethal effects of LPS.[76,77] Treatment with a potent PARP-1 inhibitor, PJ34, significantly improves survival in a porcine model of lethal bacterial peritonitis.[78]

The notion that NO-dependent activation of PARP-1 contributes to the pathogenesis of cytopathic hypoxia is also supported by clinical data. Specifically, Boulos and colleagues showed that serum samples from patients with septic shock inhibited the reduction of MTT by cultured human umbilical vein endothelial cells, whereas sera from control subjects did not have this effect. When the endothelial cells were treated with a PARP-1 inhibitor, 3-aminobenzamide, or with an NOS inhibitor, *N*-methyl-L-arginine, the impairment in mitochondrial respiration (as assessed by MTT assay) induced by sera from septic patients was significantly ameliorated.[9]

Despite the findings cited here, the PARP-1 story is more complicated than originally envisioned. It is now recognized that PARP-1 participates in activation of the proinflammatory transcription factor nuclear factor kappa-B (NF-κB). PARP-1 participates in NF-κB–dependent signaling by binding directly to the transcription factor,[79,80] binding to another coactivating molecule (the protein p300),[81] or poly(ADP-ribosyl)ating NF-κB.[82] These effects are not dependent on PARP-1–induced alterations in intracellular energy metabolism but can nonetheless explain why a genetic deficiency in PARP-1 or treatment with a PARP-1 inhibitor can alter responses to a proinflammatory stimulus such as LPS (see earlier). To further complicate matters, activation of PARP-1 conceivably can alter energy metabolism independent of any direct effects on mitochondrial function; recent data indicate that activation of PARP-1 can promote poly(ADP-ribosyl)ation of glyceraldehyde phosphate-3-dehydrogenase, a key enzyme in the glycolytic pathway.[83]

CYTOPATHIC HYPOXIA AS A CAUSE OF ORGAN DYSFUNCTION DUE TO SEPSIS

A decade ago, the notion that sepsis is associated with mitochondrial dysfunction was controversial. Indeed, a number of studies suggested that acute sepsis or endotoxemia in animal models caused an *increase* in mitochondrial function.[84,85] Today, few dispute that sepsis is associated with an acquired intrinsic derangement in cellular respiration (cytopathic hypoxia). It remains unclear, however, whether cytopathic hypoxia is an epiphenomenon or a pathophysiologic mechanism that actually contributes to organ dysfunction and, ultimately, mortality in patients with sepsis or septic shock.

For cytopathic hypoxia to impact the function or viability of cells (and hence the function of organs), the impairment in mitochondrial function has to be severe enough to cause a decrease in the cellular phosphorylation potential, the rate of ATP turnover, or both. The phosphorylation potential is determined by the relative concentrations of ATP, ADP, and Pi: phosphorylation potential = [ATP]/[ADP][Pi]. In many in vitro studies, the function or viability of cells is not markedly altered unless the ATP concentration or phosphorylation potential is substantially reduced (≤70% of normal).[86-89]

In animal models, the effects of sepsis on cellular ATP content are variable, depending on myriad factors, including the method of inducing sepsis (or systemic inflammation), the timing of the ATP measurements with respect to the onset of the inflammatory process, the tissue or organ studied, and the assay used to assess ATP concentration. When rodents are injected with LPS, ATP levels in a variety of organs typically decrease significantly,[90,91] although ATP levels in skeletal muscle are typically unchanged.[91-93] If skeletal muscle is stimulated to induce repetitive contraction, however, it is possible to detect impaired synthesis of ATP.[93] It is unclear whether LPS-induced depletion of cellular ATP concentration in rodent models of septic shock is due to impaired perfusion, mitochondrial dysfunction, or some combination of the two.

Despite the findings just cited, it is important to recognize that acute endotoxemia in rodents is probably not a good animal model for sepsis-induced multiple organ dysfunction in humans. Accordingly, it is pertinent that several studies have failed to detect evidence of cellular ATP depletion in animal models of sepsis characterized by the presence of a true focus of infection (e.g., CLP in rats).[94-97] Contrary results have been reported, however, possibly because of differences between early and late sepsis.[98] Further, in the clinical study by Brealey and colleagues cited previously, ATP levels were significantly lower in skeletal muscle biopsy samples from patients with lethal sepsis than in samples from sepsis survivors or control subjects.[32] Thus, the question of whether sepsis leads to ATP depletion must be regarded as open and worthy of further study.

Steady-state levels of ATP (or even phosphorylation potential) may not be the most important parameter. The rate at which ATP is consumed and synthesized (i.e., the ATP turnover rate) may be more important, because it is conceivable that cells could defend ATP concentration in the setting of either classic hypoxia or cytopathic hypoxia by decreasing the rate at which ATP is used; this phenomenon has been termed metabolic suppression.[99,100]

To investigate this issue, Berg and coworkers used an in vitro "reductionist" model of sepsis to test the hypothesis that ATP turnover rate is modulated by the presence of a proinflammatory milieu. Nontransformed rat enterocytes were studied under control conditions or following incubation for 24 or 48 hours with cytomix, a mixture of the proinflammatory cytokines tumor necrosis factor, IL-1β, and IFN-γ. To measure ATP turnover rate, ATP synthesis was acutely blocked by adding to the cells a mixture containing 2-deoxyglucose (to block glycolysis), potassium cyanide, and antimycin A (to inhibit oxidative phosphorylation). ATP content was measured at baseline (before metabolic inhibition) and 0.5, 1, 2, 5, and 10 minutes later. Log-linear ATP decay curves were generated, and the kinetics of ATP utilization were calculated. Remarkably, the ATP consumption rate was higher in cytomix-stimulated cells than in control cells. In contrast, the rate of ATP disappearance was similar in cytokine-naïve and immunostimulated IEC-6 cells when protein and nucleic acid synthesis was inhibited, suggesting that the increased rate of ATP synthesis following incubation with cytomix was used to support increased protein synthesis. The rates of glucose consumption and lactate production were significantly greater in cytomix-stimulated cells, suggesting that the increased rate of ATP turnover was supported by enhanced (aerobic) glycolysis. Other investigators have shown that experimental sepsis is associated with accelerated aerobic glycolysis,[101] and clinical data are available to support this view as well.[102] It is noteworthy, therefore, that Scharte and coworkers showed that proinflammatory cytokines increase the expression of glycolytic genes in cultured epithelial cells, even in the absence of hypoxia.[103]

CONCLUSION

Several lines of evidence support the notion that cellular respiration is deranged in established sepsis, not just on the basis of inadequate tissue perfusion but also on the basis of impaired mitochondrial function. If this concept is correct, a promising approach will be to develop pharmacologic strategies—for example, administration of potent and selective PARP-1 inhibitors—to restore normal mitochondrial function. Further research is needed to determine whether altered cellular respiration during sepsis truly contributes to cellular and organ dysfunction or is simply an epiphenomenon.

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This review paper was the first to introduce the term cytopathic hypoxia.

Khan AU, Delude RL, Han YH, et al: Liposomal NAD+ prevents diminished O_2 consumption by immunostimulated Caco-2 cells. Am J Physiol Lung Cell Mol Physiol 2002;282:L1082-L1091.

The authors of this paper used a "reductionist" in vitro model to provide convincing evidence that depletion of nicotinamide adenine dinucleotide, mediated by activation of the enzyme poly(ADP-ribosyl) polymerase, is a key factor in impaired cellular respiration following exposure of cultured enterocytes to a cocktail of proinflammatory cytokines.

King CJ, Tytgat S, Delude RL, Fink MP: Ileal mucosal oxygen consumption is decreased in endotoxemic rats but is restored toward normal by treatment with aminoguanidine. Crit Care Med 1999;27:2518-2524.

This study showed that ileal mucosal oxygen consumption (assessed ex vivo) is impaired in rats injected 8 hours earlier with lipopolysaccharide, but this effect is abrogated if the animals are treated with a drug that blocks the enzymatic activity of inducible nitric oxide synthase.

Chapter 37
OXIDATIVE LUNG INJURY

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KEY POINTS

1. In pulmonary tissue, smooth muscle cells, endothelial cells, alveolar cells, and leukocytes have all been shown to **produce free radicals.**
2. **Superoxide** may have the most central role in oxidative lung injury because of its dual ability to directly alter cellular proteins and to form other highly reactive radical species.
3. The **most significant sources of free radicals** in lung tissue cells are the mitochondria and endoplasmic reticulum.
4. **Nitric oxide** is highly radical as a result of an odd number of electrons and through a variety of reactions produces reactive nitrogen species.
5. The **most rapid formation of reactive nitrogen species** occurs as a result of a radical-radical reaction between nitric oxide and various free radicals.
6. **Three enzyme systems** are primarily responsible for the enzymatic component of the antioxidant defenses: (1) superoxide dismutase (SOD); (2) catalase; and (3) the glutathione system.
7. **Several nonenzymatic antioxidants contribute to the cellular defenses** by acting as scavengers of toxic radicals.
8. **Reactive oxygen and nitrogen pulmonary cytotoxicity** is primarily mediated by two mechanisms: (1) lipid peroxidation and (2) damage to DNA.
9. **A variety of pulmonary cell types are susceptible to oxidant toxicity.**
10. **Reactive oxygen and nitrogen species** can affect pulmonary artery smooth muscle contractility and endothelial cell proliferation.
11. A **combination of necrosis and apoptosis** is likely involved in **oxidant-induced lung injury.**
12. **Animal and human studies demonstrate mixed results** concerning the sensitivity of healthy lungs to hyperoxic exposure.
13. **Results of animal studies** show that oxidative lung injury plays a major role in hyperoxia-induced lung injury.
14. The antioxidant response to hyperoxia-induced free radical formation is a complex process that is dependent on changes in expression of a variety of enzymes and nonenzymatic scavenger compounds.
15. There is now substantial evidence that generation of oxidative and nitrosative species is a major contributor to inflammatory lung injury in ARDS.
16. Certain antioxidants that function well under normal physiologic conditions may become overwhelmed in ARDS, whereas others demonstrate increased expression and activity.
17. Ischemia-reperfusion lung injury continues to be a significant cause of early morbidity after lung transplantation.
18. Generation of reactive oxygen species occurs as a direct result of both anoxia-reoxygenation and ischemia-reperfusion that occurs during the procurement-storage-transplantation period.
19. Elevated levels of free iron, calcium, and activated leukocytes increase the generation of free radicals during ischemia-reperfusion of the allograft.
20. Paraquat, bleomycin, and nitrofurantoin are examples of agents with the potential for inducing oxidative lung injury.
21. Hyperoxic therapy has been implicated as the principal inciting factor in the development of bronchopulmonary dysplasia in infants.
22. Oxidative lung injury in bronchopulmonary dysplasia is primarily a result of the oxidation of surfactants, lipids, and proteins.
23. The antioxidant response in newborns with bronchopulmonary dysplasia is variable and is in large part dependent on the stage of development of the infant (i.e., preterm vs. term).
24. Limited data on the use of oxygen therapy suggest minimizing the length of exposure to an F_IO_2 higher than 0.6, utilizing oxygen-sparing interventions, and avoiding oxygen therapy in patients with lung injury secondary to specific toxins.
25. Mechanical ventilation with a low tidal volume strategy (6 mL/kg) should be utilized in patients with possible oxidant lung injury.
26. Although several studies demonstrate a potential benefit for exogenous antioxidant administration, there are not yet enough conclusive data to support its routine use in the clinical setting.

Since the discovery of oxygen in 1775 we have marveled at the life-sustaining power that it possesses. However, we have also realized that oxygen holds the potential for the spoliation of life. Early scientists such as Priestley, Scheele, Lavoisier, Laplace, and Bert all recognized this "two-faced" nature of oxygen and conducted studies to better understand its destructive nature.[1-4] These studies were the preface to the understanding that we now have of the toxic effects of oxygen and its reactive metabolites, collectively known as oxidant injury. Oxidant injury can occur throughout the body, but the lung is the most susceptible organ, and lung injury induced by reactive oxygen species is often devastating and irreversible.

GENERATION OF REACTIVE OXYGEN SPECIES

In pulmonary tissue, smooth muscle cells, endothelial cells, alveolar cells, and leukocytes have all been shown to produce free radicals.[5-8] Superoxide may have the most central role in oxidative lung injury because of its dual ability to directly alter cellular proteins and to form other highly reactive radical species. Superoxide radicals are produced by both cellular enzymatic and nonenzymatic (auto-oxidation) reactions. Enzymes capable of forming superoxide include xanthine oxidase (by the oxidation of purines and of NADH), arachidonic acid peroxidases, nitric oxide synthase, NADPH oxidase, and NADH oxidase.[9-12] Phagocytic cells in the lung can form large amounts of superoxide during bursts of respiratory activity.[13]

The most significant sources of free radicals in lung tissue cells are the mitochondria and endoplasmic reticulum.[14-16] Formation of free radicals requires the presence of molecular oxygen and is a constant process occurring in normal cellular metabolism. Molecular oxygen is reduced by the sequential addition of electrons to form the highly reactive free radicals superoxide radical (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH•):

$$O_2 \rightarrow O_2^- \rightarrow H_2O_2 \rightarrow OH\bullet \rightarrow H_2O$$

Two molecules of water are produced in the reduction of molecular oxygen in a reaction catalyzed by cytochrome oxidase in the electron transport chain in the mitochondria. Cytochrome oxidase, which contains cytochrome a and cytochrome a3, acts as the terminal electron receptor. Under normal conditions there exists a small loss of electron flow (1% to 2%) along the proximal portion of the electron transport chain. Electron loss first occurs during the reduction of NADH dehydrogenase to form a flavin semiquinone free radical, which then reacts with O_2 to form O_2^- (auto-oxidation). Ubiquinone is the second site of electron loss, and the reduction of ubiquinone forms the ubisemiquinone free radical by auto-oxidation. Another important source of O_2^- is the electron transport chain of the endoplasmic reticulum.[16] In the endoplasmic reticulum O_2^- is most likely produced from the auto-oxidation of reduced NADPH cytochrome P_{450} reductase and the reduced cytochrome P_{450}.

Regardless of its source of production, O_2^- is relatively unstable. It can react with proteins that contain transition metal groups (e.g., heme, iron-sulfur), resulting in alteration of cellular function.[17-19] The majority of O_2^- produced, however, is converted to H_2O_2 in a reaction catalyzed by superoxide dismutase[20]:

$$O_2^- + O_2^- + 2H^+ \rightarrow H_2O_2 + O_2^-$$

H_2O_2 is a more stable, nonradical compound. Most of the cellular damage by H_2O_2 results from its further reduction to form hydroxyl radicals by a series of iron catalyzed reactions. Iron is first reduced by O_2^- in the Haber-Weiss reaction, and the reduced form of iron in turn reduces H_2O_2 to form OH• in the Fenton reaction.[21] OH• is also produced directly from O_2^- in a reaction involving hypohalous acids.[22,23] Hypohalous acids are potent oxidants formed when H_2O_2 is oxidized by eosinophil-specific peroxidase and neutrophil-specific peroxidase in the presence of a halide.

GENERATION OF REACTIVE NITROGEN SPECIES

Nitric oxide (NO) is a cytotoxic agent present in many types of environmental pollutants, including cigarette smoke.[24] NO has also been shown to be produced endogenously throughout the body and serves a variety of significant regulatory functions. Nitric oxide synthase (NOS) catalyzes the formation of NO from L-arginine.[25,26] There are constitutive (NOS I, NOS III) and inducible (NOS II) forms of NOS. The constitutive forms are Ca^{++} and calmodulin dependent and synthesize small amounts of NO for brief periods. The inducible form produces large amounts of NO for extended periods.[27,28]

Nitric oxide is highly radical as a result of an odd number of electrons and through a variety of reactions produces reactive nitrogen species. In the presence of molecular oxygen, NO can be oxidized to nitrite (NO_2^-). The formation of NO_2^- leads to the oxidation of various biologic substrates in a reaction catalyzed by heme peroxidases such as MPO and EPO.[29-31] NO_2^- itself is oxidized to nitrogen dioxide radical ($NO_2\bullet$), as well as to nitrate (NO_3^-). Oxidation of NO by oxyhemoglobin (HbO_2) may lead to the formation of methemoglobin (Hb^{3+}) and NO_3^-.[32]

Potentially the most rapid formation of reactive nitrogen species occurs as a result of a radical-radical reaction between NO and various free radicals. For example, $ONOO^-$ is formed by the reaction on NO with O_2^-. $ONOO^-$ can be protonated to form peroxynitrous acid (ONOOH), a highly unstable and reactive compound capable of both oxidizing and nitrating reactions involving a variety of biochemical substrates (e.g., lipids, amino acids).[33]

ANTIOXIDANT MECHANISMS

During normal aerobic metabolism in lung cells, reactive oxygen and nitrogen species are produced that, at low levels, serve a variety of important biologic functions. However, these reactive metabolites are potentially very damaging to biologic substrates such as lipids, proteins, and carbohydrates. A system of enzymatic and nonenzymatic antioxidants exists in the lung to prevent the formation and facilitate the removal of these reactive species.

Three enzyme systems are primarily responsible for the enzymatic component of the antioxidant defenses: (1) superoxide dismutase (SOD); (2) catalase; and (3) the glutathione system. SOD is both an intracellular and extracellular enzyme,

located in the cytosol, in the mitochondria, and on the outside of the plasma membrane.[34-36] The cytosolic form of SOD contains copper and zinc and is associated with pulmonary and endothelial vascular smooth muscle cells. The mitochondrial form contains manganese and is abundant in pulmonary artery smooth muscle and endothelium.[35] During times of oxidative stress, SOD has a significant role in protecting lung cells by catalyzing the dismutation of O_2^- to H_2O_2.[37]

Catalase and the glutathione system are the central mechanisms for the reduction of H_2O_2. Catalase is a hemoprotein found in peroxisomes. It has an iron-heme active site that undergoes divalent oxidation and reduction in catalyzing the reduction of H_2O_2.[38] The glutathione system is likely more important than catalase in the reduction of H_2O_2 and is also responsible for the elimination of lipid peroxidases formed from the free radical altered lipid membranes.[39] The glutathione system is actually a redox cycle in which the key enzyme is glutathione peroxidase. Glutathione peroxidase catalyzes the reduction of H_2O_2 and lipid peroxidases by using reduced glutathione as a cosubstrate. This reaction forms glutathione disulfide, which is subsequently reduced back to glutathione by glutathione reductase.[40] Glutathione reductase activity is dependent on NADPH generated from the hexose monophosphate shunt.[41]

Several nonenzymatic antioxidants contribute to the cellular defenses by acting as scavengers of toxic radicals. Vitamin E, the most important of these compounds, protects against oxidant-induced membrane injury by scavenging lipid peroxide radicals.[42] Thioredoxins, a newly described family of proteins located in the inner mitochondrial membrane of airway epithelial cells, respond to oxidative stress by scavenging reactive species and activating other antioxidant systems such as Mn-SOD.[43] Metallothionein, a metalloprotein expressed in pulmonary endothelial cells, is thought to have an important function in intracellular iron homeostasis and as a free radical scavenger of superoxide radicals.[44] Other free radical scavengers include vitamin C, uric acid, beta carotene, taurine, albumin, and bilirubin.

PATHOPHYSIOLOGY OF OXIDATIVE LUNG INJURY

Reactive oxygen and nitrogen species are cytotoxic to virtually all types of pulmonary cells. This toxicity is primarily mediated by two mechanisms: (1) lipid peroxidation and (2) damage to DNA.

All cell membranes are made up of polyunsaturated fatty acids. The hydroxyl free radical is particularly destructive to these fatty acids by removing a hydrogen atom from the fatty acid, resulting in the formation of peroxides and peroxyradicals. These radical intermediates may then remove another hydrogen atom from a different fatty acid, leading to a chain reaction resulting in the rapid destruction of the cellular membrane.[45] In addition, membrane phospholipase A_2 may be activated during lipid peroxidation, potentially contributing to the breakdown of the lipid bilayer.[46]

Cellular DNA is also a susceptible target for reactive oxygen species. The hydroxyl radical has been shown to directly hydroxylate guanine.[47] Reactive lipid species formed during lipid peroxidation are able to cross-link DNA proteins and cause strand breaks.[48] It has been suggested that this results in the activation of poly (adenosine diphosphate-ribosyl) polymerase (PARP), resulting in excessive consumption of adenosine triphosphate (ATP) and cell death.[49] Some environmental toxins and drugs cause DNA damage through the formation of active complexes with DNA in the presence of oxygen (see section on bleomycin-induced lung injury).[50] Reactive oxygen species have also been implicated in the modulation of gene transcription. Schreck and coworkers have proposed a role for superoxide in the activation of nuclear factor-kappa B (NF-κB), a potent regulator of gene transcription.[51] Demple and associates demonstrated a superoxide effect on gene transcription that may protect the host in which superoxide activates a system (soxRS system) of transcription/translation that leads to the expression of superoxide dismutase.[52]

Oxygen free radicals also have a profound effect on pulmonary artery smooth muscle contractility and can cause vasoconstriction through several mechanisms. Superoxide radical destroys the NO that is produced in the vascular endothelium, thus blocking the vasodilatatory effect induced by NO.[53] Superoxide, in the presence of xanthine oxidase, can also directly stimulate the contraction of pulmonary artery rings, most likely through a mechanism involving protein kinase C.[54] Superoxide is also capable of stimulating the release of calcium from the sarcoplasmic reticulum, as well as increasing the microsomal ATP-dependent calcium uptake in pulmonary vascular smooth muscle cells.[55]

All pulmonary cell types are susceptible to oxidant toxicity. Pulmonary artery endothelial cells initially proliferate in response to superoxide exposure and are stimulated to release higher concentrations of superoxide than quiescent cells. Continued superoxide exposure results in DNA strand breakage resulting in the depletion of ATP and also causes membrane lipid peroxidation. Both mechanisms contribute to an inhibition of endothelial cell proliferation.[56] Bronchial and type I alveolar epithelial cell death occurs in the early stages of oxidant injury and is likely due to a pattern of necrosis rather than apoptosis.[57] Type I alveolar cells are then replaced by hyperplasia of type II alveolar epithelial cells, resulting in a thicker alveolar epithelium.[58] Clara cells, nonciliated epithelial cells distributed throughout the respiratory tree, are extremely rich in cytochrome P_{450} and thus are very sensitive to oxidant stress.[59] Naphthalene exerts its toxic effects primarily through selective damage to Clara cells.[60] Finally, although oxidant lung injury may indeed stimulate inflammatory cells to proliferate and further generate reactive oxygen species, there is some evidence that oxidants may impair the antibacterial function of these inflammatory cells. For example, O'Reilly and colleagues demonstrated impaired phagocytic function due to actin polymerization in mouse alveolar macrophages during hyperoxic exposure.[61] This process appears to be due to NO and the nitration of actin and does not occur in the absence of inducible NOS.

The mode of cell death in oxidant-induced lung cell injury and death is controversial and has been attributed to both necrosis and apoptosis. Animal studies have suggested that although apoptosis may play a key role in programmed lung cell death, necrosis is the predominant mode of death occurring in oxidant lung injury.[49] However, it has been postulated that apoptosis may play a role in limiting the extent of oxidative lung injury and in the remodeling of lung tissue during the repair phase.[62]

OXIDATIVE LUNG INJURY IN THE ICU

The specific pathology and natural history of oxidative lung injury varies with specific disease states. The cascade of events usually involves an acute phase in which cell injury results from the initial generation of reactive oxygen species. This is followed by an inflammatory phase, in which cell death occurs from the response of mononuclear cells and alveoli become obliterated with exudate and hyaline membrane formation. Finally, in extensive disease a proliferative phase usually occurs, leading to proliferation of type II alveolar cells and fibroblasts. Ultimately, fibrosis in the lung interstitium may occur.[63]

We will examine the specific mechanisms of oxidative lung injury in five specific pathologic lung conditions frequently encountered in the ICU: (1) hyperoxia-induced lung injury; (2) ARDS; (3) ischemia/reperfusion injury; (4) lung injury from exposure to toxins; and (5) bronchopulmonary dysplasia. Oxidant lung injury has been implicated in many other lung diseases, including asthma, sarcoidosis, idiopathic pulmonary fibrosis, and radiation pneumonitis. Discussion of these pulmonary disorders is beyond the scope of this chapter.

HYPEROXIA

Treatment with high concentrations of oxygen is often necessary to treat acute and chronic hypoxemia in patients with lung disease. Hyperoxia has been shown to damage alveolar epithelial cells and pulmonary vascular endothelial cells in several animal models. However, studies in humans have demonstrated mixed results concerning the ability of hyperoxic exposure to cause significant lung injury in the absence of underlying lung disease.

Results of early studies analyzing changes in vital capacity with hyperoxic exposure suggested that the safe threshold of P_IO_2 is close to 0.6 atm.[64] This estimation was supported later by data from the U.S. Navy's shallow habitat air diving (SHAD) program studying long-term survival in a compressed air environment.[65,66] During several stages of this study men underwent shallow habitat dives with a P_IO_2 of 0.51 atm and 0.57 atm for a period of 29.5 days and 28 days, respectively. All men tolerated the protocol well and there was no evidence of decreased pulmonary function. In the final arm of this study men were exposed to cycles of 0.51 atm and 0.81 atm, with a mean of 0.61 atm. These subjects demonstrated chest discomfort as well as decreases in the vital capacity that correlated with the exposure to the P_IO_2 of 0.81 atm.

Determining the threshold for oxygen toxicity in actual patients is even more difficult. Patients requiring acute oxygen therapy usually have severe parenchymal lung injury, and therefore interpretation of worsening lung injury while receiving oxygen therapy can be obscured. However, there are several reports in the literature examining the effects of hyperoxic therapy on patients receiving mechanical ventilation for reasons other than primary lung disease. Singer and associates reported that post–cardiac surgical patients exposed to 100% F_IO_2 for a mean of 24 hours demonstrated no adverse effects when compared with a similar group receiving a mean F_IO_2 of 0.32.[67] Smith and coworkers analyzed pulmonary function, radiographs, and pathology in 41 patients treated with high-frequency jet ventilation using a mean F_IO_2 of 0.92 for a mean of 4.1 days and did not find any evidence of oxygen toxicity.[68] Kobayashi described a 32-year old patient with myasthenia gravis who, because of technical limitations of a ventilator, was ventilated with an F_IO_2 of 0.80 for 150 days.[69] Despite developing blindness secondary to systemic oxygen toxicity, this patient developed no evidence of pulmonary oxygen toxicity.

In contrast to these reports demonstrating an absence of pulmonary oxygen toxicity in patients receiving hyperoxic therapy, Barber and colleagues reported adverse pulmonary effects of hyperoxic ventilation in patients with cerebral trauma.[70] Patients ventilated with an F_IO_2 of 100% for a mean of 2 days had a lower mean PaO_2, increased deadspace, and worsening of chest radiographs when compared with a similar group ventilated with room air. However, at autopsy there were no histopathologic differences discovered between the two groups, suggesting that hyperoxia-induced atelectasis may have played a greater role than direct parenchymal lung injury in explaining the clinical differences.

Therefore, the degree of sensitivity of healthy lungs to hyperoxia remains unclear. In addition, the specific underlying pathophysiologic phenomena causing the observed clinical sequelae are not known. For example, a decrease in vital capacity may result from an acute tracheobronchitis and hypoxemia could be a manifestation of absorption atelectasis. Also, as previously mentioned, patients receiving hyperoxic therapy usually have underlying lung disease and distinguishing the etiology of their lung physiology and histopathology is impossible.

Because of these difficulties in studying a human lung model of hyperoxia, there has been a strong reliance on animal studies to help elucidate the mechanisms of hyperoxic lung injury. There is now significant evidence that oxidant injury plays a principal role in hyperoxia-induced lung injury. Gerschman and colleagues first suggested that hyperoxia-induced tissue injury results from the generation of oxygen-derived free radicals.[71] Freeman and associates[14] demonstrated that hyperoxia increases oxygen free radical production in rat lungs. The cellular enzymatic and nonenzymatic (auto-oxidation) reactions generating free radicals during normoxia were previously discussed. Production from each of these sources is increased during hyperoxia, but the nonenzymatic formation of free radicals (auto-oxidation) appears to play a much more significant role.[14]

As previously described, several enzymes play important roles in the generation of O_2^- and other reactive species. These enzymes demonstrate low Michaelis-Menten kinetics. They are saturated with molecular oxygen during normoxia, and therefore their rates of reaction are not increased with higher concentrations of oxygen.[14] In addition, there appear to be negative feedback mechanisms that may lower enzyme activity during hyperoxia. For example, Elsayed and coworkers showed that hyperoxia decreases the activity of xanthine oxidase both in rat lungs and in cultured lung endothelial cells.[72] The decreased activity was reproduced with purified enzyme in the presence of oxygen free radicals, supporting the theory of a feedback mechanism.

The most important source of increased free radical production during hyperoxia is the auto-oxidation of flavins and quinones in the electron transport chains of the mitochondria and endoplasmic reticulum.[73] These reactions demonstrate first-order kinetics, and therefore the rate of formation of free radicals is proportional to the concentrations of molecular oxygen and the oxidizable substrate.[14] Grisham and coworkers estimated that during hyperoxia with 100% oxygen, 85% of the free radicals produced by

lung cells are produced in the electron transport system of the endoplasmic reticulum and the remaining 15% are generated in the mitochondria.[74]

The antioxidant response to hyperoxia-induced free radical formation is a complex process that is dependent on changes in expression of a variety of enzymes and nonenzymatic scavenger compounds. Studies of gene expression in wild-type and knockout mice have better elucidated antioxidant expression during hyperoxia.[75] Perkowski and associates demonstrated no change in the gene expression of the antioxidant enzymes catalase, manganese SOD, and copper-zinc SOD in mice exposed to greater than 95% oxygen. However, there was a moderate increase in the expression of glutathione peroxidase and heme oxygenase-1, as well as a 7-fold increase in the expression of the heavy metal binding protein metallothionein.

ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS is a lung disease characterized by a diffuse, patchy pattern of inflammation in the lung parenchyma. The pathogenesis of ARDS involves a complicated cascade of humoral and cellular responses.[76] After an initial insult (i.e., infection, sepsis, trauma, severe burns) there is a massive release of inflammatory cytokines such as tumor necrosis factor-alpha, IL-1, and IL-6, leading to the activation of lung epithelial, endothelial, and mononuclear cells. There is an increase in the expression of various adhesion molecules, selectins, and integrins that induces the extravasation and adhesion of neutrophils and eosinophils to lung tissue. The ensuing lung injury results from the inflammatory response by these activated cells. Until recently the mechanisms by which lung injury occurs have not been well understood.

There is now substantial evidence that generation of oxidative and nitrosative species is a major contributor to inflammatory lung injury in ARDS.[77] Oxidant free radicals are produced by activated neutrophils and macrophages, as well as by lung endothelial, epithelial, and alveolar cells. Similarly, synthesis of NO and other reactive nitrogen species is increased in lung inflammation.[78]

Cochrane and colleagues were the first to demonstrate evidence of oxidant activity in ARDS.[77] $Alpha_1$-proteinase inhibitor (PI), an inhibitor of elastase found in the lung, was found to be inactivated in the bronchoalveolar lavage (BAL) fluid, but not the plasma, from patients with ARDS. In addition, the activity of the inactivated $alpha_1$-PI was restored with a reducing agent. Later studies showed an increased level of H_2O_2 in the expired breath condensates from patients with acute lung injury/ARDS as compared with patients with healthy lungs.[79] Weiland and Laurent found increased superoxide levels in leukocytes isolated from the blood from patients with ARDS.[80] Evidence of accelerated superoxide generation in ARDS has been demonstrated in several recent human and experimental animal studies. Quinlan and coworkers demonstrated increased levels of hypoxanthine and xanthine, substrates for xanthine oxidase, in the plasma from patients with ARDS.[81] In an experimental in-situ lung model of endotoxin-induced ARDS in rats, increased levels of superoxide were observed by use of chemiluminescence.[82]

Nitric oxide has also been shown to possess a significant role in ARDS. NO can be produced by airway epithelial cells, endothelial cells, and type II alveolar cells, as well as by activated neutrophils and macrophages.[83,84] There is evidence that synthesis of NO and other reactive nitrogen species is increased during lung inflammation in ARDS. Sittipunt and colleagues measured increased levels of nitrate and nitrite, breakdown products of NO, in the BAL fluid from patients with or at risk for ARDS.[85] The levels of nitrate and nitrite decreased to near-normal levels several weeks after the onset of ARDS. These results were supported in a similar study by Zhu and coworkers demonstrating significantly higher levels of nitrate in pulmonary edema fluid collected with a wedged suction catheter from patients with ARDS.[86] Other studies have addressed the toxic effects of these reactive intermediates by measuring the byproducts of nitration reactions involving a variety of functionally important lung proteins. Nitrotyrosine, the end product of the nitration of the tyrosine residues of many proteins, has been found in tissues during acute inflammation.[85] Increased levels of nitrotyrosine have been shown both in pulmonary edema and BAL fluid from patients with ARDS.[85,86] Nitrated ceruloplasmin, transferrin, $alpha_1$-PI, and $alpha_1$-antichymotrypsin have all been detected in the plasma from patients with ARDS.[87] Nitrated surfactant protein A has been discovered in the edema fluid from patients with ARDS.[86] Because it has been previously suggested that surfactant protein A may play a role in the removal of infectious pathogens from the alveolar space, it has been hypothesized that the nitration of this protein may alter its function and render the patient with ARDS more susceptible to secondary infections.[88]

Together these results support a significant role for oxidant-mediated lung injury in ARDS. Therefore, antioxidant expression and activity would seem to be a principal factor in moderating damage to lung tissue. Several studies have demonstrated a decrease in the level of several antioxidants in patients with ARDS. For example; levels of glutathione, an antioxidant with the significant role of reducing H_2O_2, were found to be decreased in the BAL fluid of patients with ARDS.[89] However, levels of catalase, another antioxidant responsible for the reduction of H_2O_2, were actually increased.[90] Other studies have demonstrated an increase in the response of some antioxidants and a decrease in others in both plasma and BAL fluid from patients with acute lung injury. These results suggest that whereas certain antioxidants that function well under normal physiologic conditions may become overwhelmed in ARDS, others demonstrate increased expression and activity.

ISCHEMIA-REPERFUSION LUNG INJURY

Since 1983 lung transplantation has become the definitive therapy for patients with end-stage lung disease. However, despite improvements in the selection of donors, preservation of donor lungs, surgical techniques, and perioperative care, ischemia-reperfusion lung injury continues to be a significant cause of early morbidity after lung transplantation. Ischemia-reperfusion lung injury is characterized by a pattern of alveolar damage, pulmonary edema, and hypoxemia that occurs within the first 72 hours after transplantation.[91] Several factors likely contribute to the extent of injury, including donor lung injury, hypothermic storage, and increased organ ischemia time. Although several mechanisms for ischemia-reperfusion injury have been proposed, generation of reactive oxidative species appears to play a principal role. Oxidative stress occurs as a direct result of both anoxia-reoxygenation and ischemia-reperfusion that occurs during the procurement-storage-transplantation period.[91]

During the period in which the donor lung is not ventilated, hypoxia/anoxia results in a significant decrease in the level of ATP and a subsequent increase in the degradation product hypoxanthine.[92] Hypoxanthine is oxidized to form superoxide radicals in a reaction catalyzed by xanthine oxidase, an enzyme found in abundance in the pulmonary vascular endothelium.[9,27,97] This reaction cannot occur in the absence of oxygen, and therefore a buildup of hypoxanthine takes place during the anoxic period. On ventilation/reoxygenation with transplantation, the hypoxanthine generates high concentrations of superoxide. Zhao and colleagues demonstrated that this process is disrupted with allopurinol, an inhibitor of xanthine oxidase.[93]

Storage of the donor lung is characterized by a period of ischemia in which there is no blood flow into the lung. Oxidant generation from ischemia occurs primarily in the endothelial cells and is not dependent on hypoxia.[96] In response to the absence of the mechanical component of blood flow during ischemia, the endothelial cell membrane is depolarized, activating NADPH oxidase, nitric oxide synthase, and NF-κB.[97,98] As previously discussed, these enzymes catalyze the reactions generating reactive oxygen and nitrogen species.

Free radical–induced lung damage is influenced by other processes occurring during ischemia-reperfusion injury. Levels of free iron are increased during ischemia as a result of its release from ferritin and cytochrome P_{450}.[99,100] Iron undergoes reduction and oxidation and is responsible for catalyzing the production of hydroxyl radical from superoxide and hydrogen peroxide in the Haber-Weiss and Fenton reactions. Iron may also contribute to oxidant stress by enhancing the oxidation of glutathione and the peroxidation of lipids.[101] Iron chelators such as deferoxamine have been shown to be effective in moderating ischemia-reperfusion injury in animal models.[102] Other factors that may influence or contribute to oxidant injury include elevated levels of cytosolic calcium (increases conversion of xanthine dehydrogenase to xanthine oxidase) and leukocyte activation (increases free radical production through membrane bound NADPH oxidase system).[103,104]

TOXIN-INDUCED OXIDANT LUNG DAMAGE

Many environmental and pharmacologic compounds can cause significant lung injury. These compounds can inflict toxic effects through a variety of mechanisms and are associated with a spectrum of disease patterns.

Paraquat can cause toxic effects in the kidney, liver, and thymus, but the lung is the most common site of toxicity.[105] Animal studies have demonstrated that paraquat lung toxicity is characterized by a morphologic pattern of inflammatory cell infiltration, necrosis of type I and II alveolar cells, fibroblast infiltration and proliferation, and, finally, synthesis of large quantities of collagen. This cascade of events results in severe pulmonary fibrosis and can follow exposure by both parenteral and inhalational routes.[105-109]

The mechanisms of paraquat-induced lung injury have been well studied. Paraquat is a basic amine that, when taken up by the lung, results in significant increases in oxygen uptake and subsequent NADPH oxidation.[110] This is the first step of a redox cycle occurring in the endoplasmic reticulum of alveolar epithelial cells. Paraquat is reduced to a free radical in this reaction catalyzed by NADPH cytochrome c reductase. This free radical then immediately transfers its electron to molecular oxygen to form superoxide radical, and in the process it regenerates the original paraquat cation. The superoxide radical can then exert its direct toxicity or continue to react to form the equally dangerous hydrogen peroxide and/or hydroxyl radical. The regenerated paraquat cation is then free to restart the redox cycle, resulting in the generation of tremendous quantities of superoxide radicals.[110,111] Paraquat-induced lung injury has also been associated with increased NO synthesis, demonstrated by a decrease in injury with administration of inhibitors of NOS.[112]

With an understanding of these mechanisms of paraquat lung toxicity, one can predict the exogenous and endogenous factors that may influence the extent of lung damage. For example, Smith and Rose demonstrated that hyperoxia increases paraquat toxicity but hypoxia decreases it.[113] The host antioxidant response to paraquat toxicity is directed at the overwhelming production of superoxide. Animal studies have specifically identified important functions for glutathione, SOD, catalase, α-tocopherol, vitamin E, and selenium in counteracting paraquat-induced oxidant toxicity.[111]

Bleomycin is an antineoplastic drug used to treat various types of squamous cell cancers and lymphomas. Despite being a very effective cancer drug, its use is often limited by lung toxicity, initially manifesting as a pneumonitis and later progressing to pulmonary fibrosis.[114] The morphologic pattern of bleomycin-induced lung injury has been well studied in mice.[115] The initial stage of injury occurs within the first 4 weeks and is characterized first by vascular endothelial cell injury, followed by necrosis of type I alveolar epithelial cells, and finally by deposition of fibrin in the alveolar spaces. The second stage, typically occurring within 8 to 12 weeks, is characterized by metaplasia of type II alveolar epithelial cells, fibroblast organization and collagen deposition, and subsequent interstitial fibrosis.

The mechanisms of bleomycin-induced lung injury are not completely understood, but evidence strongly supports a role for reactive oxygen species. Scheulen and coworkers showed that cell destruction is a result of cleavage of both single- and double-stranded DNA and that this cleavage was dependent on oxygen, iron, and NADPH cytochrome P450 reductase.[116] In addition, bleomycin was found to significantly increase NADPH oxidation.[116] In response to these results, an active complex of bleomycin, iron, and oxygen has been implicated in the DNA damage associated with bleomycin lung injury, and three-dimensional models for this complex have been proposed.[117] Extracellular superoxide dismutase has been shown to play an important role in the antioxidant response to bleomycin-induced oxidative stress.[118]

Many other pharmaceutical and nonpharmaceutical agents are associated with oxidant-induced lung injury. Nitrofurantoin, an antibiotic used to treat urinary tract infections, causes lung toxicity by generation of superoxide, hydrogen peroxide, and hydroxyl radical by a mechanism similar to that of paraquat.[119] Naphthalene exposure can result in selective necrosis of pulmonary Clara cells and is likely mediated by reactive metabolites dependent on cytochrome P_{450}.[120] Vinylidine chloride (used in the plastics industry), malathion (insecticide), and 4-ipomeanol (produced by fungus in sweet potatoes) are all thought to induce oxidant-mediated lung injury through a variety of mechanisms.[121,122] Certain trace metals such as vanadium have been shown to cause lung injury through the induction of inflammation and apoptosis by reactive oxygen species.[123] Chronic exposure

to ethanol renders the lung susceptible to acute lung injury by decreasing glutathione levels and therefore indirectly increasing levels of oxygen free radicals.[124] Reactive intermediates have even been implicated in certain types of lung malignancies resulting from exposures to carcinogens, as in the case of many polycyclic aromatic hydrocarbons.[125]

BRONCHOPULMONARY DYSPLASIA

Bronchopulmonary dysplasia (BPD) is a lung disease in preterm infants that occurs usually as a complication of the respiratory distress syndrome. It is characterized by a histologic pattern of obliterative changes in the bronchioles with the formation of cysts.[126] Hyperoxic therapy has been implicated as the principal inciting factor, and in the past it has been suggested that the generation of reactive oxygen and nitrogen species is the major contributor to lung injury in BPD.[127,128] In fact, preterm infants are at particular risk for oxidative lung injury for several reasons: (1) deficiency in pulmonary surfactant; (2) decreased levels and function of antioxidant enzymes; (3) increased exposure to infections with subsequent inflammatory cytokine release; and (4) increased levels of free iron in the plasma.[129]

Recent evidence has strongly supported a role for oxidative lung damage in BPD. Oxidative lung injury in BPD is primarily a result of the oxidation of surfactants, lipids, and proteins. Several studies have demonstrated increased levels of oxidized ascorbic acid, uric acid, and *o*-tyrosine, all markers of peroxidation, in tracheal lavage fluid from preterm infants who later developed BPD.[130,131] Nogee and associates showed that superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite all inactivate surfactant protein.[132] The oxidation of surfactant protein A results in a loss in its surfactant function and possibly its ability to augment the alveolar immune response to infection.[133] Pitkanen and colleagues measured an increased level of pentane and ethane, products of lipid peroxidation, in exhaled gas from preterm infants who later developed BPD.[134] Varsila and coworkers detected higher concentrations of carbonyl groups, side chains formed during the oxidation of proteins, in tracheal aspirates from newborns with BPD.[135]

The antioxidant response in newborns with BPD is variable and is in large part dependent on the stage of development of the infant (i.e., preterm vs. term). Animal studies of preterm newborns have demonstrated a lower level of intracellular enzymatic antioxidants such as glutathione when compared with term newborns.[136,137] In addition, in preterm newborns expression of antioxidant enzymes is not increased during times of oxidative stress.[138] The diminished antioxidant defenses in the newborn coupled with the increased oxidant production associated with early infection, inflammation, and oxygen therapy contribute to the lung injury associated with BPD.

EFFECTS OF ICU THERAPEUTIC INTERVENTIONS ON OXIDANT LUNG INJURY

OXYGEN THERAPY

Oxygen is the most common "drug" administered in the intensive care setting. The detrimental effects of oxygen and its reactive metabolites have been presented in detail. Oxygen toxicity can be viewed in a dose-response curve manner, with the dose equal to the product of the P_IO_2 and the duration of exposure. Therefore, as with all drugs, the minimum dose should be used that is necessary to induce the anticipated therapeutic benefit. As previously discussed, the determination of that threshold dose has been very difficult because of a number of confounding variables inherent in any human study of hyperoxic lung injury. However, from the data available the following recommendations can be made:

- Minimizing the length of exposure to elevated F_IO_2
- Utilizing oxygen-sparing interventions such as the application of positive end-expiratory pressure during mechanical ventilation and ensuring adequate oxygen delivery to organ tissues through the maintenance of cardiac output
- Avoiding oxygen therapy in patients with lung injury secondary to specific toxins (i.e., bleomycin, paraquat, and nitrofurantoin)

MECHANICAL VENTILATION

Ventilator management has been recognized as one of the most significant factors in determining clinical outcome in acute lung injury. Mechanical ventilation itself has been shown to induce a pattern of lung injury characterized by neutrophil infiltration of the interstitium and alveolar space and subsequent diffuse epithelial and endothelial cell injury.[139] These pathophysiologic effects are similar to those observed in ARDS and likely result from mechanical stress of alveolar overdistention and high transpulmonary pressures.[140] The ARDS Network published a landmark study in 2000 demonstrating that mechanical ventilation with low tidal volumes decreases mortality in patients with ARDS.[141] Several studies have suggested that a reduction in cytokine release is in part responsible for the protective effect of low tidal volume ventilation.[142] Hammerschmidt and associates demonstrated that mechanical ventilation with a low tidal volume (6 mL/kg) strategy attenuates increases in vascular permeability in a rabbit model of hypochlorite-induced oxidant lung injury. It has been further postulated that because mechanical ventilation may influence cellular metabolism, intrinsic antioxidant enzyme expression and function may be affected by ventilation strategy.[143] This limited evidence together with the results of the ARDS Network study support a recommendation of mechanical ventilation with a low tidal volume strategy (6 mL/kg) in patients with possible oxidant lung injury. In addition, adequate extrinsic positive end-expiratory pressure should be implemented in an attempt to reduce the F_IO_2 and minimize the potential for hyperoxia-induced oxidant injury.

ANTIOXIDANTS

A better understanding of the endogenous antioxidant response to oxidant stress has generated interest in the therapeutic potential for exogenous antioxidant administration. Studies of antioxidant therapy have focused on administration of both enzymatic and nonenzymatic antioxidants in a variety of lung diseases. Robbins and coworkers demonstrated a reduction in hyperoxia-induced lung injury with the use of recombinant human superoxide dismutase.[144] Gadek and associates administered enteral nutrition supplemented with

a variety of enzymatic and nonenzymatic antioxidants to patients with ARDS and observed a decrease in oxidant production and neutrophil count in BAL fluid.[145] Overexpression of extracellular superoxide dismutase has been shown to attenuate bleomycin-induced lung pulmonary fibrosis in mice.[118] Addition of reduced glutathione to preservation solutions for transplanted organs has been shown to reduce subsequent ischemia-reperfusion injury.[146] However, although these studies demonstrate a potential benefit for exogenous antioxidant administration, there are not yet enough conclusive data to support its routine use in the clinical setting.

FUTURE THERAPY

A variety of potential strategies to prevent and treat oxidative lung injury are being studied. The results of several animal studies have suggested that sublethal endotoxin injection may confer a protective effect against oxidative lung injury.[147] Studies of exogenous antioxidants targeted at specific oxidant mechanisms continue to demonstrate potential therapeutic benefit. A good example is the potential use of heme oxygenase-1 in protecting against oxidant-induced ischemia-reperfusion injury.[148,149] Attempts at improving delivery of antioxidants to lung tissue have yielded successful results. For example, Nakamura and coworkers used intratracheal administration of copper-zinc superoxide dismutase to prevent hyperoxia and ventilator-induced lung injury in newborn piglets.[150] Gene therapy techniques are also being studied in various animal models. Danel and colleagues showed that intratracheal administration of an adenovirus vector encoding copper-zinc superoxide dismutase improves survival of rats exposed to prolonged hyperoxia.[151]

ANNOTATED REFERENCES

Gram TE: Chemically reactive intermediates and pulmonary xenobiotic toxicity. Pharm Rev 1997;49:297-342.

This is a comprehensive review of pulmonary xenobiotic toxicity. The microscopic and ultrastructural effects of hyperoxic lung injury are first reviewed, followed by a summary of the enzymatic processes involved in oxygen toxicity. The author next reviews the mechanisms and pathologic changes associated with a variety of xenobiotic agents.

Nanavaty UB, et al: Oxidant-induced cell death in respiratory epithelial cells is due to DNA damage and loss of ATP. Exp Lung Res 2002;28:591-607.

In this study, Dr. Nanavaty and colleagues address the question of whether DNA damage or apoptosis is responsible for oxidant-induced lung injury. Using a model of hydrogen peroxide induced cytotoxicity in BEAS-2B and A549 cells, they demonstrate a decrease in cellular ATP and an absence of markers of apoptosis in response to injury. These results suggest that DNA damage is one of the primary reasons for oxidant-induced cell death.

Perkowski S, et al: Gene expression profiling of the early pulmonary response to hyperoxia in mice. Am J Respir Cell Mol Biol 2003;28:682-696.

The authors measure changes in total lung gene expression in C57BL/6 mice during hyperoxic exposure. Although no changes were noted in the expression of catalase, MnSOD, and Cu-Zn SOD in response to hyperoxia, glutathione peroxidase, glutathione-S-transferase, heme oxygenase-1, and metallothionein showed moderate increases. The expression of a variety of other lung genes in response to hyperoxia is also examined.

Perrot MD, Liu M, Waddell T, Keshavjee S: Ischemia-reperfusion-induced lung injury. Am J Respir Crit Care Med 2003;167:490-511.

The authors review the current evidence concerning the development of ischemia-reperfusion-induced injury in the lung allograft. The review first examines the role of donor lung assessment and management, including the effects of cold storage. The authors then look at the technique of lung preservation and review the current strategies for the prevention and treatment of ischemia-reperfusion-induced lung injury.

Saugstad OD: Bronchopulmonary dysplasia—oxidative stress and antioxidants. Semin Neonatol 2003;8:39-49.

In this review of BPD, Saugstad summarizes the role of oxidative stress in cellular and mitochondrial processes, leading to the inflammation and fibrosis observed in BPD. He also examines the host antioxidant responses in BPD and reviews the current and future therapeutic approaches to prevent oxidative injury in BPD.

Chapter 38

APOPTOSIS IN THE CRITICALLY ILL

Patricia S. Grutkoski • Chun-Shiang Chung • Jorge Albina • Walter Biffl • Alfred Ayala

KEY POINTS

1. **Apoptotic cell death** results from one of three major pathways: cell death receptor driven (extrinsic), the mitochondrial pathway (intrinsic), or an endoplasmic reticular stress-induced process.
2. **Blood neutrophil (polymorphonuclear leukocyte [PMN]) constitutive apoptosis** is dysregulated in patients with systemic inflammatory response syndrome, acute respiratory distress syndrome (ARDS), sepsis, trauma, and severe burns. A similar response has been reported in patients with ARDS with respect to PMNs in bronchoalveolar lavage fluids.
3. **Circulating lymphocytes from patients suffering from severe burns, blunt trauma, and sepsis,** as well as from patients who have had major elective surgery (nonseptic), exhibit significantly more apoptosis (approximately 20% to 60% apoptotic) than do peripheral lymphocytes from healthy donors. Similarly, increased lymphocyte apoptosis has been detected in the spleen and gut of patients with sepsis and multiple organ dysfunction syndrome, as well as in trauma and shock patients.
4. Although alterations in apoptosis are most evident in the critically ill, and most experimental models are most obvious in tissues of immune system origin, **a variety of epithelial cells, as well as select parenchymal cells and possibly endothelial cells, may be affected by changes in this pathway.**
5. **The mediators of the apoptotic changes in critically ill patients are as different as the cell type examined.** Nonetheless, data from several experimental models suggest that selective targeting of apoptotic proteins such as caspases and death receptors may provide novel therapeutic avenues in the future.

One of the central components in the control of inflammation is the ability to sustain or to shut down or eliminate cells by regulating their cellular suicide program (apoptosis). Apoptosis is a method by which cells are eliminated from the body in a controlled manner, resulting in clearance of cells without damage to the surrounding environment. The process by which a cell undergoes apoptosis has been reviewed extensively.[1-3] Initially, apoptosis was thought to be a process by which selected cell populations could be actively deleted from specific tissues during morphogenesis and tissue remodeling[4]; it has since been extended to include a variety of roles in immune response resolution and clonal deletion.

Apoptotic cell death results from one of three major pathways: cell death receptor driven (extrinsic), the mitochondrial pathway (intrinsic), or an endoplasmic reticular stress-induced process.[1,5-7] A description of some of the more salient features of these processes is provided as an orientation to the studies discussed here (Fig. 38-1).

The extrinsic death receptor pathway is mediated by the interaction of a trimeric tumor necrosis factor (TNF) receptor (TNF-R)–like family of membrane receptors and their associated ligands, including Fas ligand (FasL), TNF, and TNF-related apoptosis-inducing ligand (see Fig. 38-1). The most studied and the best understood are the TNF–TNF-R and FasL-Fas systems. In this respect, recent studies suggest that Fas-driven apoptosis appears to go through one of two nonexclusive processes, depending on whether it takes place in a type I or type II cell.[8] Type I cells appear to use signaling via Fas-associated death domain–mediated death-inducing signaling complex formation through the activation of caspase-8, driving primarily caspase-3 activation and culminating in the activation of downstream proteases that induce nuclear apoptosis. Alternatively, in type II cells, FasL-Fas–induced cell death appears to be mediated through the subsequent activation of Bid, a cytoplasmic proapoptotic protein. Once Bid is cleaved by caspase-8, it translocates to the mitochondrial membrane, where it interacts with proapoptotic agents such as Bax protein, which in turn deactivates antiapoptotic agents such as Bcl-2, leading to mitochondrial release of cytochrome *c* and Apaf-1/caspase-9, as well as decreased mitochondrial membrane potential (organelle dysfunction). These events lead to the intrinsic apoptotic pathway, also known as the mitochondrial-driven cell death pathway.

Although much is understood about the components of the mitochondrial apoptotic transition and the consequences of activating this intrinsic pathway (protein release leading to apoptosome formation), its initiation and regulation are less clearly and less directly defined. In this respect, a wide variety of exogenous stressors, such as steroids, reactive oxygen intermediates, nitric oxide, peroxynitrite, and chemokines and cytokines (via activation or inhibition of signaling through phosphatidylinositol-3-kinase-AKT (PI3K-AKT), protein kinase (PKC), mitogen-activated protein kinase (MAPK), and other kinases), as well as the loss of essential growth factors such as interleukin (IL)-2, IL-4, and granulocyte-macrophage colony-stimulating factor (GM-CSF), can result in the induction of apoptosis through this intrinsic pathway (see Fig. 38-1). Finally, endoplasmic

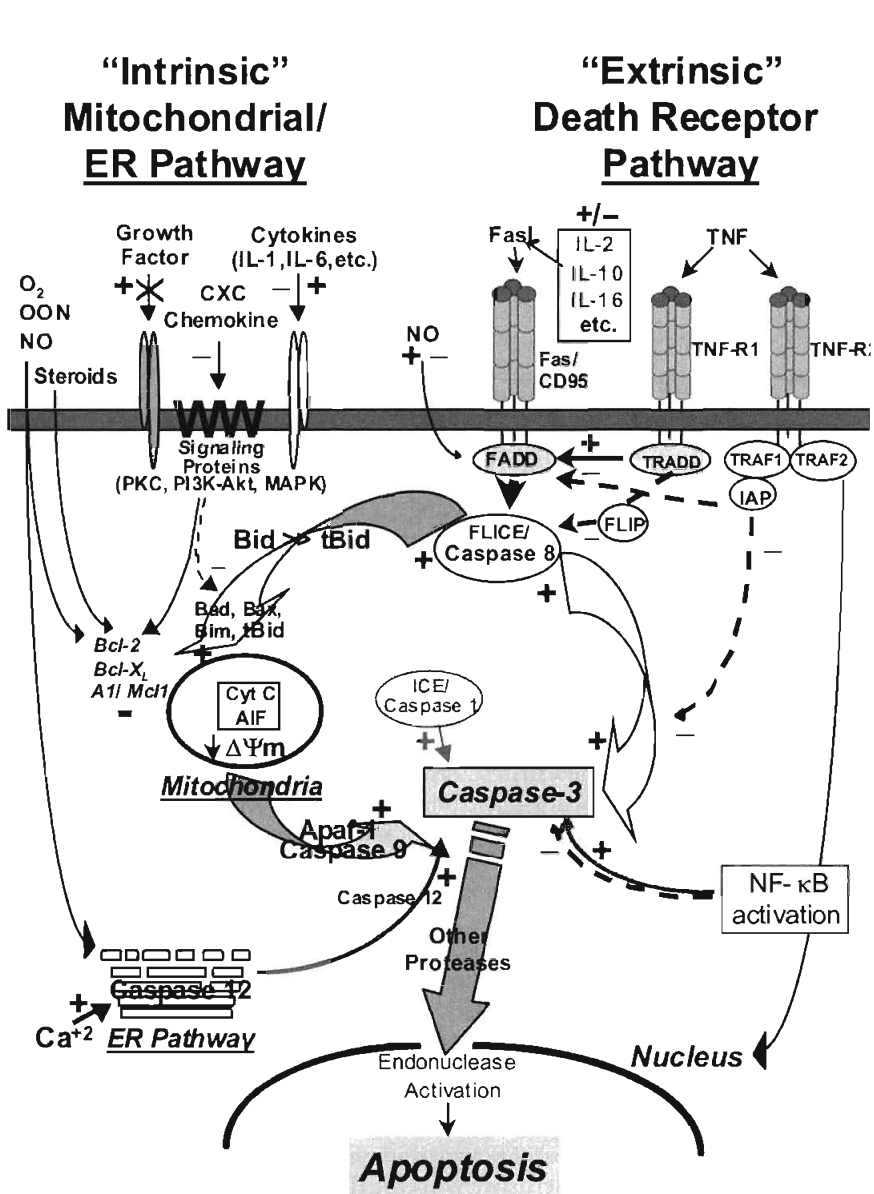

FIGURE 38–1. Central components in the mammalian apoptotic response mediated by either "extrinsic" death receptor or "intrinsic" mitochondrial or endoplasmic reticular (ER) pathways. AIF, apoptosis-inducing factor; CXC, family of alpha-chemokine; FADD, Fas-associated death domain; FLICE, FADD-like ICE; FLIP, FADD-like ICE inhibitory protein; IAP, inhibitor of apoptosis protein; ICE, interleukin-1β converting enzyme; IL, interleukin; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa; NO, nitric oxide; PKC, protein kinase C; TNF, tumor necrosis factor; TRADD, TNF receptor-associated death domain; TRAF, TNF receptor-associated factor.

reticular stress-driven apoptosis is the least well understood. This pathway is mediated by the release and activation of caspase-12. However, little is known beyond the potential role of oxidant stress and Ca^{++} as an activator of this process.

As alluded to earlier, the very process of macrophage or lymphocyte activation required to mount a competent inflammatory or adaptive immune response to a foreign pathogen sets in motion, for most cells, processes involved in mediating their own demise.[9,10] In this respect, the process by which a mature T cell is activated, via concordant T-cell receptor complex stimulation and costimulatory molecule engagement, simultaneously induces the up-regulation of death receptors (such as Fas) that make the activated T cells more susceptible to ligands that induce apoptosis.[10-12] With respect to the resolution of inflammation or local tissue injury, lymphocyte Fas-FasL–mediated fratricide is also a potentially important process, with numerous examples of lymphocyte-lymphocyte induction of cell death being documented.[13,14] Macrophages and monocytes may also use such a mechanism, with granulocytes encountered at sites of inflammation.[15]

POLYMORPHONUCLEAR LEUKOCYTE APOPTOSIS

SUPPRESSION

Polymorphonuclear leukocytes (PMNs, neutrophils) play a crucial role in the primary immunologic defense against infectious agents, and they use the apoptotic program not only for resolution but also as a means of natural cell turnover. Although the primary role for PMNs is to eliminate pathogens, they can also be detrimental, being major contributors to organ damage induced by ischemia-reperfusion, trauma, and sepsis. The importance of PMNs in organ damage and mortality has been demonstrated using anti-PMN therapies to block lung and liver damage after sepsis induced by cecal ligation and puncture (CLP),[16] anti–IL-8 therapy to block PMN infiltration into the lung after lipopolysaccharide (LPS) treatment,[17] and anti-macrophage inflammatory protein-2 (anti-MIP2) treatment to block PMN infiltration into the peritoneum after the induction

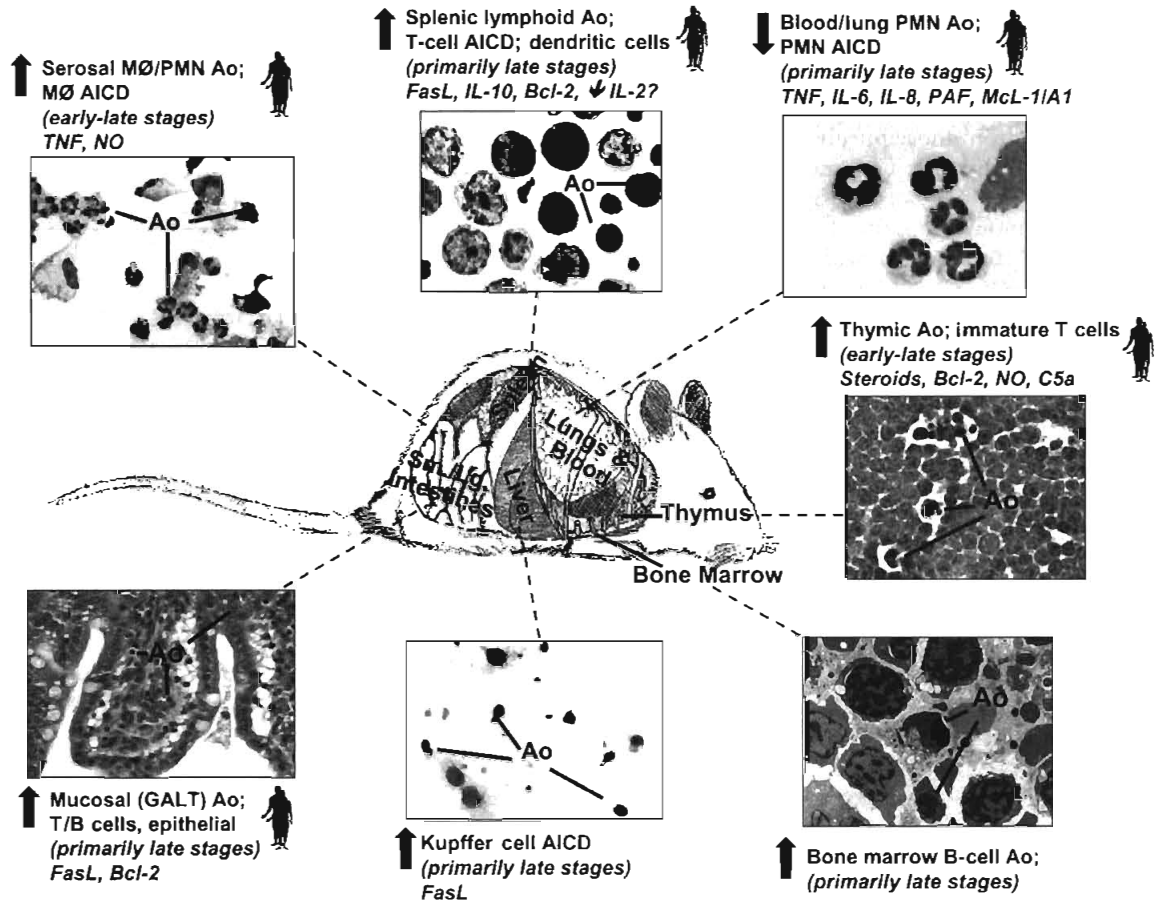

FIGURE 38–2. The frequency of apoptosis (A_o), the immune cell populations affected, the onset or expression of apoptotic changes, and the agents that mediate these cell death effects vary in mice subject to experimental sepsis and in patients (↕) with multiple organ failure due to trauma or sepsis. General increases (↑) or decreases (↓) in apoptosis in the septic mouse model are indicated either for in vivo or ex vivo cells or tissues or for activation-induced cell death (AICD) seen in vitro for a given cell population. (↕) indicates that a comparable observation has been made in humans. The stage (time period) during experimental sepsis when such apoptotic changes typically become evident is italicized in parentheses, and the mediators reported to affect apoptosis are listed last in italics. GALT, gut-associated lymphoid tissue; IL, interleukin; MØ, macrophage; NO, nitric oxide; PAF, platelet-activating factor; PMN, polymorphonuclear leukocyte; TNF, tumor necrosis factor.

of sepsis.[18] In each situation, tissue or organ damage was significantly reduced, and survival was improved.

It has been established that once PMNs are released into circulation, their apoptotic program has already been activated, and the typical half-life of an unstimulated PMN is 6 to 12 hours.[19] Because clearance of PMNs would limit the damage they could induce, it is not unexpected that peripheral blood as well as bronchoalveolar lavage PMN apoptosis is dysregulated in patients with systemic inflammatory response syndrome, acute respiratory distress syndrome, sepsis, trauma, and severe burns (Fig. 38-2).[20-25] It is also of interest to note that PMN apoptosis can be suppressed by surgery alone (elective, non–trauma related) at time points (<24 hours) that preclude the possible development of the clinical situations listed.[26]

REGULATION BY INFLAMMATORY MEDIATORS

PMNs recruited to sites of inflammation are exposed to factors that can influence apoptosis, such as bacterial products, lipids, cytokines, and changes in oxygen tension.[27] Elevated levels of cytokines such as granulocyte colony-stimulating factor (G-CSF), GM-CSF, IL-1, IL-6, IL-8, and TNF are often found in peritoneal fluid, bronchoalveolar lavage, and serum of trauma patients or experimental animals,[17,18,25,26,28-31] and each has been found, in vitro, to suppress apoptosis of PMNs from healthy volunteers.[19,25,32-34] Additionally, transmigration, bacterial products (e.g., LPS), and hypoxia have been found to suppress PMN apoptosis in vitro.[32,35,36] Similarly, when PMNs from healthy volunteers are incubated in bronchoalveloar lavage or serum from patients with burns,[23] acute respiratory distress syndrome,[29,37] or sepsis,[24] a significant reduction in apoptosis is observed. Although endothelial cells or macrophages are thought to produce a majority of these cytokines, PMNs have the ability to suppress their own apoptosis in an autocrine or paracrine manner through the production and secretion of antiapoptotic factors.[23,33,38-41]

EXTRACELLULAR MILIEU

Although the studies mentioned earlier demonstrate that inhibition of PMNs or their recruitment significantly improves the outcome of a septic insult, PMN apoptosis was not examined. In vitro experiments indicate that blood PMNs that were stimulated with various inflammatory stimuli, were subjected to in vitro migration, were exposed to various adhesins, or ingested microbes exhibit differences in

the rate at which they undergo apoptosis.[32,35,42] Therefore, PMNs in inflammatory sites would be expected to differ from those seen in the blood. This was observed in patient studies in which the PMNs isolated from the lung had different characteristics from those purified from the blood of the same patient.[43,44] Using the CLP model of sepsis, Ayala and colleagues assessed the extent of apoptosis in phagocytes expressing Gr1 (the mouse granulocyte marker) from three separate tissue sites.[45] In agreement with findings in patients, decreased apoptosis was seen in CLP mouse blood PMNs, while no change in the percentage of apoptosis was detected in the myelopoietic compartment of the bone marrow.[46] However, an increase in the percentage of $Gr1^+$ cells undergoing apoptosis was evident in cells taken from the peritoneum of the CLP mice, and the extent of apoptosis in these cells appears to be regulated by TNF.[45] Whether other death receptor or non–death receptor pathways are also involved in regulating apoptosis at this or other sites of PMN accumulation in traumatized or septic animals is unknown.

ROLE OF Bcl-2 FAMILY MEMBERS

The mechanism by which inflammatory agents suppress PMN apoptosis remains an active area of study, but numerous agents have been found that regulate members of the Bcl-2 family, which can inhibit spontaneous (mitochondrial-driven) and induced (Fas- or TNF-R–driven) apoptosis (Table 38-1). PMNs, unlike lymphoid cells, do not express Bcl-2 but do express other members of this family, such as Bcl-w, Mcl-1, Bak, Bcl-X_L, and A1,[42,44,47-51] and changes in their expression in response to stimulation are specific for the agent used. Studies by Leuenroth and associates indicate that in the hypoxic environments (mimicked in vitro) encountered in hemorrhaged animals or trauma patients, the suppression of apoptosis, at least in human PMNs, is regulated by the induction of Mcl-1.[42] Mcl-1 is also up-regulated upon stimulation with G-CSF, GM-CSF, IL-1ß, TNF, and LPS,[48,49] while these same agents have no effect on Bcl-X expression.[48] Chuang and coworkers demonstrated that messenger RNA for A1 was increased in response to G-CSF, GM-CSF, and LPS, but not IL-1ß or TNF.[49] And finally, Bax expression was down-regulated by G-CSF and GM-CSF, but not IL-8, LPS, or TNF.[44,51] Although patient data are limited, Dibbert and colleagues reported that PMNs isolated from patients with inflammatory diseases express reduced amounts of Bax, suggesting that changes observed in vitro mimic those that occur in vivo.[44] The majority of studies have concentrated on the Bcl-2 family members; changes in other pro- or antiapoptotic proteins, such as the inhibitor of apoptosis proteins (IAPs), that affect granulocyte cell death remain an area of active research.[52]

TABLE 38–1. POLYMORPHONUCLEAR LEUKOCYTE APOPTOSIS—MEDIATORS AND THE Bcl-2 FAMILY OF PROTEINS

Mediator	Mcl-1	A1	Bcl-X	Bax
G-CSF	↑	↑	↔	↓
GM-CSF	↑	↑	↔	↓
IL-1β	↑	↔	↔	nd
IL-8	↑	nd	nd	↔
TNF	↑	↔	↔	↔
LPS	↑	↑	↔	↔
Hypoxia	↑	nd	nd	nd

Arrows indicate the ability of each mediator to alter the expression of the Bcl-2 family members listed: ↑, increased expression; ↓, decreased expression; ↔, no effect.
G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; LPS, lipopolysaccharide; nd, no data (the proteins were not examined); TNF, tumor necrosis factor.

LYMPHOCYTE APOPTOSIS

IMMUNOSUPPRESSION

Although PMNs make up a large part of the innate immune system, lymphocytes (B and T cells) are the primary players in the adaptive immune response to an inflammatory challenge. This adaptive immune response involves the rapid expansion of these cells in response to cytokine and antigen stimulation. Apoptosis was initially proposed as a mechanism whereby autoreactive lymphocytes could be removed (deselected) or as a process by which the extent of immune cell activation could be contained (resolved).[1,53] However, it is apparent that this same process can contribute to the pathophysiology of disease states such as human immunodeficiency virus (HIV) immune depression, cancer, autoimmune disorders, neurodegenerative diseases, inflammatory bowel disease, and ischemic injury.[1,5,53]

Lymphocyte apoptosis is a major concern in the ICU, because many critically ill patients exhibit immunosuppression as a result of lymphocyte apoptosis from several compartments (see Fig. 38-2). Circulating lymphocytes from patients suffering from severe burns,[54,55] blunt trauma,[55] and sepsis,[56] as well as from those who have undergone major elective surgery (nonseptic),[56,57] exhibit significantly more apoptosis (approximately 20% to 60% apoptotic) than do peripheral lymphocytes from healthy donors. Hotchkiss and colleagues detected lymphocyte apoptosis in the spleen and gut of trauma and shock patients,[58-60] and Middleton and associates found a significant amount of thymocyte apoptosis in patients who died more than 3 hours after an initial trauma.[61] The loss of lymphocytes from all three compartments is thought to be directly associated with the decreased number of lymphocytes in the circulation. Unfortunately, this immunosuppression leaves patients vulnerable to infection or unable to fight existing sepsis and may result in organ failure. Until recently, the contribution of the process of apoptosis to the pathophysiology of multiple organ dysfunction in critically ill patients had not been examined.[19] As with human lymphocytes, lymphocytes from rodents subjected to burn injury[62] and sepsis (CLP)[63,64] also exhibit pronounced immunosuppression, accompanied by increased lymphocyte apoptosis. This is the model of sepsis that has provided most of our current knowledge about the role of apoptosis in the critically ill (see Fig. 38-2).

THYMOCYTE APOPTOSIS

The initial experimental studies of trauma- and sepsis-induced changes in lymphoid apoptosis focused on the thymus because it is readily accessible and highly susceptible to stress-induced apoptosis. Studies involving various trauma, burn, sepsis, and shock models all consistently reported that thymic apoptosis increases in these settings (see Fig. 38-2).[46,65-68] In the CLP model of sepsis and in burn injury, it was observed that a rise in thymic apoptosis could be detected as early as 4 hours after injury and increased through 24 hours.[46,66] This increased apoptosis in the mouse

TABLE 38–2. AGENTS INVOLVED IN LYMPHOCYTE APOPTOSIS

	Agents
Thymocyte apoptosis	
Mediators	Glucocorticoids (+), NO (+), C5a (+), TNF (↔), endotoxin (↔), Fas/FasL (↔), IL-10 (–)
Protein expression after injury	Bcl-X_L (↓), Bcl-2 (↓)
Splenocyte apoptosis—mediators	TGF-β (+), IL-10 (+), Fas/FasL (+)
GALT—mediators	Fas/FasL (+), endotoxin (↔)

+, ability to promote lymphocyte apoptosis; –, ability to suppress lymphocyte apoptosis; ↔, no effect on lymphocyte apoptosis; ↓, decreased protein expression.
GALT, gut-associated lymphoid tissue; IL, interleukin; NO, nitric oxide; TGF, transforming growth factor; TNF, tumor necrosis factor.

thymus appears to be primarily a response to glucocorticoids, and possibly nitric oxide (NO), rather than to endotoxin or death receptors such as Fas and TNF-R. Treatment with mifepristone, a glucocorticoid receptor antagonist, but not the neutralizing Fas-fusion protein, blocked thymic apoptosis (Table 38-2).[46,66] Support for a putative role of NO in thymic apoptosis comes from in vitro data in which thymocytes cultured with LPS-activated endothelial cells, which produce NO, or with NO donors exhibited increased apoptosis.[69] Another putative mediator of thymocyte apoptosis, either directly or indirectly, is the complement anaphylatoxin C5a; blocking its activity with anti-C5a therapy inhibited thymic apoptosis after CLP in rats.[67] Additionally, because cytokines play a prominent role in lymphocyte activation and apoptosis, Oberholzer and coworkers were able to inhibit thymocyte apoptosis during sepsis by using targeted expression of IL-10, resulting in reduced blood bacteremia and improved mortality.[70] This is of interest because IL-10 is generally regarded as an anti-inflammatory cytokine, and it has been found to have a proapoptotic effect on the circulating lymphocytes of trauma patients.[57]

SPLENOCYTE APOPTOSIS

In addition to thymic apoptosis, apoptosis in the spleen has been documented after burn injury and trauma and in cases of sepsis (see Fig. 38-2).[58,65,71-73] Just as the degree of lymphocyte apoptosis correlates with disease severity in patients, splenic apoptosis is correlated with the severity of burns; no apoptosis could be detected in the spleens of mice subjected to burns covering 18% of their total body surface area,[68] but it could be detected in mice subjected to burns covering 25% and 40%, with the level of apoptosis higher in the 40% group.[71] Similarly, Guan and associates demonstrated that in rats subjected to multitrauma events (hemorrhage ± multiple fractures), apoptosis rates were directly correlated with trauma severity.[65] Studies by Hiramatsu and Hotchkiss and their colleagues showed evidence of increased splenic lymphocyte apoptosis in septic mice, associated with increased mortality.[72,73] Histologic analysis of spleens from septic human patients, but not from nonseptic patients, demonstrated that apoptosis in the spleen involves primarily B cells and $CD4^+$ T cells.[58] Interestingly, in Rag-1 mice, which are deficient in B and T cells, apoptosis was still detected in thymic and splenic cell populations.[73] In vitro experiments to determine whether the increased lymphoid apoptosis in these tissues is associated with immune hyporesponsiveness indicated that mitogenic stimulation of splenocytes isolated from mice 24 hours after CLP causes a significant increase in the rate of activation-induced cell death (AICD).[64] This increase in AICD also appears to be restricted to T cells of the helper ($CD4^+$) lineage.[64]

APOPTOSIS IN THE GUT

A number of other lymphoid tissues also appear to actively undergo increased apoptosis following the onset of sepsis or shock (see Fig. 38-2). However, unlike in the thymus, where apoptosis is evident as early as 4 hours after CLP, apoptosis in other tissues typically does not appear until later (>12 hours). Mixed bone marrow cells showed an increase in apoptosis at 24 hours, but not at 4 hours, following CLP.[46] Although phenotypic and morphologic assessment indicated that most of the increase in apoptosis in the thymus was in the immature T-cell population ($CD4^+CD8^+$ and $CD8^-D4^-$ cells), the increase in bone marrow cell apoptosis was associated with only the B-lymphocyte population. Gut-associated lymphoid tissues, such as Peyer's patches, also exhibit increased apoptosis in response to polymicrobial sepsis.[72,74] As with the bone marrow, these changes were restricted to the B-cell population, which exhibited an increase of Fas antigen expression; this therefore appears to be an example of AICD in sepsis.[1] Chung and coworkers reported similar findings following traumatic shock.[46] The functional aspect of this increased in vivo apoptosis appears to be related to the endogenous stimulation of immunoglobulin A production by B lymphocytes and increased nuclear c-Rel expression.[75]

These findings are not restricted to the Peyer's patches; similar findings have been observed in the B-lymphocyte subset of the lamina propria (see Fig. 38-2).[46] Assessment of lamina propria mononuclear cell (LPMC) preparations from septic mice indicates that there are increases in the percentage of apoptosis in $CD4^+$ and $CD8^+$ cells, as well as macrophages, at both 4 hours (except for $CD4^+$) and 24 hours.[46] This is associated with a significant increase in the mixed LPMC IL-2, -10, and -15 gene expression observed at 24 hours, but not at 4 hours, after CLP. These findings correlate well with the in situ observations by Hiramatsu and colleagues, who reported evidence of increased apoptosis in Peyer's patches and in lymphoid cells lining the small and large intestines in mice 24 hours after CLP.[72] Hotchkiss and coworkers also documented that increased intestinal lymphoid apoptosis is a common finding in patients undergoing surgery after major trauma.[59] Intriguingly, it has been reported that the phenotypically distinct intestinal intraepithelial lymphocyte population also exhibits changes associated with increased apoptosis.[46] This appears to be a FasL-Fas antigen-mediated process independent of endotoxin sensitivity and may be a reflection of localized immune cell activation in response to sepsis (see Table 38-2).

CYTOKINES

One of the common effects of burn, trauma, and sepsis in both patients and animal models is a significant change in the expression of a number of pro- and anti-inflammatory cytokines, including TNF, IL-1, IL-4, IL-6, IL-10, IL-12, and IFN-γ.[76-79] The plasma concentration of several of these cytokines has been correlated with disease severity and levels of lymphocyte apoptosis in both patients and experimental animals.[57,76,77,80] Two cytokines that are prominent in burn

injury, trauma, and sepsis are TNF and IL-1β, and modulation of their activity in animal models led to several clinical trials, but without success.

One cytokine that has been shown to have a direct effect on lymphocyte apoptosis is transforming growth factor beta, which induces lymphocyte apoptosis and is expressed at high levels that correlate with increased splenic lymphocyte apoptosis after burn injury.[71] In contrast, the roles of the other cytokines in lymphocyte apoptosis are vague but nevertheless important to survival. Because the balance between pro- and anti-inflammatory cytokines is crucial to survival, the importance of IL-10 and IL-13 as regulatory molecules has been demonstrated. Through the use of neutralizing antibodies, IL-13 has been shown to have a protective effect on organ damage (i.e., liver, lung, kidney) and ultimately on survival, primarily by limiting the expression of cytokines such as TNF, MIP-2, and keratinocyte-derived cytokine (KC).[81] Similarly, Hasko and associates showed that mice deficient in IL-10 (IL10–/–) had higher levels of TNF, IL-1β, IL-2, IL-6, IL-12, and IFN-γ than did wild-type controls during sepsis, and that this deficiency resulted in increased apoptosis in the thymus.[82] In support of this, Ayala and coworkers demonstrated that splenocytes isolated from septic IL10–/– mice or wild-type splenocytes cultured with antibodies to IL-10 had reduced AICD.[64] The proapoptotic effect of IL-10 on increased AICD in the circulating lymphocytes of surgical trauma patients has also been reported.[57] Finally, O'Sullivan and colleagues found that patients and mice with trauma or burn injuries had suppressed IL-12 levels, and mice receiving IL-12 had decreased mortality after CLP.[78] Taken together, these data implicate several pro- and anti-inflammatory cytokines present in the critically ill that can directly or indirectly affect the apoptotic changes in immune cells.

MONOCYTE-MACROPHAGE AND DENDRITIC CELL APOPTOSIS

Regarding macrophages, the majority of work has assessed the in vitro response to stimuli such as LPS, TNF, IL-1, IL-10, IFN-γ, FasL, and NO.[83,84] As with the other immune cells mentioned earlier, the response of macrophages to apoptotic stimuli also appears to be time dependent.[84] Although most of the components of the FasL-Fas and TNF pathways are evident, it is less clear whether a comparable series of anti-apoptotic gene products is present. The macrophage response to polymicrobial sepsis appears to be tissue specific. Evidence of ex vivo apoptosis can be seen in peritoneal (serosal) macrophages isolated as early as 4 hours after CLP, and it increases over time; however, a small but significant decrease in the basal apoptosis frequency is evident in liver macrophages.[85] Interestingly, if they are subsequently challenged in vitro with an inflammatory stimulus such as LPS, both these macrophage populations become considerably more apoptotic than do comparative sham-CLP animal cells.[85,86] This is associated with a functional disability in their capacity to release proinflammatory cytokines, such as IL-1 and IL-6, and with decreased caspase-1 but increased caspase-3, -8, and -9 activity.[84] The role of FasL-Fas signaling in these changes also appears to be tissue specific. In peritoneal macrophages, apoptosis and cytokine release do not appear to be affected by FasL-Fas activation, but in liver macrophages, changes are seen.[87] To the extent that such changes in macrophage apoptosis and function may be just an aberration seen in mice, it is worth noting that Williams and coworkers reported similar observations in circulating monocytes derived from the blood of septic patients.[88] Finally, Hotchkiss and associates found that dendritic cells in patients who succumbed to sepsis also appear to exhibit increased evidence of apoptosis[89]; however, the mechanisms responsible for this are not clear. Studies examining dendritic cell apoptosis suggest that although they contribute to the fratricide of other cells, they may not be affected by FasL-Fas signaling themselves.[90] This remains to be determined in sepsis.

EFFECTS OF APOPTOTIC CELLS

Although we have discussed the potential direct pathologic effects of the apoptotic process on various cell lineages of the immune system, it is important to appreciate that the interaction with and clearance of apoptotic cells can have a significant effect on the host's immune response. The process of apoptotic cell clearance is primarily, but not exclusively, regulated by macrophages.[91] This process is mediated by the recognition of a variety of ligands expressed on apoptotic cells by receptors, primarily on macrophages, used to mediate the apoptotic cells' removal (Fig. 38-3). Through a pinocytotic mechanism, fibroblasts and epithelial cells may also contribute to apoptotic cell clearance.[92] The interaction of macrophages with apoptotic cells induces the expression of an anti-inflammatory phenotype in the macrophages. Until recently, there were few supportive data, but one could speculate that this might contribute to the anergy seen in macrophages isolated from septic mice or patients.[93] In this respect, Hotchkiss and colleagues recently showed that the administration or adoptive transfer of apoptotic lymphocytes derived from septic mice could suppress T helper 1 cytokine responsiveness while preserving the T helper 2 anti-inflammatory response associated with the immune-suppressive phenotype seen in experimental sepsis.[94]

Alternatively, the documented inability of monocytes or macrophages from septic, shocked, or traumatized animals to phagocytize materials at normal levels may contribute to the inadvertent accumulation of apoptotic cells in various hematopoietic, lymphatic, and immune tissues (see Fig. 38-3). In turn, the inability to appropriately clear these dying cells may allow them to progress to a state of secondary necrosis, producing localized bystander injury in the tissue. Such a scenario has been suggested by Vandivier and coworkers as a possible mechanism for tissue inflammation and the enhanced susceptibility to infection seen in cystic fibrosis patients.[95,96] It remains to be determined whether such defects in the macrophage-mediated clearance of apoptotic cells contribute to the changes seen in septic mice.

ANTIAPOPTOSIS THERAPIES

The importance of lymphocyte apoptosis in the development of multiple organ failure and subsequent death has been clearly demonstrated by the use of therapies to block the process at several steps in the apoptosis pathway. Starting at the cell surface, Chung and associates demonstrated that the use of Fas-fusion protein, which blocks FasL binding to cell surface Fas, preserves organ function and blood flow in mice subjected to CLP and reduces septic mortality (Fig. 38-4).[97] Hotchkiss and colleagues used several methodologies to inhibit apoptosis after CLP to assess its importance

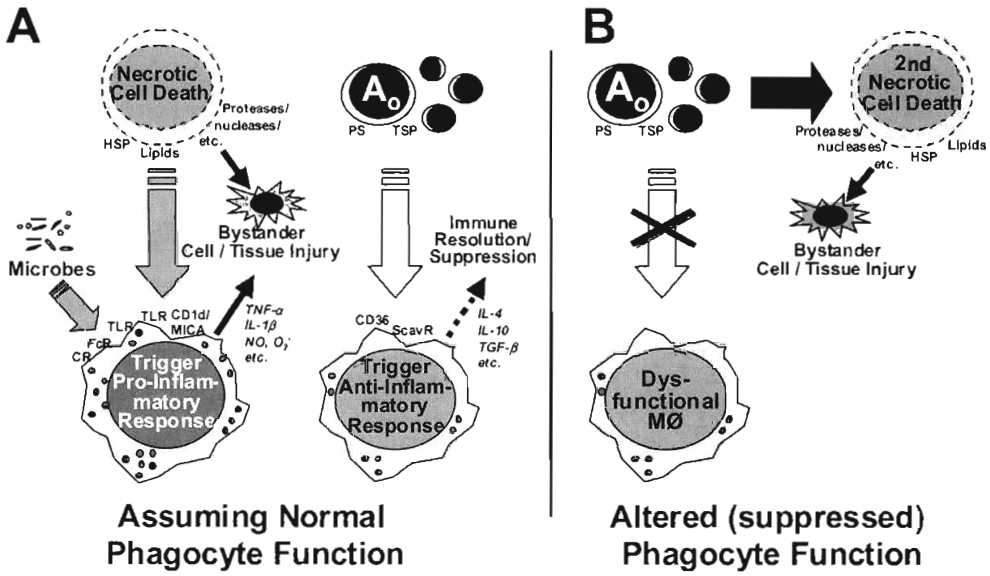

FIGURE 38–3. *A*, Depiction of the clearance of necrotic and apoptotic cell materials, as well as the effect of this process on the macrophage phenotype (proinflammatory versus anti-inflammatory), when phagocytic function is normal. *B*, The scheme in which phagocytic function is compromised, blocking apoptotic cell clearance and subsequently allowing apoptotic cells to move into secondary necrosis; this, in turn, produces bystander tissue injury. CD1d/MICA, nonvariant major histocompatibility class 1–like antigen family; CD36, cell differentiation antigen 36; CR, complement receptor; FcR, immunoglobulin constant region receptor; HSP, heat shock protein; IL, interleukin; MØ, macrophage; NO, nitric oxide; PS, phosphatidylserine; ScavR, scavenger receptor that binds PS; TGF, transforming growth factor; TLR, Toll-like receptor; TNF, tumor necrosis factor; TSP, thrombospondin.

in the pathology of sepsis (see Fig. 38-4).[98,99] Because caspase activity, particularly caspase-3, is crucial to all forms of apoptosis, they were able to use several pharmacologic caspase inhibitors to block lymphocyte apoptosis, which resulted in decreased apoptosis and increased survival. Similarly, sepsis did not induce lymphocyte apoptosis in caspase-3 –/– mice when compared with their background controls.[98] Finally, similar to the regulation of apoptosis in PMNs, expression of members of the Bcl-2 family of proteins has been found to be altered in lymphocytes either stimulated in vitro or isolated from animals subjected to trauma or sepsis (see Table 38-2). Lee and coworkers demonstrated that CD40 can inhibit Fas-mediated apoptosis in a B-cell lymphoma cell line through the induction of Bcl-X and A1.[100] Thymocytes isolated from protein kinase B transgenic mice were found to have resistance to a variety of apoptotic stimuli, and this correlated with elevated levels of Bcl-X_L.[101] Bcl-X_L was found to be significantly reduced in thymocytes after CLP,[67,102] and thymic apoptosis in response to sepsis was associated with decreased Bcl-2[102]; therapies that blocked apoptosis and improved survival either restored or increased Bcl-2 expression.[70,102] In light of this, it is no surprise that mice overexpressing Bcl-2 in T cells had improved survival in sepsis, which correlated with a lack of lymphocyte apoptosis in both the thymus and the spleen (see Fig. 38-4).[103]

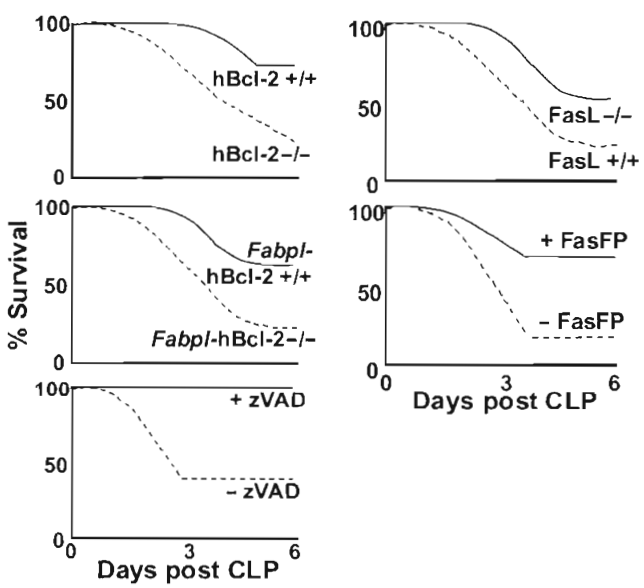

FIGURE 38–4. Results of survival studies illustrating the efficacy of directly inhibiting aspects of apoptosis in sepsis using the transgenic overexpression of the human Bcl-2 gene (under either a lymphoid restricted promoter [hBcl-2] or an intestinal epithelial cell restricted promoter [fabpl-hBcl-2]), pan-specific caspase inhibition (zVAD),[98] and death receptor inhibition in animals deficient in FasL (FasL–/–)[46] or administered Fas-fusion protein (FasFP) 12 hours after cecal ligation and puncture (CLP).

NON–IMMUNE CELL APOPTOSIS

At this point, it should be clear that a significant amount of experimental as well as clinical evidence exists for the presence of marked apoptotic changes and potential pathologic sequelae in both animals and patients with sepsis and multiple organ failure syndrome. Surprisingly, demonstration of apoptosis in nonimmune tissues and cells has been substantially more difficult in the clinical setting.

For example, although apoptosis in the vascular endothelium has been proffered as an explanation for the frequently observed loss of hemodynamic responsiveness in critically ill patients and certain septic animal models, there is a paucity of direct evidence for such an event.[104] This is due in large part to the difficulty of assessing this process directly in experimental animals, let alone patients. Nonetheless, some indirect evidence of apoptosis-induced shedding of $CD34^+$ cells into the bloodstream of critically ill patients has been

observed by Mutunga and Miniagar and their respective colleagues.[105,106]

Another potentially interesting apoptotic target is the surface of epithelial and mucosal cells. These cells, being at the mucosal interface, turn over via apoptotic processes on a regular basis. However, because mucosal sloughing and gut barrier dysfunction are common aspects of sepsis, trauma, and critical illness, it has been hypothesized that increased apoptotic cell death may contribute in a pathologic fashion to organ dysfunction in the gut[107,108] and in the lungs.[109] Experimental support for a pathologic role of gut epithelial cell apoptosis has been provided by Coopersmith and associates, who showed that septic mortality could be reduced in mice expressing the epithelial cell restricted overexpression of the human Bcl-2 gene (see Fig. 38-4).[107,110] Hotchkiss and colleagues also documented that, along with the predominance of lymphoid apoptosis seen in septic patients succumbing to their illness, there was consistent evidence of intestinal epithelial cell apoptosis; a similar but more transient observation was made in trauma patients undergoing bowel resection.[60] Epithelial cell injury in the lung has also been observed experimentally,[109,111,112] but its clinical contribution to chronic or acute lung injury remains to be clearly established. Further, the degree of interaction between immune cell subpopulations undergoing apoptosis and the extent of changes in epithelial cell apoptosis is unknown at present.

Beyond these observations and the substantial data provided by various experimental situations in vitro or in vivo,[113-120] there is little evidence of changes in the apoptotic process in the liver parenchyma, heart, kidney, or brain in the clinical setting of sepsis or multiple organ failure. This does not mean that apoptosis is not playing a role, but merely that it is not overt, or that the form of cell death induced in these organs, tissues, and cells is not solely apoptotic.

CONCLUSION

Our understanding of the mechanisms by which multicellular organisms regulate cell life and death via apoptosis has grown tremendously over the past few years. It is now clear that septic or traumatized animals and patients exhibit alterations in the apoptosis of cells in both the innate (PMNs) and the adaptive (lymphocytes) arms of the immune system. Even though PMN apoptosis is suppressed under similar conditions in which lymphocytes undergo increased apoptosis, the consequence of each appears to contribute to significant pathologic alterations in host cell function, which is associated with an increase in organ damage and mortality. However, we are just beginning to understand the mechanisms and mediators (e.g., FasL, TNF, IL-8, Bcl-2, Mcl-1, NO, steroids) that regulate these changes. The data clearly show the complexity of the apoptotic response, thus justifying the need to increase our understanding of apoptosis in the critically ill. This will require the use of complex and clinically comparable models of shock, trauma, burn, and sepsis in which the cells of each lineage can be assessed at various sites and times after insult. Such information will provide us with new insight into the pathobiology of the critically ill and may offer better therapeutic targets for the management of these devastating conditions.

ANNOTATED REFERENCES

Ayala A, Xu YX, Ayala CA, et al: Increased mucosal B-lymphocyte apoptosis during polymicrobial sepsis is a Fas ligand but not an endotoxin mediated process. Blood 1998;91:1362-1372.

This prospective animal modeling study illustrates that gut lymphoid apoptosis observed during experimental sepsis may be an effect of extrinsic, death receptor–driven apoptosis as well as intrinsic processes.

Coopersmith CM, Stromberg PE, Dunne WM, et al: Inhibition of intestinal epithelial apoptosis and survival in a murine model of pneumonia-induced sepsis. JAMA 2002;287:1716-1721.

This prospective, randomized experimental animal study demonstrates the contribution of increased intestinal epithelial cell apoptosis to the morbidity and mortality from pneumonia-induced sepsis using gut epithelial cell restricted overexpression of the antiapoptotic gene Bcl-2.

Hotchkiss RS, Chang KC, Grayson MH, et al: Adoptive transfer of apoptotic splenocytes worsens survival, whereas adoptive transfer of necrotic splenocytes improves survival in sepsis. Proc Natl Acad Sci U S A 2003;100:6724-6729.

This study documents a potential link (in the experimental setting of mouse polymicrobial sepsis) between the development or presence of increased lymphocyte apoptosis and the subsequent capacity of these cells (through their phagocytosis or clearance) to induce an immune-suppressive state in mice. The state of immune suppression is a hallmark of morbidity in this system in both the experimental setting and the clinical condition.

Hotchkiss RS, Swanson PE, Freeman BD, et al: Apoptotic cell death in patients with sepsis, shock and multiple organ dysfunction. Crit Care Med 1999;27:1230-1251.

This prospective study of patients dying from sepsis and multiple organ failure demonstrates a strong association between the development of significant lymphocyte and intestinal epithelial cell apoptosis and septic mortality.

Hotchkiss RS, Tinsley KW, Swanson PE, Karl IE: Endothelial cell apoptosis in sepsis. Crit Care Med 2002;30:S225-S228.

This article summarizes the understanding of the apoptotic process in endothelial cells and the difficulties encountered in demonstrating this form of cell death in vivo, both in experimental models of infection, sepsis, and inflammation and in the critically ill.

Hotchkiss RS, Tinsley KW, Swanson PE, et al: Prevention of lymphocyte cell death in sepsis improves survival in mice. Proc Natl Acad Sci U S A 1999;96:14541-14546.

This was one of the first prospective, randomized animal studies to document the potential of an antiapoptotic therapy (caspase inhibition) to block mortality in a model of polymicrobial sepsis.

Jimenez MF, Watson WG, Parodo J, et al: Dysregulated expression of neutrophil apoptosis in the systemic inflammatory response syndrome. Arch Surg 1997;132:1263-1270.

This study was one of the first to demonstrate that peripheral blood neutrophils obtained from septic patients exhibit a substantially depressed ability to undergo spontaneous apoptosis.

Kim Y-M, Kim T-H, Chung H-T, et al: Nitric oxide prevents tumor necrosis factor α–induced rat hepatocyte apoptosis by the interruption of mitochondrial apoptotic signaling through S-nitrosylation of caspase-8. Hepatology 2000;32:770-778.

This is one of several studies from this laboratory that illustrates the capacity of nitric oxide, like several other inflammatory agents present in critically ill patients, to be either antiapoptotic or proapoptotic.

Chapter 39
CELLULAR SIGNALING

Michael B. Fessler • Jerry A. Nick

KEY POINTS

1. **Intracellular signal transduction** describes mechanisms that allow an individual cell to coordinate responses to extracellular stimuli.
2. Intracellular signaling occurs primarily through **sequential phosphorylation of proteins.**
3. Although highly conserved, **signaling mechanisms are often adapted** for different uses by different cell types.
4. **Central signaling pathways** participate in multiple responses to a variety of receptors and stimuli.
5. Signaling pathways represent **potential targets to modify specific cellular responses.**

Signal transduction refers to sequential molecular interactions triggered within the cell in response to external conditions (e.g., ultraviolet radiation, heat, osmotic stress) or ligands (e.g., bacterial lipopolysaccharides, cytokines) that lead, in turn, to induction of specific cellular responses (e.g., transcription/translation, adhesion, chemotaxis). Intracellular signaling involves precisely timed, compartmentalized, specific, and reversible interactions between proteins and underlies biologic phenomena of health and disease alike, ranging from cellular proliferation to immunity to sepsis. Increasingly, the potential of cellular signaling molecules as diagnostic markers and therapeutic targets is being realized. A basic understanding of the principles of signal transduction and of the important cellular signaling cascades is necessary to evaluate current research in critical care medicine and may be of increasing use to the clinician.

BASIC PRINCIPLES OF SIGNAL TRANSDUCTION

PHOSPHORYLATION CASCADES AND ACTIVATION OF KINASES

Virtually all cellular signaling pathways described to date are regulated by protein phosphorylation. The phosphorylation of a target protein by a protein *kinase*—an enzyme that covalently attaches phosphate to the side chain of either serine, threonine, or tyrosine—can have multiple effects on the protein, including modulation of its enzymatic activity, stability, subcellular localization, and interaction with other proteins. Many signaling pathways involve *cascades* of two or more kinases in series in which an "upstream" kinase is phosphorylated, resulting in activation of the enzyme, with subsequent phosphorylation of a "downstream" kinase, which in turn is activated and able to phosphorylate specific substrates or additional kinases. Rare examples exist of inactivation of a target enzyme by phosphorylation (e.g., phosphorylation of glycogen synthase kinase 3 by protein kinase B).[1]

SIGNAL AMPLIFICATION AND REDUNDANCY

Fundamental principles determining the sensitivity of a signaling pathway to a stimulus are signal *amplification* and *redundancy.* Whereas a single-step phosphorylation pathway would yield an inefficient 1:1 molecular communication between external cellular ligand and cellular effector, multiple-step phosphorylation cascades utilizing kinases of increasing abundance in series permit multiplicative *signal amplification.* In a related fashion, an arrangement involving isolated, parallel signaling pathways with completely distinct stimuli and downstream functions would permit neither flexibility nor responsiveness to combinations of stimuli. This is avoided by the common phenomenon of *signal redundancy:* stimuli may activate more than one cascade, cascades may be activated by multiple different stimuli, and effector kinases may have overlapping substrate specificities.

REGULATION AND SPECIFICITY OF SIGNAL TRANSDUCTION

Many signaling molecules ubiquitous to human cells are co-localized in the cytoplasm and have overlapping or redundant downstream effects. Several sophisticated strategies have been identified that result in the pathway regulation and specificity necessary for effective, stimulus-appropriate signal transduction to occur. Considerable specificity may occur simply through maintenance in the cell of low "copy numbers" of particular kinases and their respective substrates. Because of this, research strategies that use transfection to investigate the functional role of signaling molecules (e.g., overexpression at nonphysiologic levels in cell lines) may unfortunately induce artifactual protein interactions. Larger-scale pathway regulation is made possible by counter-regulatory *phosphatases* and by interpathway signaling *crosstalk.* In addition to the specificity of receptor-ligand docking interactions, specific signaling protein-protein interactions are made possible by *scaffolding/anchoring/adaptor proteins* and by *protein interaction domains.*

PROTEIN INTERACTION DOMAINS

Virtually all signaling proteins described to date are constructed in a modular fashion from a combination of catalytic and interaction domains. Paired interaction domains in different proteins couple them into multi-protein complexes, thereby orchestrating complex signaling events. The extensive list of protein interaction domains described to date can be grouped into separate families characterized by their ligand specificity (Table 39-1). Prototypical examples include SH2 and PTB domains (recognizing phosphotyrosine motifs); 14-3-3, FHA, and WD40 domains (recognizing phosphoserine/threonine motifs); and PH and FYVE domains (recognizing specific phospholipids to allow for membrane targeting). Further layers of complexity are imparted by the preference of certain interaction domains for particular flanking amino acids in the ligand, thereby permitting differential localization of protein isoforms within the cell. The inclusion of multiple interaction domains of varying ligand specificity in a single protein results in extensive combinatorial possibilities, as well as intraprotein interactions through folding.

SCAFFOLD, ANCHORING, AND ADAPTOR PROTEINS

In addition to specific motif recognition of ligands by kinases, specific kinase-substrate interactions are facilitated by co-localization of proteins on scaffold, anchoring, or adaptor proteins at specific subcellular sites. In this manner, efficient kinase-kinase information flow may be facilitated or, alternatively, signaling molecules may be sequestered in a latent state in proximity to their upstream activating receptor. A prototypical example of such a scaffolding protein is that of the JIP proteins, which regulate JNK activation via possessing separate binding sites for both JNK and its upstream kinases, MKK7, MLK3, and HPK1.[2] Furthermore, JIP1/2 can form large cytoplasmic protein complexes through their ability to homo- and hetero-oligomerize and have SH3 and PTB domains, presumably facilitating complex regulatory protein-protein interactions. A second prototypical example of a scaffolding protein is that of the A kinase anchoring proteins (AKAPs), which are thought to co-localize protein kinase A (PKA) in an inactive form with its substrates and regulators at specific subcellular sites, presumably poising PKA to respond to local fluxes in cyclic adenosine monophosphate concentration.[3]

KINASE INACTIVATION BY PHOSPHATASES

The regulatory counterpart to phosphorylation by kinases is dephosphorylation by phosphatases. In addition to signal transduction, numerous cellular processes ranging from metabolism to RNA splicing are regulated by phosphatases.[4]

TABLE 39–1. COMMON PROTEIN INTERACTION DOMAINS AND THEIR ASSOCIATED RECOGNITION MOTIFS

Protein Interaction Domain	Binding Specificity
SH2, PTB	Phosphotyrosine
14-3-3, FHA	Phosphoserine/threonine
PH, FERM, FYVE, C1, C2	Phospholipid
WW, GYF, SH3, EVH1	Proline-rich sequences
EF-hand	Calcium binding

Although it is estimated that greater than 1000 phosphatase genes exist in the human genome, the complex variety of these mediators can be simplified down into three functional families: (1) those targeting phosphoserine and/or threonine residues, (2) those targeting phosphotyrosine residues, and (3) dual-specificity phosphatases targeting phosphotyrosine and/or threonine residues. While some degree of substrate specificity is intrinsic to all phosphatases, an additional layer of specificity is imparted by the combinatorial effects of regulatory molecules included in larger functional phosphatase complexes.

CROSSTALK

Although most signaling pathways were initially conceptualized as completely independent and parallel, it is now evident that signaling often involves a network of more than one pathway. For example, the three MAPK subfamilies can regulate one another both at upstream and downstream levels. Tumor necrosis factor-alpha (TNF-α) activates the guanosine triphosphatase p21rac, in turn activating the MKKK p65PAK, which activates MKK3, 4, 6, and 7, and thereby both the p38 and JNK pathways. Downstream, in the TNF-α–stimulated human neutrophil, p38 regulates the JNK pathway via protein phosphatase-2A.[5] Examples also exist of crosstalk between MAPK and non-MAPK pathways; for example, ERK has been reported to inhibit transforming growth factor-beta (TGF-β) signaling via phosphorylation of Smad2/3, which inhibits its nuclear retention.[6]

PROTOTYPICAL INTRACELLULAR SIGNALING CASCADES

MITOGEN-ACTIVATED PROTEIN KINASES

The MAPK superfamily, which includes the extracellular-regulated kinase 1 and 2 (ERK1/2 or p42/p44), p38, and c-jun NH_2-terminal kinase (JNK) families, is a highly conserved signaling system that regulates biologic functions ranging from embryogenesis to acute hormonal responses. MAPKs are serine/threonine kinases regulating an array of specific substrates (e.g., transcription factors, cytoskeletal proteins, other kinases) and are the final kinase in a three-kinase cascade (Fig. 39-1). Specifically, MAPK activation requires phosphorylation of both a threonine and tyrosine residue by a specific MAPK kinase (MKK), which requires activation by a serine/threonine MAPK kinase kinase (MKKK). This canonical understanding of a three-kinase pathway for the MAPKs has been challenged by reports that p38α can be activated by TAB1, which is not an MKK but rather an adaptor protein.[7] Moreover, new members continue to be added to the MAPK superfamily (e.g., ERK3, ERK5, ERK7), with over 20 MAPK isoforms described to date. For the sake of brevity, only the three classic, well-described MAPK families are discussed. MAPKs are examples of signaling molecules that can phosphorylate substrates within the cytosol but can also enter the nucleus to regulate transcription via activation of transcription factors. MAPKs are of particular interest in defining mechanisms of cellular response in the context of critical care medicine.

p42/44 (ERK 1/2) MAPK

The ERK subfamily has two MAPK isoforms, ERK 1 and 2, and follows the characteristic three-tiered design of the

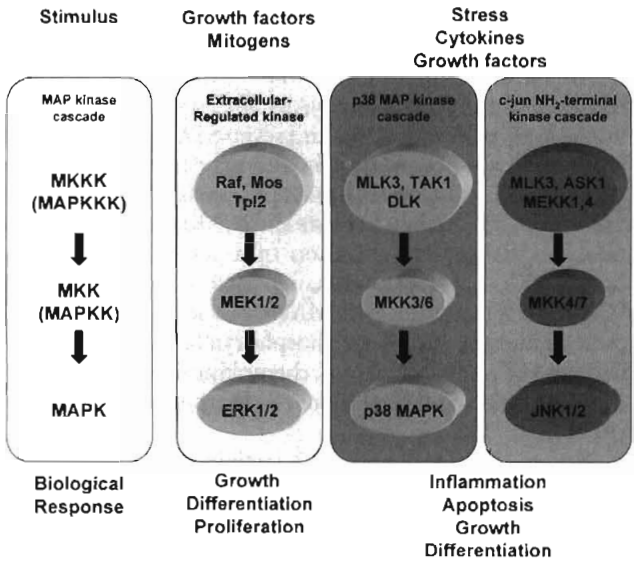

FIGURE 39–1. Mitogen-activated protein kinase (MAPK) cascades. The three major MAPK pathways are parallel signaling cascades, which include a MAPK kinase kinase (MKKK), a MAPK kinase (MKK), and a MAPK. After exposure of the cell to external stimuli, a variety of signaling mechanisms ultimately result in the phosphorylation (and activation) of serine/threonine kinases serving as MKKKs. The activated MKKK, in turn, phosphorylates one or more MKK-family members, which are then capable of phosphorylating both a threonine and tyrosine residue on one or more MAPKs. Once activated, the MAPKs serve as serine/threonine kinases, which phosphorylate an array of specific substrates within the cytosol (e.g., cytoskeletal proteins and other kinases) and nucleus (i.e., transcription factors).

MAPK superfamily, proceeding from raf kinase (MKKK) to MEK1/2 (MKK) to ERK1/2 (MAPK) (see Fig. 39-1). Raf, itself a proto-oncogene, is, in turn, activated at the plasma membrane by the proto-oncogenic G-protein ras. The ERK pathway is activated by several mitogens, including platelet-derived growth factor, epidermal growth factor, angiotensin II, TGF, insulin, and thromboxane A_2, and is generally considered to be a proliferation, transformation, and differentiation pathway. Nevertheless, the ERK1/2 pathway also plays a role in inflammation, because it may be activated in monocytes by both lipopolysaccharide and cellular adherence and is involved in monocytic production of proinflammatory cytokines (e.g., TNF-α).[8] Downstream substrates of ERK1/2 include MNK-1, Elk-1, and SAP-1.

p38 MAPK

The p38 subfamily has five known isoforms: p38α (also known as stress-activated protein kinase 2, or SAPK2), p38β, p38β2, p38δ (SAPK3), and p38γ. Each p38 isoform is characterized to varying extent by differences in tissue localization, preferred upstream activator, and potential substrates. The two major upstream activators of p38 are MKK3 and MKK6, although MKK6 is less abundant in leukocytes. In the neutrophil, MKK3 activates p38α.[9] Several diverse proteins appear capable of acting as MKKKs for the p38 pathway, including TAK1 and ASK-1. The p38 pathway is a major regulator of the inflammatory response, because it is activated by a broad range of proinflammatory stimuli (e.g., tumor necrosis factor, interleukin-1, platelet-activating factor, heat shock) and microbial stimuli (e.g., lipopolysaccharide, peptidoglycan) and plays a central role in many proinflammatory cellular responses[9] (e.g., production of TNF, interleukin [IL]-1, IL-6, and IL-8 by monocytes and neutrophils; oxidative burst, degranulation, chemotaxis, and adhesion in neutrophils; and E-selectin expression in endothelium). Other roles include regulation of T-helper-1 (Th1) differentiation and cytokine production by lymphocytes. Important p38 substrates include the serine kinases MAPK-activated protein kinase-2 (MAPKAP-K2) and MAPKAP-K3, pro-inflammatory transcription factors (e.g., ATF-2, NFκB),[9] phospholipase A_2, MAPK-interacting kinase-1 (MNK-1), myocyte enhancer factor 2, CHOP, SAP-1, and Elk-1. Studies suggest a selective role for p38 MAPK in cellular regulation at both the transcriptional and translational levels.[10]

C-jun NH_2-Terminal Kinase (JNK)

JNK is encoded by three different genes, yielding 10 isoforms with differing tissue expression (e.g., *JNK1* and *JNK2* are ubiquitous, whereas *JNK3* is limited to brain, heart, and testis). JNK is activated by two MKKs—MKK4 and MKK7, which, in turn, can be activated by at least 13 different MKKKs. Most proximally, it is thought that the JNK pathway can also be activated by the rho family small G-protein axis of cdc42/rac/p21-activated kinase. Like p38 MAPK, JNK can be activated by a number of stress-related stimuli (e.g., TNF, IL-1, ultraviolet radiation). Because of only very recent development of a chemical inhibitor for JNK, its role in the inflammatory response remains less clear than that of p38. Nevertheless, studies in a variety of cell types indicate a role in apoptosis,[11] TNF expression,[12] T-cell proliferation and differentiation,[13] and endothelial E-selectin expression.[14] JNK substrates include transcription factors such as ATF-2, Elk-1, and C-jun (a component of the proinflammatory AP-1 transcription complex regulating multiple cytokine genes).

PROTEIN TYROSINE KINASES

Protein tyrosine kinases (PTKs) are classified into two distinct categories: receptor tyrosine kinases and cytoplasmic kinases. The former, typified by such mitogen receptors as the insulin receptor and epidermal growth factor receptor, have autophosphorylating activity, thereby creating recognition motifs on the cytoplasmic domain of the receptor for SH2-containing proteins, such as the adaptor protein GRB2. By contrast, cytoplasmic PTKs, typified by the SRC, JAK, SYK, and ABL families, play an important upstream role in multiple signaling cascades by either phosphorylating receptor endodomains or activating other signaling proteins. For example, SRC has been reported to play a role upstream of raf activation in the ERK1/2 pathway whereas SYK and LYN have been reported in B-cell receptor signaling.

JAK-STAT CASCADES

Chemokines and cytokines are two distinct classes of small (i.e., 8 to 30 kDa) mediators that play a wide spectrum of roles in the activation, maturation, and homing of leukocytes to sites of inflammation. The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway represents one of the initial signaling pathways that mediates the response of cells to cytokines and chemokines (Fig. 39-2). In this pathway, ligand-induced receptor subunit dimerization allows recruitment and activation of tyrosine kinase JAKs, which phosphorylate tyrosine residues on the cytoplasmic domain of the receptor. The phosphorylated receptor subunits

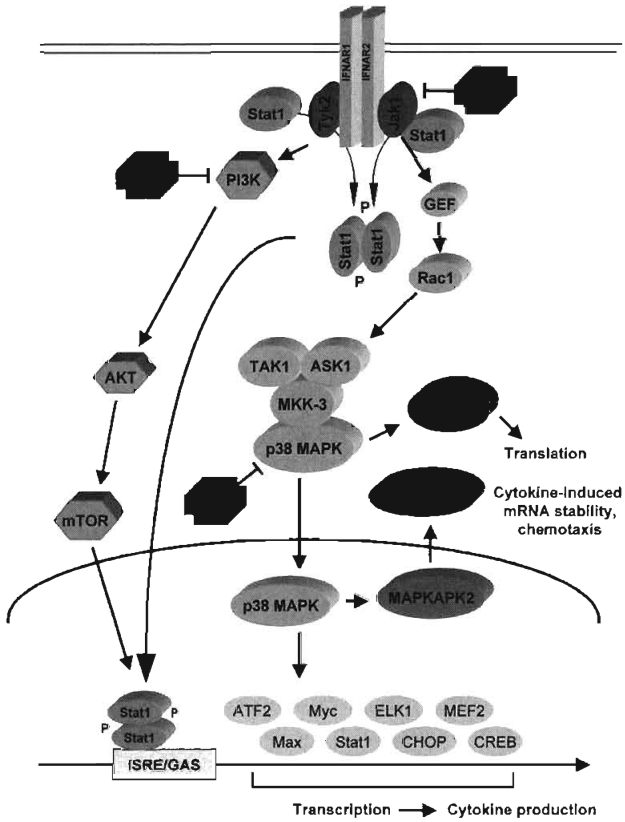

FIGURE 39–2. Potential relationship of major signaling pathways. Signal transduction by interferon-alfa (IFN-α) represents one of the best defined pathways to date and serves well as a backdrop to illustrate the potential regulatory interactions that exist between distinct signaling pathways (e.g., JAK/STAT, MAPK, PI3K, phosphatases) in coordinating the cellular response to an external stimulus. Signaling relationships depicted in this diagram are compiled from studies in a variety of cell types under a broad range of conditions and may well not be applicable to every human cell. Janus-family tyrosine kinase/signal transducer and activator of transcription (JAK/STAT) signaling: IFN-α binds to a type I IFN receptor (composed of subunits IFNAR1 and IFNAR2), which is associated with JAK-family members Tyk-2 and Jak-1. The receptor subunits provide docking sites for specific STATs, which are phosphorylated by JAKs, dissociate from the receptor, form dimers, and then translocate into the nucleus where they modulate transcription by binding to the promoters of cytokine-regulated genes. MAPK signaling: Crosstalk with the MAPK pathways may also occur as JAKs can regulate activation of small G-proteins such as rac1 via activation of guanine exchange factors (GEFs), and rac1, in turn, can activate the p38 MAPK cascade. p38 MAPK phosphorylates cytosolic proteins such as MAPK interacting kinase (MNK1/2) and also translocates to the nucleus, where it enhances cytokine transcription via activation of a broad array of transcription factors, and regulates stability of cytokine mRNAs via phosphorylation of the kinase MAPK activated protein kinase-2 (MAPKAPK-2). Phosphoinositol 3-kinase (PI3K) signaling: Activation of JAKs has also been linked to PI3K activation, which can then serve to activate AKT (protein kinase B). AKT is central to a wide range of signaling pathways, including activation of STATs via mammalian target of rapamycin (mTOR). Regulation by phosphatases: An important mechanism for limiting signal transduction is dephosphorylation (resulting in deactivation) of kinases by phosphatases. Protein tyrosine phosphatases (PTPs) such as SH2-containing phosphatase 1 (SHP1) dephosphorylate JAKs and MAPKs. JAK activates SHP2, which, in turn, dephosphorylates Tyk-2 and Jak-1. Protein serine/threonine phosphatases such as phosphoprotein phosphatase 2A and 2C (PP2A and PP2C) serve to dephosphorylate AKT and p38 MAPK, respectively.

then provide docking sites for specific members of a family of latent cytoplasmic transcription factors termed the *signal transducers and activators of transcription* (STATs) via their SH2 domains. Recruited STATs are activated via tyrosine phosphorylation by JAKs and form homodimers or heterodimers that translocate to the nucleus where they modulate transcription by binding to the promoters of cytokine-regulated genes. Specificity of JAK-STAT signaling is generated by the existence of four JAK and seven STAT isoforms. STAT4 and STAT6 have been described to play an important regulatory role in a murine model of sepsis.[15] Crosstalk with other signaling pathways exists since JAKs can regulate Rac1 phosphorylation via activation of a substrate-protein that functions as a guanine exchange factor for Rac1. In turn, Rac1 can activate the p38 MAPk cascade and the ERK1/2 cascade and the ERKs can phosphorylate and enhance activation of STAT.[16] In addition, chemokine-induced activation of JAKs results in activation of phosphoinositol-3-kinase (PI3K).

Negative regulation of JAK activity occurs in part by dephosphorylation of a critical tyrosine residue by protein tyrosine phosphatases (PTPs) such as SHP-1 and -2, which also bind to receptors via their SH2 domains, or by binding JAKs directly.

CLINICAL SIGNIFICANCE OF SIGNAL TRANSDUCTION

SIGNALING MOLECULES AS POTENTIAL DIAGNOSTIC MARKERS

The number of reports of signaling molecule modification in human disease continues to grow and, with it, the potential for harvesting new diagnostic and prognostic information from patient specimens. For example, in one clinical study, the quantity of p38 MAPK activation in alveolar macrophages proved to be a superior predictor of patients at risk for acute respiratory distress syndrome and for multiple organ dysfunction syndrome compared with a panel of standardized clinical parameters.[17] In inflammatory bowel disease, p38α expression is increased in intestinal lamina propria macrophages and neutrophils.[18] In acute respiratory distress syndrome, increased activation of the downstream proinflammatory transcription factor nuclear factor-kappa B (NF-κB) is detected in alveolar macrophages,[19] whereas decreased NF-κB or Akt activation in peripheral leukocytes predicts improved survival.[20]

SIGNALING PATHWAYS AS THERAPEUTIC TARGETS

Because of the ubiquitous expression of signaling molecules, and the differing role of particular molecules in various tissue types, systemic inhibition of signaling events carries with it the potential for uncertain side effects and even antagonism. For example, whereas endothelial p38 MAPK activation inhibits platelet aggregation by inducing prostacyclin production,[21] platelet p38 activation promotes platelet aggregation.[22] Moreover, specific signaling molecules may function in widely different roles in different cell types (e.g., ERKs regulate proliferation in many cell types but play a role in adhesion in neutrophils). Nevertheless, under certain conditions, specific cell types may be targeted. For example, the IC_{50} of p38-regulated TNF-α release by murine alveolar macrophages is 3 logs greater than that by murine neutrophils.[23]

Despite the aforementioned challenges, multiple chemical inhibitors of different MAPK family members have been

developed in recent years. A MEK1/2 inhibitor has shown promise in pancreatic carcinoma. Inhibitors of p38 MAPK have shown promise in multiple animal models of arthritis, endotoxic shock, pancreatitis, ischemia-reperfusion injury, and acute pulmonary inflammation,[23,24] and clinical trials are underway for the treatment of rheumatoid arthritis and psoriasis. A recently developed JNK inhibitor appeared beneficial in a rat model of arthritis,[25] whereas a dual p38/JNK inhibitor has shown promise in Crohn's disease.[26] Furthermore, recent studies suggest that even *post-injury* treatment with a p38 MAPK inhibitor, as would occur in patient care, is effective in inhibiting ongoing inflammation.[24]

CONCLUSION

Significant progress has been made over the past decade in our understanding of the intracellular events that couple receptor-ligand binding to subsequent inflammatory and immune responses of the cell. Because proinflammatory events regulated by the MAPK, JAK-STAT, and other signaling cascades have been implicated in the pathogenesis of both acute respiratory distress syndrome and multiple organ dysfunction syndrome, it is probable that in upcoming years such signaling mediators will enter common parlance in the intensive care unit as both diagnostic biomarkers and therapeutic targets.

ACKNOWLEDGMENT

This work was supported by grants from the National Institutes of Health (HL068743) and American Heart Association (0275035N).

ANNOTATED REFERENCES

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This encyclopedic reference serves well to illustrate the complexity of interactions between many of the signaling pathways described in this chapter (e.g., MAPKs, JAK/STAT, PI3K) in the context of interferon signaling. The biomedical functional relevance of the pathways is also illustrated.

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In this review, the authors discuss current concepts of the interplay of endothelium and primary immune cells in generating the pathophysiology of sepsis syndrome, as well as of the interdependent role of signaling pathways and the transcription factors they activate.

Chapter 40
RECEPTOR PHYSIOLOGY

Frederick J. Ehlert

KEY POINTS

1. Physiologic receptors can be divided into four families, based on structural and functional properties: nuclear receptors (ligand-activated gene regulatory proteins), ligand-regulated enzymes, ligand-gated ion channels, and G protein–linked receptors.
2. There are five classes within the ligand-regulated enzyme family: receptor tyrosine kinases, which phosphorylate signaling proteins on tyrosine residues; tyrosine kinase–associated receptors, which associate with enzymes having tyrosine kinase activity; receptor tyrosine phosphatases, which cleave phosphotyrosine ester groups on signaling proteins; receptor serine-threonine kinases, which phosphorylate signaling proteins containing serine and threonine residues; and receptor guanylyl cyclases, which catalyze the formation of cyclic guanosine-3′,5′-monophosphate within the cytosol.
3. Hydropathy analysis of the primary sequences reveals at least three families of ligand-gated ion channels: the four transmembrane receptors, which include nicotinic acetylcholine receptors, 5-HT_3 receptors, glycine receptors, and $GABA_A$ receptors; the excitatory amino acid receptors; and the P2X purinergic receptors.
4. The GTPase cycle is set in motion when an agonist activates a G protein–linked receptor.

The idea of a "receptor" was first introduced by Ehrlich and Langley around the turn of the 20th century in an attempt to explain the remarkably selective and potent effects that some natural and synthetic chemicals had on biologic tissues. They argued that pharmacologic agents must interact specifically with macromolecular components in tissue to produce physiologic effects. This idea, of course, is now a readily demonstrable fact. Researchers have identified hundreds of receptors and determined the primary sequence of many of these proteins through gene cloning. The precision of our knowledge about receptors is perhaps most spectacularly illustrated by the nicotinic acetylcholine receptor. Electron micrographic analysis of crystallized nicotinic acetylcholine receptors from *Torpedo* has produced high-resolution pictures showing a channel-like structure with a central pore, presumably representing the microscopic tunnel through which positive cations flow when the receptor binds its neurotransmitter, acetylcholine.[1]

The identification of receptors as the target for many drugs has an important corollary. It implies that drugs do not create new responses in tissues; rather, they start, stop, or modulate natural physiologic functions. For example, synthetic muscarinic agonists are able to elicit contractions of intestinal smooth muscle because they bind with muscarinic receptors and trigger a signaling cascade that results in the mobilization of calcium and the activation of contractile proteins in the muscle. Obviously, this signaling pathway evolved to respond not to synthetic drugs but to the neurotransmitter acetylcholine. The idea that drugs use physiologic mechanisms also applies to responses that are somewhat more complex than the readily quantifiable responses in peripheral tissues. For instance, the sensation of euphoria and well-being produced by opiate drugs, such as morphine and heroin, implies the existence of reward pathways in the brain whose natural function is to provide positive reinforcement to the organism under appropriate conditions.[2]

Within this general context, one can define many classes or types of receptors. There are the so-called physiologic receptors, which mediate the effects of a variety of neurotransmitters, peptide and steroid hormones, biogenic amines, and eicosanoids. In addition, enzymes, transport proteins, and ion channels are important receptors for a variety of drugs that usually, but not always, block the function of these proteins. Finally, the cytoskeleton and DNA itself may constitute the "receptor" for some agents.

This chapter reviews some of the quantitative aspects of drug-receptor interactions and provides a brief survey of the major families of physiologic receptors and their signaling mechanisms.

RELATIONSHIP BETWEEN RECEPTOR OCCUPANCY AND RESPONSE

RECEPTOR THEORY

The binding of a reversible drug to a receptor usually obeys the following scheme:

$$D + R \leftrightarrow DR \qquad \text{[Equation 1]}$$

in which D denotes the drug concentration, R denotes the receptor concentration, and DR denotes the drug-receptor complex. At equilibrium, the relationship between the drug-receptor complex and the drug concentration is:

$$[DR] = \frac{[D] \cdot R_T}{[D] - K_D} \qquad \text{[Equation 2]}$$

in which R_T denotes the total concentration of receptors and K_D denotes the equilibrium dissociation constant of the

drug-receptor complex. The K_D has units of concentration (e.g., molar) and is equivalent to the concentration of drug required for half-maximal receptor occupancy. The K_D is a measure of the observed affinity of a drug for a receptor. The lower the K_D, the higher the affinity. This scheme is usually called the law of mass action. Its consequences adequately reflect the manner in which a variety of drugs bind with receptors under physiologic conditions.

The size of the response elicited by a drug depends on its intrinsic efficacy and the percentage of receptors that it occupies. It is easier to understand the property of intrinsic efficacy if we consider how the drug-receptor complex behaves in the absence of other ligands or endogenous neurotransmitters. In the absence of drugs, most native receptors are silent. An agonist is a drug that binds to the receptor, turns it on, and triggers a response. The property that enables the agonist to turn on the receptor is called *intrinsic efficacy*. An antagonist is a drug that lacks intrinsic efficacy but is capable of binding to the receptor. Such agents have no effect by themselves but are capable of antagonizing the action of an agonist, whether it is an exogenous drug or an endogenous neurotransmitter. The amount of intrinsic efficacy can vary widely among different drugs, and drugs with small or intermediate levels of intrinsic efficacy are called *partial agonists*.

INVERSE AGONISTS

This general framework may not be sufficient to account for the behavior of all receptor systems. For example, the guanosine triphosphatase (GTPase) activity elicited by opiate receptors is already active in the absence of agonists when this function is measured in brain homogenate in a hypotonic buffer.[3] Under these conditions, the addition of agonists causes a further increase in the GTPase activity, whereas antagonists either have no effect or inhibit the ongoing basal GTPase activity. In other words, if the receptor is already turned on in the absence of agonists, some antagonists can actually turn off the receptor. Most of the few native receptors that behave in this fashion have been shown to do so under nonphysiologic conditions. However, some mutated forms of receptors have been shown to be constitutively active.[4]

SPARE RECEPTORS CONCEPT

Figure 40-1 shows the relationship between occupancy and response for a highly efficacious agonist (Fig. 40-1*A*), a less efficacious agonist (Fig. 40-1*B*), and a partial agonist (Fig. 40-1*C*). In Figure 40-1*A*, the concentration-response curve for the agonist lies to the left of the occupancy curve, indicating that it requires only a low level of receptor occupancy to produce a maximal response. This behavior is typical for a highly efficacious agonist. In Figure 40-1*B*, there is closer agreement between the two curves, so that the response is proportional to receptor occupancy. Although this less efficacious agonist is capable of eliciting a maximal response, it can do so only at a much higher level of receptor occupancy compared with the more efficacious agonist shown in Figure 40-1*A*. In Figure 40-1*C*, the agonist has little intrinsic efficacy, so it is incapable of eliciting a maximal response even when the receptors are fully occupied. Consequently, the agonist is designated a partial agonist.

When an agonist is capable of eliciting a maximal response at a submaximal level of receptor occupancy (e.g., Fig. 40-1*A*), the situation is referred to as *spare receptors*. Unfortunately, this term has created considerable confusion in the pharmacologic literature. The term does not imply that some of the receptors are extra or unnecessary; rather, it means that only a small fraction of the total functional receptor population needs to be occupied by the agonist to elicit a maximal response. The presence of spare receptors enhances the potency of the agonist because lower concentrations of the agonist can produce effective responses. The functional activity of the total receptor population can be appreciated by considering what happens when some of the receptors are inactivated. After partial receptor inactivation, the concentration-response curve of a highly efficacious agonist shifts to the right without a decrease in the maximal response. The loss in potency associated with inactivation of some of the receptors illustrates that spare receptors are functional and maintain the sensitivity of the receptor system. Another important point is

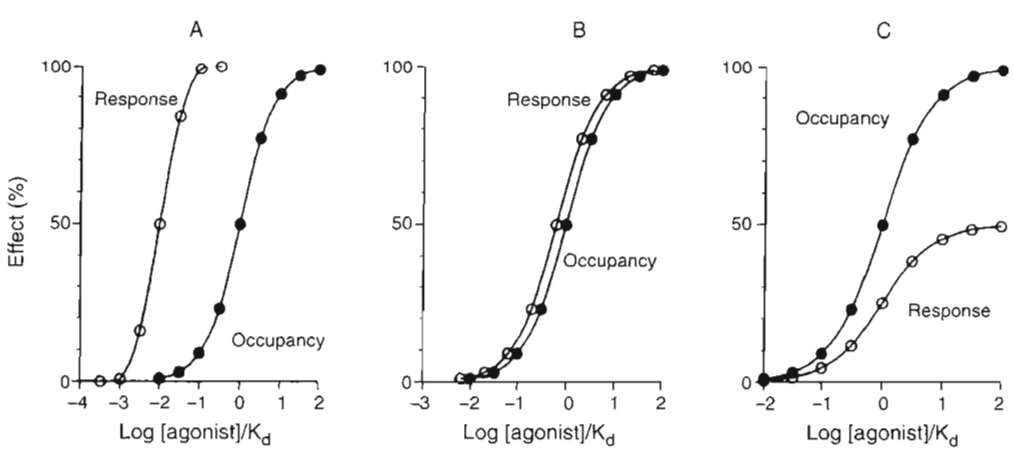

FIGURE 40–1. Relationship between receptor occupancy (●) and response (○) for a highly efficacious agonist *(A)*, a less efficacious agonist *(B)*, and a partial agonist *(C)*. Both occupancy and response are expressed as percentages of their maximum values and are plotted on the ordinate scale. The concentration of the agonist is expressed on the abscissa as a log of the ratio of the agonist concentration divided by the equilibrium dissociation constant of the drug-receptor complex (K_d).

that the presence of spare receptors does not imply that there are excess receptors relative to effectors. In fact, the converse is usually the case. In many signaling cascades, there is divergence along every step in the pathway. That is, one receptor may interact with several effector molecules, and each effector generates several second messenger molecules, and so forth. This divergence leads to amplification and thereby enables a relatively small number of agonist-receptor complexes to generate a significant physiologic response.

ANTAGONIST DISSOCIATION CONSTANT

Because antagonists lack intrinsic efficacy, all that is necessary to describe their interaction with a receptor at equilibrium is the K_D. This parameter can be estimated by measuring an agonist concentration-response curve in the absence and presence of the competitive antagonist. A competitive antagonist will shift the log concentration-response curve of an agonist to the right in a parallel fashion without causing a decrease in the maximal response. The K_D of the antagonist can be estimated from the shift in the dose-response curve using the following equation:

$$CR - 1 = [A]/K_D \qquad \text{[Equation 3]}$$

in which CR (concentration ratio) denotes the EC_{50} value of the agonist (concentration of agonist causing a half-maximal response) in the presence of the antagonist divided by that measured in its absence, and $[A]$ denotes the concentration of the antagonist.

SECONDARY ALLOSTERIC SITES

The relationships described earlier are adequate to account for the interactions of agonists and antagonists with the primary recognition site of a receptor. Some receptors have secondary allosteric sites where drugs can also bind and modify the ability of primary ligands to activate the receptor. One such example is the gamma-aminobutyric acid-A ($GABA_A$) receptor.[5] This receptor is a chloride channel that is regulated by the neurotransmitter GABA. When GABA binds to its site on the $GABA_A$ receptor, it causes the chloride channel to open. In addition to the GABA recognition site, there are other allosteric sites, including one for benzodiazepine-like drugs. A tranquilizing benzodiazepine, such as diazepam, binds to the allosteric site and increases the affinity of GABA for its site on the channel, thereby enhancing the effects of GABA. This allosteric effect can account for the pharmacologic properties of benzodiazepines, which include relief from anxiety, sedation, and protection against seizures. In contrast, some β-carboline derivatives bind to the allosteric site and inhibit the binding of GABA. These compounds have been called *inverse agonists* because they elicit responses that are opposite to those of benzodiazepines (i.e., anxiety, convulsions). However, they are more appropriately referred to as allosteric GABA antagonists because they produce their effects by antagonizing GABA. In addition, there are some compounds that bind to the allosteric site and have no effect on the binding of GABA. These compounds (e.g., Ro 151788) are called benzodiazepine antagonists, and although they have no effects by themselves, they antagonize both the tranquilizing effects of benzodiazepines and the convulsant effects of β-carbolines.

RECEPTOR FAMILIES

Physiologic receptors can be divided into four families, based on structural and functional properties[6]:

1. Nuclear receptors (ligand-activated gene regulatory proteins)
2. Ligand-regulated enzymes
3. Ligand-gated ion channels
4. G protein–linked receptors

Each family has a distinct overall structure and general function that are shared by all its members. Within each family, there is usually, but not always, a considerable amount of sequence homology. Previously, regions of high homology within a given family enabled molecular biologists to use low-stringency hybridization techniques to identify additional members of the same family; today, genome databases can be queried to identify potentially new members. In some instances, the endogenous ligands for the cloned receptor protein have not been identified, leading to their designation as *orphan receptors*. A cursory survey of the four receptor families follows.

NUCLEAR RECEPTORS

The nuclear receptors function as ligand-activated gene regulatory proteins that bind to DNA and regulate the activity of specific genes in a ligand-dependent manner.[7] This family includes receptors for thyroid hormone, retinoids, vitamin D, and the various steroid hormones, including glucocorticoids, mineralocorticoids, androgens, progesterone, and estrogen. Most of these receptors are located in the nucleus. Not surprisingly, the ligands for these receptors can readily penetrate the plasma membrane, and their access to the receptor is controlled by hormone binding proteins and by enzymatic processing of the ligand itself.

Receptors belonging to the nuclear receptor superfamily all share a similar structure having three major domains.[7] Near the center of the sequence is a highly conserved domain of 66 to 68 amino acids that constitutes the DNA binding region of the receptor. In this domain, the sequence forms two loops that are held in place by a zinc atom that interacts with cysteine residues on opposite sides of the loop. Each of the two loops is called a *zinc finger*, and many proteins that bind with DNA have a zinc finger–like structure. The second major domain of this family of receptors is the carboxy-terminal region, which functions as the ligand binding domain. This region of the receptor also shows considerable sequence homology, particularly among the androgen, glucocorticoid, mineralocorticoid, and progesterone receptors, which have structurally similar ligands (i.e., steroids). The third major domain is the amino-terminal region, which shows the greatest variation in size and the least conservation in sequence. This domain of the receptor is thought to mediate transcriptional activation.

A variety of evidence supports the existence of these distinct functional domains on steroid receptors. Perhaps the most dramatic evidence comes from studies of chimeric receptors in which a domain from one receptor is replaced with the corresponding domain from another. For example, when the 66–amino acid DNA binding region of the estrogen receptor is replaced with that of the glucocorticoid receptor, a chimeric receptor is formed that turns on a

glucocorticoid-inducible gene in the presence of estradiol.[8] Truncated receptors have also yielded clues about functional domains, as well as the mechanism of ligand-induced activation. For example, glucocorticoid receptor mutants lacking most of the ligand binding domain demonstrate constitutive activity.[9] That is, the truncated receptor binds to DNA and causes transcriptional activation in the absence of hormone. Apparently, the ligand binding domain of the glucocorticoid receptor normally prevents DNA binding and transcriptional activation, whereas the binding of the hormone relieves this tonic inhibition. Finally, several cases of hormonal resistance have been attributed to point mutations in the ligand binding domain resulting in diminished hormone binding.[7]

Although the details are unclear, the binding of hormone to its receptor triggers the formation of receptor dimers that subsequently bind to DNA.[7] The site on DNA where binding occurs is called the *hormone response element.* These sites are located in the regulatory regions of steroid-induced genes, and several have been identified. The consensus sequences of hormone response elements exhibit dyad symmetry, which is consistent with the idea that a receptor dimer interacts with the hormone response element.

LIGAND-REGULATED ENZYMES

The ligand-regulated enzymes represent a huge family of cell surface receptors. The unifying structural feature of these receptors is the presence of an extracellular ligand binding domain that regulates an intracellular domain that either has intrinsic enzymatic activity or associates with an enzyme. In most instances, the two domains of the receptor are connected by a single transmembrane-spanning region. There are five classes within the ligand-regulated enzyme family:

1. Receptor tyrosine kinases (RTKs), which phosphorylate signaling proteins on tyrosine residues
2. Tyrosine kinase–associated receptors, which associate with enzymes having tyrosine kinase activity
3. Receptor tyrosine phosphatases, which cleave phosphotyrosine ester groups on signaling proteins
4. Receptor serine-threonine kinases, which phosphorylate signaling proteins containing serine and threonine residues
5. Receptor guanylyl cyclases, which catalyze the formation of cyclic guanosine-3′,5′-monophosphate (GMP) within the cytosol

Receptor Tyrosine Kinases

The RTK family includes receptors for numerous growth factors, including insulin, fibroblast growth factor, epidermal growth factor, and platelet-derived growth factor. The structural and functional properties of these receptors have been reviewed.[10,11] As mentioned earlier, members of this family have an extracellular ligand binding domain, an intracellular tyrosine kinase domain, and a transmembrane-spanning domain (Fig. 40-2). Most growth factor receptors are formed from a single polypeptide chain; however, the class II RTKs, which include receptors for insulin and insulin-like growth factor, are heterotetrameric, consisting of two α and two β subunits connected by disulfide bonds (see Fig. 40-2). The two α subunits contribute to the ligand binding domain, whereas the two β subunits traverse the membrane and possess the tyrosine kinase activity. The class I and II RTKs, which include the epidermal growth factor receptor and the insulin receptor, have cysteine-rich regions in their extracellular ligand binding domains. Another class, which includes the fibroblast growth factor receptor, has three immunoglobulin-like domains in the extracellular ligand binding portion of the receptor. The tyrosine kinase domain is the most highly conserved domain among the different classes of RTKs. This domain contains an adenosine triphosphate binding site and a tyrosine acceptor site. In the class III RTKs, these two functional regions of the kinase domain are separated by a hydrophilic, proline-rich sequence of 77 to 107 amino acids. The results of studies of chimeric receptors constructed from heterologous ligand binding and kinase domains provide further support for the existence of autonomous functional domains. In each case, the hybrid receptors displayed the appropriate ligand specificity and kinase activity.

Ligand binding to monomeric RTKs results in dimerization, which is a prerequisite for growth factor–dependent

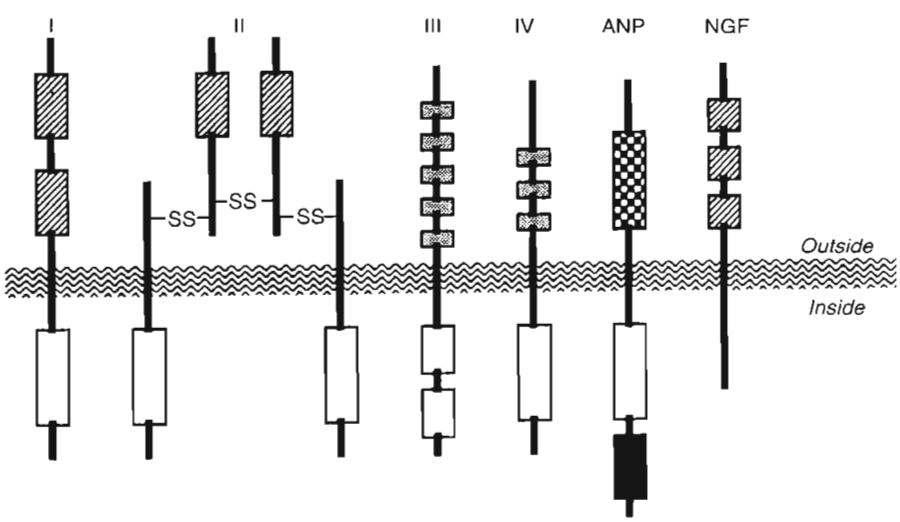

FIGURE 40–2. Structure of different members of the ligand-regulated enzyme superfamily of receptors. The figure shows the transmembrane topography of the primary sequences of the receptor tyrosine kinases (I, II, III, and IV), the receptor for atrial natriuretic peptide (ANP), and the receptor for nerve growth factor (NGF). The boxes indicate the various functional domains of the receptor, which are shaded according to the following scheme: diagonal lines, cysteine-rich domain; shaded, immunoglobulin domain; checkered, ANP binding domain; open, tyrosine kinase domain; and black, guanylyl cyclase domain.

kinase activation. Interestingly, the kinase activity of the tetrameric insulin receptor, which is analogous to an epidermal growth factor receptor dimer, is much greater than that of the dimeric αβ form of the insulin receptor. The results of ligand binding studies have demonstrated that growth factors bind to dimeric receptors with a higher affinity compared with monomers, suggesting that the tighter binding of the growth factor to the dimer provides the drive for receptor aggregation. Once made active by their respective ligands, all growth factor receptors autophosphorylate on several tyrosine residues. This autophosphorylation triggers a complex signaling pathway that is characterized by a series of protein-protein interactions and the phosphorylation of signaling proteins on tyrosine residues. The details of the signaling pathway can vary, depending on the receptor and the cell type.

When a growth factor triggers the autophosphorylation of its receptor, various signaling proteins bind to the receptor and become activated. These signaling proteins typically contain SH-2 domains that have high affinity for specific phosphotyrosine residues on the receptor. Myriad intracellular signaling proteins contain SH-2 domains, and these proteins are thought to mediate the effects of growth factors by binding to specific phosphotyrosine residues on the receptor.[12] These target proteins include the phosphoinositide-specific phospholipase Cγ (PLCγ), GTPase-activating protein, and members of the Src family of tyrosine kinases. In addition, several adapter proteins have been identified that lack enzymatic activity but contain both SH-2 and SH-3 domains. These adapter proteins are thought to bind to phosphotyrosine on the receptor via their SH-2 domains and to other signaling proteins via their SH-3 domains. Examples of adapter proteins are Grb2 and SHC, which enable mSOS to associate with the growth factor–receptor complex. The docking of mSOS to the receptor via adapter proteins enables mSOS to interact with the intracellular guanosine triphosphate (GTP) binding protein, Ras, and cause it to give up its bound guanosine diphosphate (GDP) and take up GTP. Once bound with GTP, Ras initiates a protein kinase signaling cascade that results in the activation of mitogen-activated protein kinase. This kinase triggers a variety of events associated with cellular growth and differentiation. The activity of Ras is inhibited by GTPase activating protein, which increases the intrinsic GTPase activity of Ras, thereby converting it from the active GTP bound form to the inactive GDP bound form.

Receptor Guanylyl Cyclases

Another member of the ligand-regulated enzyme superfamily is the receptor for atrial natriuretic peptide (ANP).[13,14] This receptor contains an extracellular ligand binding domain for ANP, a single transmembrane-spanning domain, and an intracellular domain that has guanylyl cyclase activity (see Fig. 40-2). The binding of ANP to this receptor causes an increase in the concentration of cyclic GMP inside the cell. This second messenger activates a cyclic GMP-dependent protein kinase, which ultimately triggers a variety of responses, including diuresis, natriuresis, and vasorelaxation. Interestingly, the extracellular domain of the ANP receptor is homologous with an ANP binding protein that is thought to have a role in the clearance of ANP from the circulation. The proximal portion of the intracellular domain is homologous to the kinase domain of RTKs, although no ANP-induced kinase activity has been detected. The most distal portion of the intracellular domain represents the catalytic domain, and it is homologous to the soluble form of guanylyl cyclase.

LIGAND-GATED ION CHANNELS

The ligand-gated ion channels represent a large superfamily that includes receptors for acetylcholine (nicotinic acetylcholine receptor), GABA ($GABA_A$ receptor), glycine, and various excitatory amino acids (e.g., glutamate, aspartate).[6] As the name implies, members of this superfamily are ion channels that open up and conduct an ionic current when an agonist binds on them. They share some homology with voltage-gated ion channels. In the case of the nicotinic acetylcholine receptor of the neuromuscular junction and the *Torpedo* electric organ, the ionic current is carried by positive monovalent cations, primarily sodium, whereas neuronal nicotinic receptors carry a rapidly desensitizing current of primarily calcium.[15] In the case of excitatory amino acid receptors, the ionic current is carried by both sodium and calcium, whereas inhibitory amino acid receptors (i.e., GABA and glycine receptors) carry a chloride current. The ligand-gated ion channels have a characteristic oligomeric structure consisting of different proteins (subunits) that come together to form the channel. Molecular cloning has revealed the existence of different structural groups of ligand-gated ions channels that are categorized on the basis of how many times the chain of amino acids composing their subunits crosses the membrane. Thus, hydropathy analysis of the primary sequences reveals at least three families:

1. The four transmembrane (4TM) receptors, which include nicotinic acetylcholine receptors, $5\text{-}HT_3$ receptors, glycine receptors, and $GABA_A$ receptors
2. The excitatory amino acid (3TM) receptors
3. The P2X purinergic (2TM) receptors

The overall structure of the ligand-gated ion channels shows homology with many of the voltage-regulated ion channels, such as the sodium channel and the L-type calcium channel.[6] Although the ligand-gated ion channels are primarily chemosensitive, their gating characteristics are modified by the potential of the membrane. Conversely, although the voltage-gated ion channels are primarily potential sensitive, they are also modified by a variety of agonistic and antagonistic ligands that bind at different sites on the channel and are often allosterically linked to one another. When considered from this viewpoint, the ligand- and voltage-gated ion channels form a large superfamily of receptors.

The 4TM receptors are pentameric complexes composed of at least two α subunits, which have been shown to contain the binding site for the endogenous ligand. These binding sites are thought to exist at the interface between one side of the α subunit and its adjacent subunit. As mentioned at the outset, precise information about nicotinic acetylcholine receptors has been obtained through analysis of its crystal structure. Accordingly, the nicotinic acetylcholine receptor of the neuromuscular junction has a pentameric structure consisting of two α_1 subunits and one β_1, one γ, and one δ subunit. These subunits are arranged like the staves in a barrel-like structure, with a central pore that is thought to be the channel of the receptor.[1] Although the precise subunit structure of neuronal nicotinic receptors and the other ligand-gated ion channels has not been determined unequivocally, it is thought to be analogous to that of the neuromuscular

nicotinic acetylcholine receptor, in that they are both pentameric with two α subunits. An approach that has been useful for drawing inferences about the subunit structure of other members of the 4TM family involves injecting the messenger RNA (mRNA) for different subunits into *Xenopus* oocytes and examining the functional activity of the expressed subunits pharmacologically.[16,17] For example, when an α subunit from the group α_2, α_3, and α_4 is expressed in combination with a β_2 subunit in *Xenopus* oocytes, functional receptors are formed, which presumably have a pentameric structure composed of two α and three β subunits. Similar results are obtained when an α subunit from the same group (i.e., α_2, α_3, or α_4) is expressed in combination with β_4 subunits. Also, α_5 subunit channels are thought to form in combination with α_3 and β_4 subunits. In most instances, the pharmacologic properties of each of the receptors exhibit different profiles from nicotinic agonists as well as some antagonists. It has also been shown that α_7, α_8, and α_9 subunits form functional homomeric channels in *Xenopus* oocytes, presumably consisting of five identical subunits. Moreover, recombinant homomeric $GABA_A$ receptors have been formed by injecting only mRNA for the α subunit into *Xenopus* oocytes, indicating that functional GABA-regulated ion channels can be formed from only α subunits.[18] However, these homomeric channels do not retain all the complex allosteric interactions characteristic of native $GABA_A$ receptors, and it is entirely possible that homomeric channels do not occur naturally. It is thought that the GABA binding sites form at the interface between α and β subunits of $GABA_A$ receptors and that benzodiazepine binding sites occur at the interface between α and γ subunits.[19] Several different subtypes of the individual subunits have been cloned for both the nicotinic and $GABA_A$ receptors, which raises the theoretical possibility of a large number of channel subtypes based on different combinations of the known subunits. However, functional studies in which the different mRNA subunits are expressed in *Xenopus* oocytes suggest a much smaller number of subtypes. These different subtypes of channels have different pharmacologic properties and sometimes unique developmental profiles.

Ligand-gated ion channels are widespread throughout the central and peripheral nervous systems and are responsible for rapid synaptic neurotransmission, characterized by synaptic delays of less than half a millisecond. The nicotinic acetylcholine receptor is present at the neuromuscular junction, where it is responsible for eliciting skeletal muscle contraction in response to impulse flow from motor neurons. These receptors are the targets for the neuromuscular blocking agents used as adjuncts to general anesthesia.[20] The $GABA_A$ receptor represents the major inhibitory neurotransmitter receptor in the brain, and it is an important target for a variety of drugs used to treat anxiety, convulsions, and insomnia.[21] Excitatory amino acid receptors are also abundant in the brain, and inhibitors of these ion channels may have a role in preventing the neuronal damage associated with brain ischemia following stroke.

G PROTEIN–LINKED RECEPTORS

Structure

The G protein–linked family of receptors is the largest, and it includes receptors for light, odorants, and a variety of endogenous neurotransmitters and signaling molecules, including acetylcholine (muscarinic acetylcholine receptor), catecholamines, histamine, serotonin, eicosanoids, lipids, amino acids, proteins, peptides, chemokines, nucleotides, and hormones.[6] These receptors trigger responses by binding with heterotrimeric G proteins, which in turn activate various effectors, including ion channels and enzymes that generate second messengers (see later discussion). Besides being involved in neurotransmission at a variety of synapses and junctions throughout the brain and peripheral autonomic nervous system, members of this family are also involved in the special sensory functions of vision, taste, and olfaction.[22] The light receptor in the retina, rhodopsin, consists of a tightly bound complex between a protein called opsin and a photoactive ligand called 11-*cis*-retinal.[23,24] When light shines on 11-*cis*-retinal, it isomerizes to the *trans* isomer, which induces a conformational change in rhodopsin, causing it to activate a G protein called transducin. Ultimately, transducin initiates a cascade of events leading to a hyperpolarizing response in the retinal ganglion cell. This signaling pathway is so highly amplified that a single photon of light has a 50% probability of triggering a response in the retinal ganglion cell. G protein–linked receptors are also involved in olfaction to a remarkable extent. The results of searches of genomic databases indicate that there may be approximately 400 to 500 types of genes for odorant receptors in the nose, each of which may be receptive to a different spectrum of odorants.[25] These searches also suggest the presence of about 400 nonolfactory G protein–coupled receptors.

Receptors belonging to the G protein–linked class all share a similar structure consisting of seven highly conserved, transmembrane-spanning domains of α helix that are connected to the less conserved amino-terminal, carboxy-terminal, and intra- and extracellular loops. Previously, it had been assumed that the three-dimensional structure of G protein–linked receptors conformed to that of bacteriorhodopsin, which had been determined by x-ray diffraction.[26] More recently, the x-ray structure of bovine rhodopsin was determined.[27] In bovine and bacteriorhodopsin, the transmembrane domains run perpendicular to the plane of the membrane and circumscribe a central pore. Retinal neurotransmitters and the neurotransmitters for muscarinic and catecholamine receptors are thought to bind at a site within the pore. Accordingly, point mutations in a highly conserved aspartic acid residue in the third transmembrane segment cause a loss in agonist binding at muscarinic[28] and beta-adrenergic receptors.[29] Not surprisingly, the part of the receptor involved in G protein coupling is a relatively large, hydrophilic domain that projects into the cytoplasm—namely, the third cytoplasmic (i3) loop. The strongest evidence for the coupling role of the i3 loop comes from studies of chimeric receptors in which the i3 loop of one receptor is replaced with that from another. For example, when the i3 loop of the muscarinic receptor was switched with that of the beta-adrenergic receptor, the chimeric receptor triggered beta-adrenergic effects in response to muscarinic agonists.[30,31] Analogous results have been observed in studies of chimeras constructed from a variety of other G protein–linked receptors. Interestingly, the i3 loops of several receptors are constitutively active by themselves.[32] Thus, the ligand binding domain (seven transmembrane segments) of G protein–linked receptors probably exerts a tonic inhibitory effect on the i3 loop, and the binding of neurotransmitter relieves this inhibition.

G Proteins

The G proteins involved in receptor signaling are heterotrimeric, consisting of α, β, and γ subunits.[33,34] The βγ subunits form a tightly bound complex that functions as a unit. The α subunits of heterotrimeric G protein are close relatives of many other low-molecular-weight G proteins that lack βγ subunits, such as the Ras protein mentioned earlier. These small G proteins participate in numerous metabolic processes within the cell, including some that have little to do with transmembrane signaling at the cell surface. The basic function that G proteins accomplish at the expense of GTP hydrolysis is transportation between two destinations. In the case of the low-molecular-weight G protein elongation factor Tu, there is a transport of transfer RNA complexes on the ribosome, whereas in the case of heterotrimeric G proteins, the G protein shuttles between the receptor and its effector. Thus, nature uses G proteins for a variety of roles, and the involvement of heterotrimeric G proteins in receptor signaling at the cell membrane probably represents a highly specialized function.

The α subunit of heterotrimeric G proteins shows the greatest diversity, and more than 20 different types of α subunits have been cloned.[22] By contrast, the βγ subunits seem to have fewer subtypes, and it appears that more than one type of α subunit can associate with the same dimer of βγ subunits. The α subunit confers selectivity for different receptors as well as effectors; however, the degree of selectivity is not absolute (see later discussion). For example, the M_2 subtype of the muscarinic receptor can interact with more than one type of G protein (e.g., G_o and $G_{i1\text{-}3}$[32]), and a single G protein of the G_i family can interact with more than one type of receptor (e.g., M_2 muscarinic and D_2 dopamine). However, receptors that interact with G_i and G_o are usually ineffective at interacting with G_s, and vice versa.[35] Generally, a given receptor usually, but not always, exhibits selectivity for one of three G protein families–$G_{i/o}$, G_s, or G_q. There is also selectivity at the level of the G protein–effector interaction. For example, members of the G_i family can mediate an inhibition of adenylyl cyclase activity; however, these G proteins are much less effective at coupling receptors to phospholipase Cβ (PLCβ). The α subunit of G proteins binds GTP, resulting in activation and a dissociation of the GTP-α complex from the βγ subunits. In addition, the α subunit has GTPase activity that hydrolyzes GTP to GDP, causing the inactive GDP-α complex to coalesce with the βγ subunits. The α subunits of some G proteins are also substrates for bacterial toxins that catalyze the adenosine diphosphate (ADP) ribosylation of the α subunit. For example, cholera toxin causes an ADP ribosylation of the α subunit of G_s, the G protein that stimulates adenylyl cyclase activity. This ADP ribosylation causes an inhibition of GTPase activity, resulting in an irreversible activation of G_s and, consequently, adenylyl cyclase. In contrast, pertussis toxin causes the ADP ribosylation of G_i and G_o, which prevents receptor-mediated activation of G_i and G_o. Transducin is a substrate for both cholera toxin and pertussis toxin.

GTPase Cycle

Figure 40-3 shows what happens inside the cell when an agonist activates a G protein–linked receptor:

1. Initially, the G protein is in its trimeric form, with GDP tightly bound to it. This inactive form of the G protein is a prerequisite for receptor interaction because the agonist-receptor complex cannot interact with free α or βγ subunits, only with the trimeric complex. Although the cell contains high concentrations (approximately 0.1 mM) of GTP, this nucleotide cannot compete GDP off the G protein because the dissociation rate of GDP from the α subunit is negligible.
2. The binding of agonist to its receptor causes a conformational change so that the i3 loop can interact with the G protein. This interaction allows the agonist to increase the rate of dissociation of GDP so that GTP can now bind to the G protein.
3. The binding of GTP causes a dissociation of the GTP α subunit from both the βγ subunits and the receptor, resulting in activation.
4. The GTP–α subunit complex and the free βγ subunits then turn on their respective effectors and ultimately trigger the cell's response to the agonist (Table 40-1).

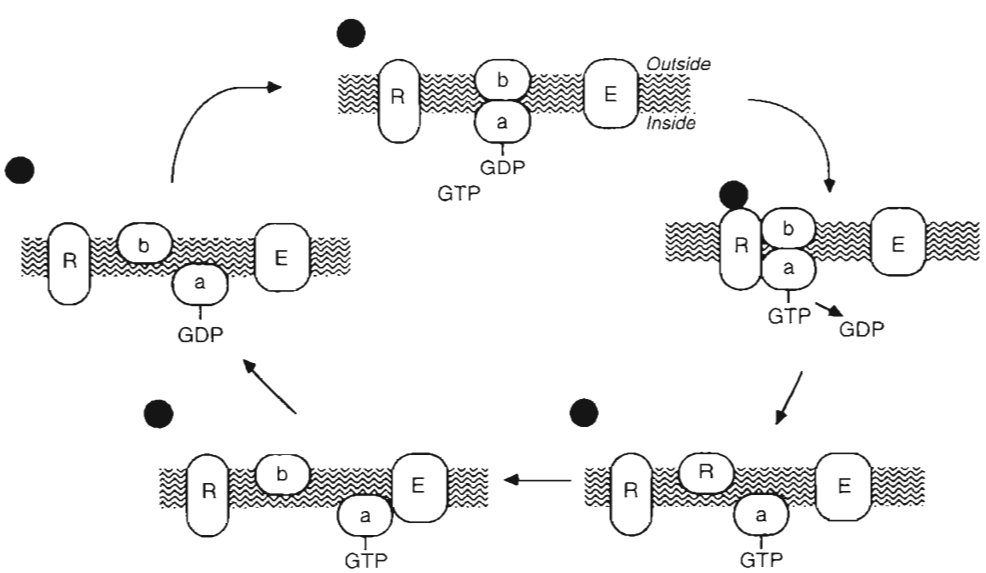

FIGURE 40–3. Receptor-activated GTPase cycle. Diagram of the interaction of an agonist *(black filled circle)* with its receptor (R) and the α (a) and βγ (b) subunits of a G protein. E, effector; GDP, guanosine diphosphate; GTP, guanosine triphosphate.

TABLE 40–1. SIGNALING MECHANISMS OF G PROTEIN–LINKED RECEPTORS

G Protein Family	Representative Receptors	Effect of G Protein Subunits on Enzymes and Ion Channels
G_s	β-adrenergic D_1 dopamine H_2 histamine	$G_{s\alpha}$ stimulates adenylyl cyclases (I to IX), opens calcium channels
G_i/G_o	M_2 and M_4 muscarinic D_2 dopamine α_2-Adrenergic	$G_{i\alpha}$ inhibits adenylyl cyclases (I, V, VI) $G_{i\beta\gamma}$ stimulates adenylyl cyclases (II, IV, VII), opens potassium channels $G_{o\beta\gamma}$ closes calcium channels
$G_{q/11}$	M_1, M_3, and M_5 muscarinic α_2-Adrenergic Angiotensin II	$G_{q\alpha}$ stimulates PLCβ $G_{11\alpha}$ stimulates PLCβ
G_T	Mammalian rhodopsin	Stimulates cGMP phosphodiesterase

cGMP, cyclic guanosine monophosphate; PLCβ, phospholipase Cβ.
Data from Hepler JR, Gilman AG: G-Proteins. Trends Biochem Sci 1992;17:383-387; and Tang WJ, Hurley JH: Catalytic mechanism and regulation of mammalian adenylyl cyclases. Mol Pharmacol 1998;54:231-240.

5. The turn-off mechanism is the GTPase activity of the α subunit, which hydrolyzes GTP. The resulting GDP α subunit then coalesces with the βγ subunits to form the trimeric complex, which is inactive.
6. The cycle can repeat itself, provided that agonist is occupying the receptor.
7. Another important protein, RGS (regulator of G protein signaling), increases the GTPase activity of the G protein (not shown in the figure).[36]

Several experimental observations support the scheme described, and a few of these are mentioned here. Muscarinic agonists cause the M_2 receptor to form a stable complex with G_i that can be identified on Western blots with antibodies to G_i or the M_2 receptor.[35] In contrast, antagonists do not promote the formation of a receptor–G protein complex. Moreover, the ability of the ligand to promote the ternary (agonist–receptor–G protein) complex is proportional to the intrinsic efficacy of the agonist.[37] This relationship is shown in Figure 40-4 for M_2 muscarinic receptors in the heart. The propensity of the agonist to generate the ternary complex can be measured in a binding assay; this parameter is denoted by "Receptor-Gi Cooperativity" in Figure 40-4*A*. It can be seen that the cooperativity is proportional to intrinsic efficacy for a number of agonists. Another conspicuous feature of most G protein–linked receptors is that the binding of ligands to the receptor is modified by GTP in manner that is proportional to the intrinsic efficacy of the ligand. Both GTP and GDP cause a reduction in agonist binding affinity, but not antagonist affinity. The relationship between intrinsic efficacy and the inhibitory effect of GTP (GTP shift) on ligand binding to M_2 muscarinic receptors in the heart is shown in Figure 40-4*B* for a number of ligands. The proportional relationship between the negatively cooperative effects of GTP on agonist binding and the intrinsic efficacy of the agonist is readily apparent from the plot.

The relationships shown in Figure 40-4 provide insight into how the receptor works. In considering the figure, it is important to note that both GDP and GTP inhibit agonist affinity, but not antagonist affinity. This effect is allosteric because the agonist and the guanine nucleotide act at different sites. Therefore, the nature of the interaction between the two types of ligands is called *negative heterotropic cooperativity.* One of the properties of allosteric interactions is that they are reciprocal; that is, if GDP or GTP reduces the affinity of the agonist, then the agonist must reduce the affinity of the guanine nucleotide to precisely the same extent.[38] This agonist-mediated reduction in the affinity of GDP causes it to dissociate from the G protein more rapidly, allowing GTP to compete it off the G protein. Although this increase in the dissociation kinetics of GDP is achieved at the cost of reducing the affinity of GTP, it does not result in a decrease in the binding of GTP, because GTP is maintained at saturating concentrations inside the cell. For example, the K_D of GTP analogs for the G protein is in the nanomolar (10^{-9} M) range, whereas the concentration of GTP inside the cell is in the millimolar (10^{-3} M) range. Thus, it can be seen that the agonist-receptor complex works by increasing the dissociation kinetics of GDP from the G protein and that this effect is mediated by negative heterotropic cooperativity.

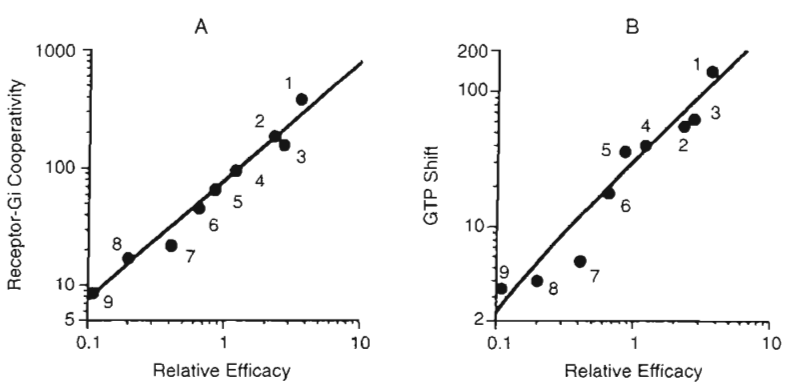

FIGURE 40–4. Correlation between relative efficacy and agonist binding properties at M_2 muscarinic receptors. *A*, The positive heterotropic cooperativity between the binding of the agonist and G_i is plotted against the relative efficacy of the agonist as determined by inhibition of adenylyl cyclase activity. *B*, The ratio of the concentration of the agonist in the presence and absence of guanosine triphosphate (GTP) is plotted against the relative efficacy of the agonist. 1, oxotremorine-M; 2, carbachol; 3, *cis*-dioxolane; 4, oxotremorine; 5, (+)-aceclidine; 6, (–)-aceclidine; 7, *N*-methylaceclidine; 8, BM5; 9, BOK1. (Data from Ehlert FJ: The relationship between muscarinic receptor occupancy and adenylate cyclase inhibition in the rabbit myocardium. Mol Pharmacol 1985;28:410-421.)

SIGNALING MECHANISMS OF G PROTEIN–LINKED RECEPTORS

G protein–linked receptors mediate myriad responses at the level of the whole tissue; however, at the subcellular level, these responses seem to be triggered by a relatively small number of transduction mechanisms. This situation illustrates that diversity is achieved through divergence in the signaling pathway, and that the factors that determine the intermediate and distal parts of the signaling mechanism are tissue specific. Thus, calcium mobilization resulting from activation of a PLCβ-linked receptor in smooth muscle may cause contraction,[39] whereas in an exocrine gland, the same transduction mechanism may cause secretion. Some of the major transduction mechanisms of G protein–linked receptors are summarized here and listed in Table 40-1.

CALCIUM MOBILIZATION

Perhaps the most universal mechanism for triggering a response is to increase the concentration of calcium within the cell.[40] Not surprisingly, several different signaling mechanisms ultimately affect the level of calcium within the cytoplasm. One common mechanism for elevating calcium is through activation of PLCβ, an enzyme that hydrolyzes the phospholipid phosphatidylinositol-4,5-bisphosphate (PIP_2) into inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG).[41,42] This membrane-bound enzyme is activated by numerous receptors that signal through the G_q family of G proteins (see Table 40-1). The two hydrolysis products, IP_3 and DAG, act as second messengers within the cell.[42] IP_3 causes a release of calcium from the endoplasmic reticulum, and DAG activates protein kinase C. IP_3 is phosphorylated in some cells to inositol-1,3,4,5-tetrakisphosphate (IP_4), which appears to have a role in assisting IP_3 to mobilize calcium.[43] Both IP_3 and IP_4 are unstable and are sequentially hydrolyzed by phosphatases back to inositol, which is then recycled for synthesis of new PIP_2. The final phosphatase in the sequence, myoinositol-1-phosphatase, is inhibited by lithium. Ultimately, this inhibition leads to an accumulation of inositol-1-phosphate and a depletion in inositol and inositol-containing phospholipids (e.g., PIP_2) within the brain. This depletion can lead to a dampening in receptor signaling through the PLCβ pathway, and it has been suggested that this dampening is the mechanism by which lithium attenuates the symptoms of manic-depressive psychosis.[44] Once calcium is elevated in the cell, it can mediate a variety of effects by binding to calmodulin and activating a variety of kinases and phosphatases. The protein kinase C that is activated by DAG also mediates numerous effects, and it is the target for some tumor-promoting phorbol ester derivatives.

ADENYLYL CYCLASE

Another important signaling mechanism within the cell is the regulation of adenylyl cyclase (see Table 40-1). G protein–linked receptors that affect adenylyl cyclase can be divided into two categories, depending on whether they stimulate or inhibit the enzyme.[22] G_s mediates the stimulation, whereas in most instances, G_i mediates inhibition through a distinct group of receptors. Nine different isoforms of adenylyl cyclase (AC1 to AC9) have been identified, and all these are activated by the α subunit of G_s (i.e., α_s).[45,46] The α_i subunit inhibits AC1, AC3, AC5, AC6, AC8, and AC9, whereas βγ subunits increase the activity of AC2, AC4, and AC7 in a manner dependent on activation by α_s. Once cyclic adenosine monophosphate (cAMP) rises within the cell, it can mediate a variety of effects through activation of cAMP-dependent protein kinase (protein kinase A). The turn-off mechanism for cAMP is phosphodiesterase, which rapidly hydrolyzes cAMP into AMP.

RECEPTOR CROSS-TALK

There are several possibilities for cross-talk between receptors that stimulate adenylyl cyclase and those that activate PLCβ. For example, AC1 (abundant in brain), AC3, and AC8 are activated by calcium.[47] Also, calcium stimulates phosphodiesterase in some tissues. Moreover, the stimulation of adenylyl cyclase caused by G_s-linked receptors is enhanced by activation of protein kinase C in some tissues. Finally, α_s-mediated stimulation of AC2 and AC4 has been shown to be greatly potentiated by the βγ subunits, which provides yet another mechanism for receptor cross-talk.

In addition to the second messenger systems described earlier, G protein–linked receptors can affect a variety of ionic conductances.[48] In several instances, these effects are mediated indirectly by second messengers, whereas in other cases, there is direct coupling of G proteins to ion channels. One such example is in the heart, where muscarinic receptors and beta-adrenergic receptors cause reciprocal changes in the conductivity of inwardly rectified potassium channels. These effects are mediated by G_i and G_s, respectively, and represent the mechanisms by which the vagus nerve slows heart rate and the cardiac sympathetic nerves increase heart rate.

CELLULAR SIGNALING AND CANCER

Most cancer cells contain mutations in their DNA that presumably cause tumorigenesis.[49] These mutations are of two general forms: *recessive*, which result in a loss of function of tumor suppressor genes, and *dominant*, which result in a gain in function. The genes that contain these dominant mutations are designated oncogenes, and their normal counterparts are referred to as proto-oncogenes. Invariably, proto-oncogenes code for proteins that are part of normal receptor signaling cascades within the body. For example, truncated forms of the epidermal growth factor receptor lacking the ligand binding domain are constitutively active and cause tumorigenesis.[10] Relatively small changes in signaling proteins are oncogenic in numerous instances. For example, point mutations in G_i have been implicated in carcinoma of the ovary and adrenal gland, whereas point mutations in G_s are present in adenomas of the pituitary gland and carcinoma of the thyroid.[50] Interestingly, these point mutations result in a loss of the GTPase activity of these G proteins, causing them to become constitutively active. There are numerous other examples of oncogene products that are mutated signaling proteins, including ligand-regulated gene regulatory proteins, RTKs, G protein–linked receptors, and low-molecular-weight G proteins, including Ras. Thus, in numerous instances, tumorigenesis is caused by overactive, unregulated receptor signaling.

DIVERSITY AND REDUNDANCY

In considering the diverse mechanisms by which information is transmitted throughout the body by way of receptor signaling, one is struck by two seemingly opposite principles of nature: diversity and redundancy.[51] Nature is redundant in the sense that only four different types of mechanisms can account for the function of what may turn out to be more than a thousand different types of physiologic and sensory receptors. Also, the same general GTPase cycle is harnessed for innumerable functions within the cell, including protein synthesis, secretion, neurotransmission, taste, olfaction, and vision. To accomplish these diverse tasks, nature modifies a given mechanism in an extraordinary number of ways. An appreciation of the diversity and redundancy of nature will aid in the future unraveling of biologic mechanisms and in the development of therapeutic agents to treat disease.

ACKNOWLEDGMENTS

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Chapter 41

PROSTAGLANDINS, THROMBOXANES, LEUKOTRIENES, AND OTHER PRODUCTS OF ARACHIDONIC ACID

James A. Cook • Hongkuan Fan • Perry V. Halushka

KEY POINTS

1. **Eicosanoids include a broad range of arachidonic acid metabolites,** including the cyclooxygenase products thromboxane B_2, prostaglandin E_2, prostacyclin, and 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2, and the lipoxygenase products leukotriene B_4, C_4, D_4, and E_4 and lipoxin A_4.
2. **Eicosanoid synthesis and action can be inhibited by a variety of receptor antagonists and synthesis inhibitors,** the most recently developed of which are the cyclooxygenase 2 inhibitors.
3. **Both cyclooxygenase products and lipoxygenase products are increased** in animal models of endotoxemia, sepsis, and lung injury.
4. **Employment of specific cyclooxygenase or lipoxygenase synthesis inhibitors or specific arachidonic acid metabolite receptor antagonists** attenuates the sequelae or improves survival in animal models of endotoxemia, sepsis, and lung injury.
5. **Lipoxin A_4 and the J series of prostaglandins (cyclopentenone prostaglandins) are anti-inflammatory** and may play a role in inflammation resolution.
6. **Studies demonstrate increased synthesis** of thromboxane, prostacyclin, and leukotriene in patients with septic trauma or acute respiratory distress syndrome and suggest a deleterious role for thromboxane.
7. **Clinical trials with the nonsteroidal anti-inflammatory drug ibuprofen in severely septic patients** did not improve survival but reduced the febrile response and tachycardia and increased oxygen consumption and lactic acidosis.
8. **Combination drug therapy** with eicosanoid synthesis inhibitors, receptor antagonists, or anti-inflammatory eicosanoids may be more effective in sepsis or acute respiratory distress syndrome.

The first report of the biologic activity of what were subsequently identified as prostaglandins (PGs) was published in 1930, when it was found that extracts of seminal fluid contracted uterine tissue.[1] Von Euler attributed the activity of the extract to lipid substances that he named *prostaglandins*, because he thought they came from the prostate.[2] The structures of two of the prostaglandins (PGE_2 and $PGF_{1\alpha}$) were subsequently elucidated by the use of gas chromatography–mass spectrometry, and with this discovery, research in the field grew rapidly.[3] Thromboxane B_2 (TXB_2) was isolated by Samuelsson and colleagues in 1978 from human platelets.[4] It is the stable metabolite of TXA_2, whose structure was deduced at the time and was later proved to be correct. The name *thromboxane* was chosen because the substance causes platelet aggregation (thrombosis) and has an oxane ring system. It was ultimately shown that a rabbit aorta-contracting substance was TXA_2.[5] Prostacyclin (PGI_2) was discovered in 1976.[6]

The next major group of arachidonic acid metabolites to be discovered and characterized was the leukotrienes (LTs). Their name derives from the observation that they are made by leukocytes and have triene structures.[7] The sulfidopeptide leukotrienes were shown to be the active principals of the slow-reacting substance of anaphylaxis, released from mast cells and neutrophils.[7] Arachidonic acid, dihomo-γ-linolenic acid, and eicosapentaenoic acid are precursors of prostaglandins, thromboxanes, and leukotrienes. The first two are also known as *eicosatetraenoic acid* and *eicosatrienoic acid*, respectively; thus, the name *eicosanoids* is used generically for the products of these fatty acids.

The products of fatty acid cyclooxygenase and lipoxygenase pathways are named with letters and numbers. The letters for the cyclooxygenase pathway metabolites refer to substitutions on the cyclopentane ring; for the leukotriene pathway, the letters refer to the amino acids coupled with the fatty acid.[7] The numbers refer to the number of double bonds present on the side chains.

SITES OF SYNTHESIS AND PHARMACOLOGIC ACTIVITY OF THE EICOSANOIDS

FATTY ACID CYCLOOXYGENASE PRODUCTS

The pathway for the metabolism of arachidonic acid is shown in Figure 41-1. PGA, PGB, and PGC are nonenzymatic

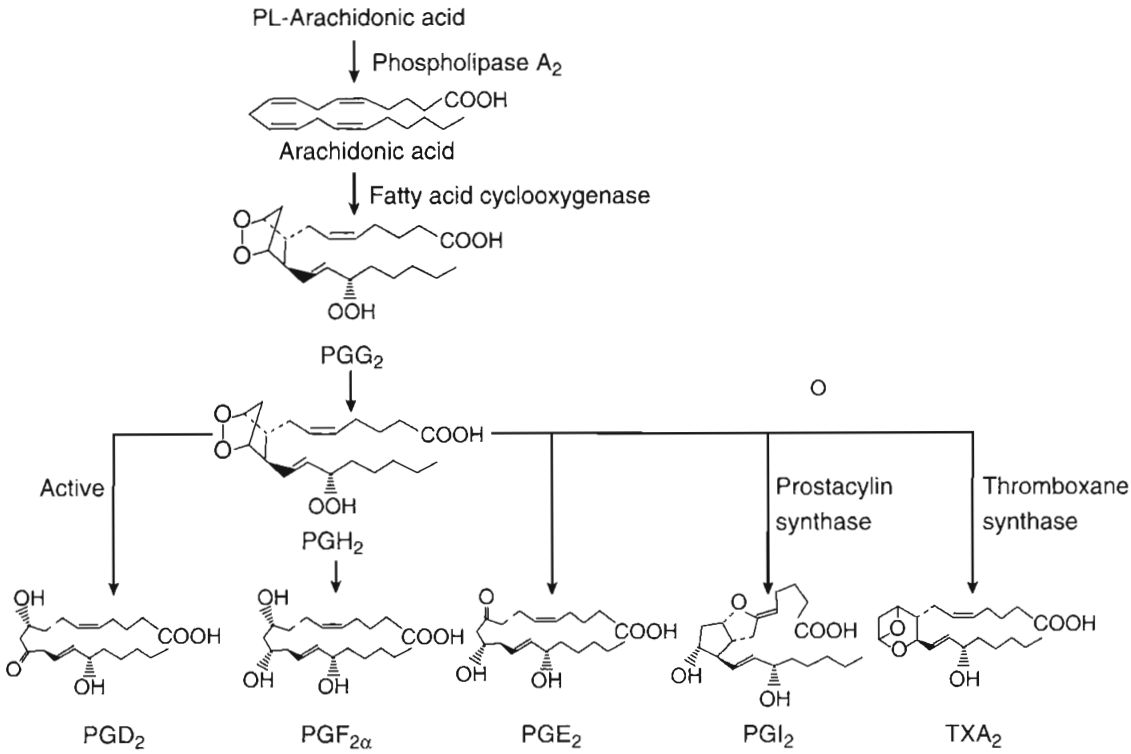

FIGURE 41–1. Metabolism of arachidonic acid. PG, prostaglandin; PGI_2, prostacyclin; PL, phospholipase; TXA_2, thromboxane A_2. (From Wagner TR, Halushka PV, Cook JA: Cyclooxygenase products in septic endotoxic shock. In Neugebauer EA, Holaday JW [eds]: Handbook of Mediators in Septic Shock. Boca Raton, Fla, CRC Press, 1993, pp 395-418.)

dehydration products of PGE_2 and are considered artifacts of the extraction procedure. However, PGA is a vasodilator. PGD_2 is synthesized in large quantities by mast cells, being the major cyclooxygenase metabolite in this cell. It and its major metabolite, 9α, 11β, $PGF_{2\alpha}$, are potent bronchoconstrictors and are overproduced in mastocytosis.[8] Depending on the vascular bed, it may be either a vasoconstrictor or a vasodilator. Vasodilatation usually occurs at lower doses; however, PGD_2 also constricts the pulmonary artery. It is synthesized by platelets and inhibits platelet aggregation by increasing intraplatelet cyclic adenosine monophosphate (cAMP) levels. It has yet to be determined whether its synthesis is increased in shock.

PGE_2 is synthesized mainly by the kidneys, platelets, and blood vessels, but it is also synthesized by many other tissues in smaller amounts. It is a vasodilator, natriuretic, and diuretic; inhibits gastric acid secretion; and contracts uterine tissue. Depending on the tissue, PGE_2 can bind to four subtypes of receptors, designated EP_1, EP_2, EP_3, and EP_4. Seven EP_3 splice variants have been identified in humans.[9] The EP receptors are classic heptahelical G protein–coupled receptors.[10] EP_1 is coupled to Gq and activates phospholipase C. EP_2 and EP_4 couple to G_s and stimulate the synthesis of cAMP, whereas EP_3 is coupled to G_i, which inhibits cAMP formation. The EP_1, EP_3, and EP_4 receptors have also been shown to be expressed on nuclear membranes of endothelial cells, suggesting a potential level of control in nuclear events.[11] PGE_2 synthesis is significantly increased in shock syndromes (discussed later).

$PGF_{2\alpha}$ is synthesized in many tissues in variable amounts and is increased in sepsis. It is a bronchoconstrictor and venoconstrictor, and it contracts uterine smooth muscle. All these actions are mediated by $PGF_{2\alpha}$ receptors (FP).[10,12]

PGI_2 is synthesized by endothelial cells, macrophages, lungs, and kidneys. It is a vasodilator and antiaggregatory substance with a half-life of about 10 minutes; it spontaneously hydrolyzes to form the stable but inactive metabolite 6-keto-$PGF_{1\alpha}$. The major urinary metabolite of 6-keto-$PGF_{1\alpha}$ is 2,3-dinor-6-keto-$PGF_{1\alpha}$. The major biochemical action of PGI_2 is to stimulate adenylate cyclase. To date, only one class of PGI_2 receptors (IP) has been identified.[10,12]

TXA_2 is synthesized in large quantities by platelets, macrophages, monocytes, and lungs. It is unstable and has a half-life of only 30 seconds; it spontaneously hydrolyzes to form the stable but inactive TXB_2. The major plasma metabolite of TXB_2 is 11-dehydro-TXB_2. The major urinary metabolites are 11-dehydro-TXB_2 and 2,3-dinor-TXB_2. TXA_2 is a potent vasoconstrictor, bronchoconstrictor, and proaggregatory substance. Based on pharmacologic criteria, two subtypes of receptors have been identified for TXA_2. One is associated with platelet aggregation, and the other is associated with vascular smooth muscle cell contraction.[8,10,12] There is also a splice variant of the platelet receptor, which was first discovered in endothelial cells. Platelet aggregation and TXA_2 synthesis are markedly increased in shock syndromes.

Leukotriene B_4 (LTB_4) is synthesized by white blood cells, macrophages, and synoviocytes.[13] It is a potent chemotactic substance for white blood cells.

LTC_4 is synthesized by white blood cells, lung parenchymal tissue, and macrophages. It is converted to LTD_4, an active metabolite of LTC_4. It is a vasoconstrictor and bronchoconstrictor and increases capillary permeability and bronchial mucus secretion. Its synthesis is increased during sepsis and acute respiratory distress syndrome (ARDS).[14] The urinary excretion of *N*-acetyl LTE_4, a metabolite of LTD_4, is increased in ARDS and shock.[15]

ARACHIDONIC ACID RELEASE

Release of arachidonic acid from membrane phospholipids is the rate-limiting step in the formation of eicosanoids in nonpathologic states.[16] Stimulation of cells by hormonal and nonhormonal agonists results in activation of phospholipase (PL) A_2, C, or D. Activation of PLA_2 results in the release of arachidonic acid from the *sn2* position of phosphatidylcholine and phosphatidylethanolamine.[17] Isozymes of PLA_2 have demonstrated a specificity for catalyzing the release of arachidonic acid preferentially from either phosphatidylcholine or phosphatidylethanolamine.[18] PLA_2 has several subtypes. There is cytosolic PLA_2, which is Ca^{++} dependent, and secretory forms of PLA_2 designated PLA_2-I and PLA_2-II.[14] PLA_2-I is secreted by pancreatic acinar cells and is important in phospholipid digestion in the diet. PLA_2-II is secreted by inflammatory cells and has been shown to increase in plasma in response to a variety of inflammatory conditions such as sepsis, trauma, and pancreatitis.[19-22] Cytosolic PLA_2 is intracellular and is activated by a number of stimuli, including tumor necrosis factor (TNF), interleukin (IL)-β, bradykinin, and many other inflammatory stimuli.[23,24] PLC cleaves phosphatidylinositol 4,5-bisphosphate, resulting in inositol-1,4,5-trisphosphate and 1,2-diacylglycerol, both of which function as intracellular second messengers.[25-28] Diglyceride lipase then releases the arachidonic acid from the diacylglycerol.[29,30] The metabolite 1,2-diacylglycerol stimulates protein kinase C.

A variety of agonists can stimulate PLD.[31] Both guanine nucleotide regulatory proteins and kinases are coupled to receptor-mediated regulation of PLD. PLD activation requires a cofactor, phosphatidylinositol 4,5-bisphosphate. The metabolite phosphatidic acid produced by PLD may play a role in growth regulation, activation of Ca^{++}-independent forms of protein kinase C, neutrophil respiratory burst activity, stimulation of lysophosphatide acid receptors, and vesicle trafficking.[32]

The particular phospholipid substrate providing arachidonic acid in response to a specific stimulus may influence whether lipoxygenase or fatty acid cyclooxygenase products are formed. Resident murine macrophages, in response to stimuli that activate the lipoxygenase pathway, demonstrate dependence on the PLC–diglyceride lipase pathway,[33] whereas endotoxin- or phorbol myristate acetate–induced prostaglandin formation is independent of the PLC–diglyceride lipase pathway.

FATTY ACID CYCLOOXYGENASE (PROSTAGLANDIN H SYNTHASE)

Fatty acid cyclooxygenase (PGH synthase) catalyzes the committed step in the conversion of arachidonic acid to the prostaglandin endoperoxides PGG_2 and PGH_2.[34] PGH_2 is the direct precursor for primary prostaglandins and TXA_2. Fatty acid cyclooxygenase has been found in most of the organs of all mammalian species but not in all cell types.[33] Subcellular studies demonstrate that cyclooxygenase is an integral membrane protein concentrated in the endoplasmic reticulum, as well as in the nuclear envelope and the plasma membrane.[35,36] Cyclooxygenase is approximately 68 kDa; species variations are attributed to different amounts of *N*-glycosylation and mannose carbohydrate side chains.[37] Two sites of enzymatic activity have been proposed,[38] and heme-binding sites are conserved.[39]

Cyclooxygenase possesses two enzymatic activities.[40] The first activity cyclizes an oxygen molecule in a bis-dioxygenase configuration at carbon (C)-9 and C-11, converting arachidonic acid to PGG_2. PGH synthase then uses another oxygen molecule to peroxidize this unstable metabolite at C-15, converting PGG_2 into PGH_2. The bound heme of cyclooxygenase is believed to act as the electron transfer site in these reactions. PGH_2 is the substrate for the enzymes responsible for the synthesis of PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and TXA_2. The final product profile is dependent on the specific cell type.

Many fatty acids are substrates for cyclooxygenase, but arachidonic acid is the most common in vivo.[32] Cyclooxygenase is inhibited by aspirin and all the nonsteroidal anti-inflammatory drugs (NSAIDs). Aspirin irreversibly inhibits the enzyme by covalently acetylating a serine residue. In platelets, the inhibition lasts for the life of the platelet (7 to 10 days), because platelets are not capable of synthesizing new enzyme.

In the early 1990s, two isoforms of cyclooxygenase were identified: COX-1 and COX-2. These two isoforms have been extensively characterized. COX-1 is the constitutive, continuously expressed form that is thought to play a role in normal homeostatic processes in platelets, the kidneys, and the gastrointestinal tract. COX-2 is the inducible form.[41] Its synthesis is stimulated by inflammatory stimuli such as lipopolysaccharide and IL-1 and by growth factors.[41,42] Both enzymes are inhibited by aspirin, indomethacin, and other NSAIDs.

Pharmacologic studies led to the development of a new generation of COX-2 inhibitors (e.g., celecoxib [Celebrex], rofecoxib [Vioxx]). The COX-2 inhibitors retain the anti-inflammatory properties of traditional nonselective NSAIDs, but without the gastrointestinal bleeding side effects. The widespread use of COX-2 inhibitors proved that they are as active as traditional NSAIDs in reducing pain and fever.[43,44] It became apparent, however, that although COX-2 inhibitors have a better profile in terms of gastrointestinal mucosal protection, they still have renal side effects.[45] They may also produce a prothrombotic state, but this is controversial. Studies suggest that COX-2 also has a physiologic role, particularly in the kidney. The COX-1–COX-2 model does not accommodate acetaminophen, which has antipyretic and analgesic properties but no anti-inflammatory effects. Because acetaminophen is not an anti-inflammatory drug, this suggests that its pharmacologic effects cannot be explained by COX-2 inhibition.[46] Recent studies by Chandrasekharan and coworkers suggest that COX-3, a COX-1 variant, is inhibited by acetaminophen and other analgesic and antipyretic drugs.[47]

LIPOXYGENASE

The lipoxygenase pathways of arachidonic acid metabolism involve three species of lipoxygenases: 5-lipoxygenase, 12-lipoxygenase, and 15-lipoxygenase.[48-50] These enzymes insert a molecule of oxygen into arachidonic acid at C-5, C-12, and C-15, respectively, forming the 5-, 12-, and 15-hydroxyeicosatetraenoic acids (HETEs).

5-Lipoxygenase demonstrates several unique characteristics compared with the other human lipoxygenases. It is dependent on adenosine triphosphate and Ca^{++} for activation, as well as three additional components.[51,52] One of these components is an 18-kDa protein, called 5-lipoxygenase-activating protein (FLAP), that is required for both the translocation and the activation of 5-lipoxygenase.[51,53] 5-Lipoxygenase metabolizes arachidonic acid to 5-hydroperoxyeicosatetraenoic acid

(5-HPETE). 5-HPETE is further metabolized to 5-HETE and LTA_4. LTA_4 is an unstable intermediate that is rapidly metabolized to LTB_4 by LTA_4 hydrolase or to LTC_4 by LTC_4 synthase. LTC_4 consists of glutathione covalently bound to arachidonic acid at the C-6 position (a sulfidopeptide leukotriene). The glutamic acid moiety of glutathione is cleaved by a γ-glutamyltranspeptidase to produce LTD_4. LTD_4 is further metabolized by a peptidase or a cysteinyl-glycinase to form LTE_4. LTE_4 can be *N*-acetylated and subsequently excreted in the urine.

12-Lipoxygenase metabolizes arachidonic acid to 12-HPETE and the metabolites di-HETE and tri-HETE. 12-Lipoxygenase is found in platelets and is the predominant lipoxygenase in brain tissue.

15-Lipoxygenase is approximately 70 kDa in size.[54] Its activity is preferentially expressed only in certain cells,[55] but the biologic role of 15-lipoxygenase in these cell types is not fully understood.[56] Recent evidence suggests that lipoxins (LX) that are generated by 15-lipoxygenase may be involved in inflammation resolution. Polymorphonuclear leukocytes (PMNs) and tissue resident cells can generate LXs, which appear to regulate leukocyte function. LXA_4 and its metabolically stable analogs can inhibit PMN-mediated inflammation in vivo in a variety of tissues.[57] The LXs can augment monocyte chemotaxis and phagocytosis of apoptotic leukocytes and can modulate the expression of chemokines and cytokines.[58] It has been proposed that peripheral blood PMNs exposed to PGE_2 (produced in inflammatory exudates) switch eicosanoid biosynthesis from the predominantly 5-lipoxygenase pathway leading to LTB_4 production to the 15-lipoxygenase pathway producing LXA_4. The latter may function as a "stop signal" for inflammation.[59]

OTHER METABOLITES

The J series of prostaglandins (cyclopentenone PGs) is formed by progressive nonenzymatic dehydration of PGD_2 (Fig. 41-2). What makes the cyclopentenone PGJ_2 family unique is that, unlike other prostaglandins, it has no known membrane receptor. Instead, PGJ_2 and its metabolites interact with a class of nuclear receptors that comprise the peroxisome proliferator-activating receptor (PPAR) family (specifically, PPAR-γ). The PPAR family is ligand-activated by nuclear transcription factors, which form a heterodimer with retinoid X receptor, and binds to a PPAR-responsive element, the promoter region of specific inflammatory genes.[60] The 15-deoxy-$\Delta^{12,14}$-PGJ_2 metabolite is the most potent ligand for PPAR-γ. Activation of PPAR-γ can transrepress the activation of many transcription factors, including nuclear factor kappa-B (NF-κB), activator protein-1, signal transducers of transcription, and nuclear factor of activated T cells. PPAR-γ is found in a variety of cells, including macrophages, dendritic cells, and B and T lymphocytes.[61-65] There is a rapidly expanding literature that PPAR-γ may play a role in regulating inflammation and immunomodulation.[66] However, many studies have shown that PPAR-γ ligands have anti-inflammatory effects only at concentrations that far exceed those required for activation of PPAR-γ.[67] It has been shown that these ligands (e.g., 15-deoxy-$\Delta^{12,14}$-PGJ_2) clearly have PPAR-γ–independent activities through the covalent modification of critical cysteine residues in the inhibitor of NF-κB, the p50 NF-κB subunit, and extracellular signal-regulated kinase (ERK).[68-70]

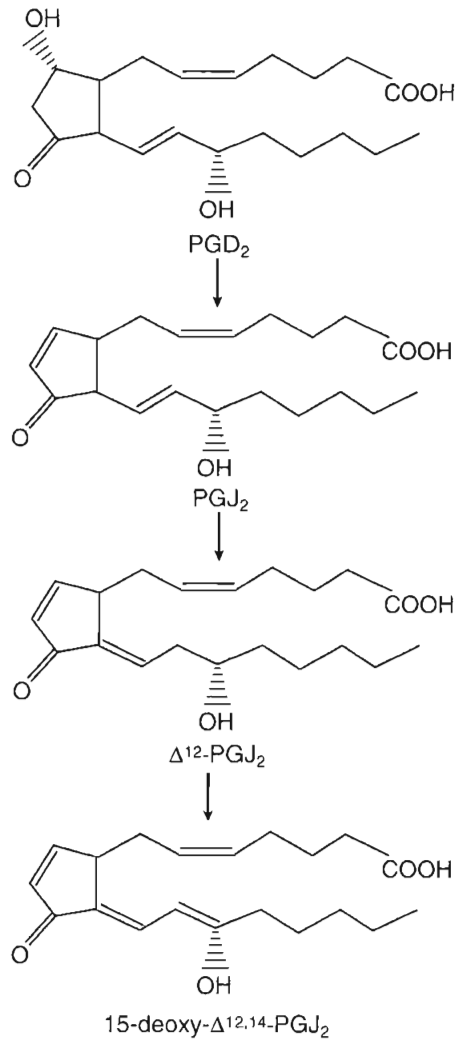

FIGURE 41–2. Metabolism of PGD_2 to 15-deoxy-$\Delta^{12,14}$-PGJ_2. PG, prostaglandin.

Cytochrome P_{450} can also oxygenate arachidonic acid at various sites.[71] This results in the production of a multitude of epoxides that have diverse biologic properties. These metabolites are usually synthesized in large quantities by the liver and kidneys. Whether these products are increased in sepsis remains unknown.

Isoprostanes are a novel group of nonenzymatically generated arachidonic acid metabolites.[72] They are formed directly by free radical oxidation of arachidonic acid while still esterified to the two positions of membrane phospholipids. Isoprostanes are structurally similar to prostaglandins and may exert some of their effects through the activation of TXA_2 receptors. They cause vasoconstriction, change in platelet shape, and increased pulmonary permeability.[73] Although they are generated under oxidative stress, the potential role of isoprostanes in ARDS and sepsis remains to be determined.

INCREASED SYNTHESIS OF EICOSANOIDS IN ENDOTOXEMIA AND SEPSIS

The seminal observation that eicosanoids may be involved in the pathogenesis of endotoxic shock was made by Northover and Subramanian in 1962.[74] They demonstrated that dogs treated with aspirin before exposure to endotoxin had an

improved survival compared with control animals. At that time, it was not known that aspirin inhibited prostaglandin synthesis. In 1976, Herman and Vane demonstrated increased levels of PGE-like material in the renal veins of dogs given endotoxin.[75] Taken together, these two observations suggested that eicosanoids were important in the pathogenesis of septic shock.

Increased synthesis of eicosanoids in response to endotoxemia and sepsis occurs in several animal species and in humans. Increased plasma levels of TXB_2 and 6-keto-$PGF_{1\alpha}$ can be demonstrated in rats with experimental endotoxemia and sepsis.[48,76-78] Similar profiles of TXB_2 and 6-keto-$PGF_{1\alpha}$ in plasma are observed in endotoxemic or septic sheep,[79,80] pigs,[76,81-85] and baboons.[86,87] The relative amounts of TXB_2 and 6-keto-$PGF_{2\alpha}$ are influenced by the experimental route and frequency of endotoxin administration.[88,89]

5-Lipoxygenase products are also increased in endotoxemic animals and in patients with sepsis and ARDS.[90] In endotoxemic rats, Hagman and colleagues reported increases in biliary *N*-acetyl LTE_4, a stable metabolite of sulfidopeptide leukotrienes.[91] LTC_4 levels are increased in the lungs of rats with experimental endotoxemia.[92] Increased LTB_4 levels are found in bronchoalveolar lavage fluid of endotoxemic pigs[93] and in lung lymph in endotoxemic sheep.[94] Induction of cecal ligation and puncture (CLP) in mice was associated with eightfold higher levels of LTB_4 in peritoneal exudate compared with the sham group.[95] Slotman and coworkers compared the effect of sepsis and hemorrhagic shock on eicosanoid protection in a porcine model.[96] In sepsis-induced by *Aeromonas hydrophila*, there was an early peak in plasma TNF (at 60 minutes), followed by a rise in peak LTB_4 and LTC_4/D_4 levels (180 minutes). TXB_2 and 6-keto-$PGF_{1\alpha}$ continued to increase over the 4-hour duration of the study. In contrast, there was no increase in eicosanoids or TNF in the hemorrhagic group. These studies have implications for the development of therapies for these pathologic insults. Indeed, increases in sulfidopeptide leukotrienes and LTB_4 have been demonstrated in the bronchoalveolar lavage fluid of patients with ARDS, a complication associated with sepsis.[15,97-101]

EFFECT OF EICOSANOID SYNTHESIS INHIBITORS, RECEPTOR ANTAGONISTS, AND ANTI-INFLAMMATORY EICOSANOIDS

More direct evidence that eicosanoids mediate endotoxin-induced sequelae is provided by observations that the inhibition of eicosanoid synthesis or the blockade of specific receptors protects animals from shock sequelae (Fig. 41-3). Because PLA_2-II is increased in sepsis,[20] some studies examined the potential beneficial effect of inhibitors of PLA_2-II. The putative selective PLA_2-II inhibitor SB203347 and eucalyptus bioflavonoids (Quercetin), which alter neutrophil PLA_2-II release, improved survival in murine endotoxic shock.[102] PLA_2-II enzyme-deficient mice exhibited prolonged survival and reduced plasma cytokine in response to endotoxemia compared with wild-type subjects. PLA_2-II may, in part, potentiate lipopolysaccharide (LPS) shock by augmenting cellular responses to LPS. PLA_2-II potentiated LPS-induced IL-6 production in whole blood and binding of LPS to PMNs.[103]

Numerous NSAIDs have been evaluated for potential therapeutic benefit in endotoxemia and sepsis in animal models.[48] These compounds, when used in experimental sepsis or endotoxemia, have generally been found to improve survival or survival time and to reduce cardiopulmonary dysfunction and indices of tissue injury.[48,76-78] Among the most extensively studied prototype NSAID is ibuprofen. In various species with endotoxemia and sepsis, ibuprofen has been shown to improve systemic hypotension, pulmonary hypertension, protein and fluid extravasation, lung water flux, airway resistance, and oxygen delivery.[48,78,83,88,104-106] In some studies, however, ibuprofen did not improve shock sequelae.[106] Ibuprofen also alters neutrophil function, including inhibition of neutrophil aggregation, organ infiltration, and adherence.[104,106] As with

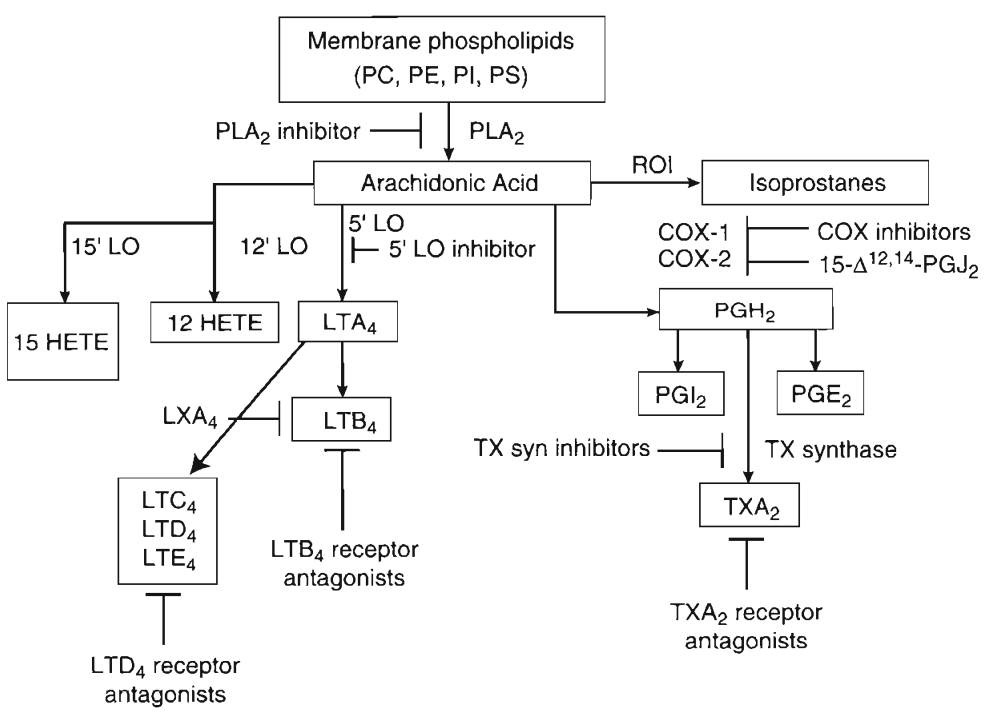

FIGURE 41–3. Metabolism of membrane phospholipids. COX, cyclooxygenase; HETE, hydroxyeicosatetraenoic acid; LO, lipoxygenase; LT, leukotriene; LXA_4, lipoxin A_4; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PG, prostaglandin; PI, phosphatidylinositol; PLA_2, phospholipase A_2; PS, phosphatidylserine; ROI, reactive oxygen intermediates; TXA_2, thromboxane A_2.

other NSAIDs, it is likely that some of these salutary effects are the result of pharmacologic actions of ibuprofen other than inhibition of fatty acid cyclooxygenase. These actions include potential inhibition of LTB_4 production,[106] superoxide anion production,[106] scavenging of hydroxyl radicals,[107] and burn-induced inhibition of fibrinolysis.[108]

A major concern in the use of NSAIDs is their renal and gastrointestinal side effects. By inhibiting COX-1–dependent prostaglandin synthesis in those organs, NSAIDs can render septic animals more susceptible to renal failure[109,110] and gastrointestinal ulceration. The renal effects of NSAIDs can be reversed, at least in part, by the use of dopamine.[111] These side effects are due to the fact that NSAIDs inhibit both COX-1, the enzyme responsible for homeostasis in the kidneys and gastrointestinal tract, and COX-2, which is induced by LPS and probably mediates the increase in prostaglandin synthesis in sepsis. COX-2–selective drugs are currently approved for the treatment of arthritis and pain, and they may prove to have some benefit in the treatment of sepsis. NS-398, a selective COX-2 inhibitor, blocks inflammatory prostaglandin synthesis but does not inhibit gastric prostaglandin production and does not produce gastric erosion.[112] L-745,337, also a COX-2–selective inhibitor, has been found to reduce the core body temperature increase induced by LPS in rats.[113] However, selective inhibition of COX-2 with NS-398 did not provide long-term protection to mice subjected to endotoxin shock or sepsis induced by CLP.[114] In another study, the effect of selective COX-2 inhibitors (DFU and NS-398) or nonselective COX inhibitors (diclofenac and proquazone) on survival in murine endotoxemia was assessed.[115] Only specific dosages of DFU, NS-398, and proquazone prevented endotoxin-induced lethality. The investigators concluded that the effect of COX inhibitors on endotoxin shock is highly dose- and compound-dependent. Other studies with multiple injury models have shown that treatment with NS-398 in mice subjected to burns and *Pseudomonas aeruginosa* infections improved survival and absolute neutrophil count and reduced macrophage PGE_2 production.[116] The survival of mice traumatized by femur fracture and hemorrhage was improved by N-398.[117] Increases in in vivo IL-6 and in vitro Kupffer cell IL-6 production were inhibited in mice subjected to hemorrhage and subsequent CLP-induced sepsis.[118] Recent studies in COX-2–deficient mice suggest that COX-2–derived eicosanoids are deleterious in endotoxemia. Compared with endotoxemic wild types, COX-2–deficient mice exhibited improved survival, blunted inflammatory cell infiltration of tissues, suppressed NF-κB activation, and increases in the anti-inflammatory cytokine IL-10.[119] As even more selective COX-2 inhibitory drugs become available, more definitive assessment of COX-2 involvement in trauma and sepsis may be ascertained.

Pretreatment with TXA_2 synthase inhibitors or TXA_2 receptor antagonists improves survival time or attenuates certain shock sequelae in endotoxemic animals. The pathophysiologic events ameliorated by these pharmacologic agents include pulmonary hypertension,[120,121] reduced cardiac output, hypotension,[122,123] decreased renal blood flow, decreased glomerular filtration rate,[121,123,124] thrombocytopenia,[120-125] renal glomerular fibrin deposition,[126] and renal glomerular microthrombi.[123] Most studies have shown that the beneficial effects of these drugs are not obtained if they are given after endotoxin. However, in a porcine study, the TXA_2 synthase inhibitor dazmegrel, when administered 3 hours after endotoxin infusion in a chronically instrumented young piglet model, was shown to reduce pulmonary hypertension and hypoxemia.[127] Other studies have not demonstrated improved outcome in sepsis and endotoxic shock.[128] Presumably, in these experiments, mediators other than TXA_2 dominate to produce pathophysiologic sequelae contributing to the development of shock and mortality. Use of TXA_2 receptor antagonists in endotoxemia may have several advantages over the use of TXA_2 synthase inhibitors. TXA_2 receptor antagonists block the effects of both PGH_2 and TXA_2 to activate TXA_2 receptors and do not produce shunting of PGH_2 to PGE_2 synthesis.

The 5-lipoxygenase inhibitor diethylcarbamazine improved the survival of mice in endotoxic shock,[93] and CGS8515 attenuated endotoxin-induced hemoconcentration and hypotension in rats.[129] AA-861, another 5-lipoxygenase inhibitor, attenuated endotoxin-induced neutropenia and concomitant oxygen radical synthesis in rats[130] and improved survival in endotoxemic mice.[131] L-651,392 blocked endotoxin-induced pulmonary hypertension and bronchoconstriction and increased arterial-alveolar oxygen difference and lung microvascular permeability in sheep.[94] Inhibition of 5-lipoxygenase by MK-886 attenuated hypotension and partially reversed the impaired vascular responsiveness to phenylephrine and acetylcholine.[132] MK-886 also inhibited coronary vasoconstriction and loss of myocardial contractility induced by *Escherichia coli* hemolysin in perfused rat hearts.[133]

Further evidence for the role of lipoxygenase products in endotoxin-induced shock sequelae is provided by studies using specific leukotriene receptor antagonists in experimental endotoxemia. The sulfidopeptide leukotriene receptor antagonist FPL57231 attenuated endotoxin-induced bronchoconstriction and pulmonary hypertension in sheep and cats.[134,135] The LTD_4 receptor antagonist SKF104353 prevented endotoxin-induced hemoconcentration and thrombocytopenia and improved survival time in rats.[136] The LTD_4/E_4 receptor antagonist LY171883 improved endotoxin-induced hypotension, hemoconcentration, and leukopenia in rats. SKF104353 and LY171883 were shown to prevent acute splanchnic permeability changes induced by endotoxin in rats[137] and mesenteric ischemia in pigs.[76] The LTB_4 receptor antagonist LY233978 has been shown to attenuate endotoxin-induced leukopenia, hemoconcentration, and hypotension in rats.[138] The LTB_4 antagonist LY306669 attenuated lung injury in a porcine endotoxemic model.[139] However, the protective effect of inhibitors of leukotriene biosynthesis or receptor antagonists may depend on the experimental model. MK-886 and an LTB_4 receptor antagonist, CP-105,696, reduced neutrophil infiltration into the peritoneal cavity, increased the peritoneal bacterial count, and reduced the survival rate in rats rendered septic by CLP.[95]

Some studies used combination therapy with cyclooxygenase inhibitors and leukotriene receptor antagonists or lipoxygenase inhibitors. Young and Passmore examined the effect of combined therapy with ibuprofen and LY171883 in canine endotoxic shock.[140] Combined blockade was more effective in maintaining blood pressure and cardiac output but provided no greater protection of renal blood flow or glomerular filtration rate. Turner and colleagues demonstrated good protection with a combined cyclooxygenase and lipoxygenase inhibitor (SKF86002) in a rat model of endotoxin-induced ARDS.[141] The inhibitor blocked the increase in lung wet-dry ratio, total bronchoalveolar lavage protein, hemoconcentration, and thrombocytopenia.

In contrast to the deleterious effects of certain eicosanoids (e.g., TXA_2), other prostanoids (e.g., PGE_1, PGI_2, 15-deoxy-$\Delta^{12,14}$-PGJ_2) may be beneficial in shock. PGI_2 infusion has been shown to be protective in canine endotoxic shock.[142] Prolonged PGE_1 infusion also had beneficial hemodynamic effects in hemorrhagic shock.[143] The cyclopentenone prostaglandin 15-deoxy-$\Delta^{12,14}$-PGJ_2 has been shown to be beneficial in several in vivo models of inflammation.[144-146] Although 15-deoxy-$\Delta^{12,14}$-PGJ_2 has been touted as the endogenous ligand for PPAR-γ, it is clear that it has PPAR-γ–independent effects that may be anti-inflammatory. The latter include inhibition of ERK1/2 and NF-κB signaling in response to microbial stimuli.[68,70,147,148] Recently, 15-deoxy-$\Delta^{12,14}$-PGJ_2 was found to improve the survival of rats subjected to polymicrobial sepsis induced by CLP and to inhibit tissue NF-κB and activator protein-1 signaling, tissue neutrophil infiltration, and cytokine production.[149]

SIGNIFICANCE OF EICOSANOIDS IN CRITICALLY ILL PATIENTS

Several studies have reported increased PLA_2-II, TXB_2, 6-keto-$PGF_{1\alpha}$, PGE_2, and $PGF_{2\alpha}$ levels in patients with septic shock.[150-152] Plasma PLA_2-II levels have been shown to correlate with hypotensive episodes and mortality in patients with acute sepsis and multiple organ failure. Oettinger and colleagues evaluated the relationship between plasma TXB_2 and 6-keto-$PGF_{2\alpha}$ levels and the severity of organ dysfunction in 106 patients with Gram-negative septic shock.[152] As in other studies, TXB_2 and 6-keto-$PGF_{1\alpha}$ levels were elevated throughout the course of sepsis but were highest during the early phase. TXB_2 levels were higher in hypodynamic patients than in hyperdynamic patients, whereas the opposite was observed for 6-keto-$PGF_{1\alpha}$. Patients in the hyperdynamic group had improved lung and kidney function, as determined by alveolar-arterial PO_2 gradient and creatinine clearance. In patients who underwent esophagectomy, which is associated with a high incidence of ARDS, there was a significant postoperative increase in postpulmonary TXB_2 levels only in patients who developed ARDS.[153] In patients with traumatic head injury, there was an increase in the TXB_2/6-keto-$PGF_{1\alpha}$ ratio in plasma, which positively correlated with the severity of injury and death.[154] Collectively, these studies demonstrate increased thromboxane and prostacyclin synthesis in patients with sepsis, trauma, or ARDS and suggest a deleterious role for thromboxane.

Leukotriene levels were also increased in several clinical situations. Seeger and coworkers reported increased LTB_4 metabolites in the bronchoalveolar lavage fluid of patients with ARDS.[101] Elevated sulfidopeptide leukotriene levels have also been reported in the bronchoalveolar lavage fluid, blood, and urine of patients with trauma or ARDS.[97,99,155] Higher leukotriene levels correlated with poor prognosis. Acutely ill patients with elevated plasma LTB_4 levels had a greater risk of developing ARDS than did those with lower levels.[100] Urinary excretion of LTE_4 was higher in trauma patients who developed ARDS than in those who did not have ARDS.[155]

There have been some clinical trials with eicosanoid inhibitors. Despite the association between increased plasma PLA_2-II concentration and sepsis severity, a human phase II trial in severe sepsis demonstrated that PLA_2-II inhibition was of no benefit.[156] The NSAIDs may have beneficial effects in the treatment of patients with trauma or sepsis. Faist and coworkers studied the effect of indomethacin in a randomized, prospective study of 43 patients undergoing major surgical trauma.[157] The cellular immune status was evaluated preoperatively and up to a week after surgery. In contrast to untreated patients, patients receiving indomethacin exhibited an improvement in delayed-type hypersensitivity responses and mitogen-induced lymphocyte transformation and a lower rate of opportunistic infection. These results suggest that NSAIDs, by preventing the impairment of cell-mediated immunity, may reduce susceptibility to sepsis after surgery.

Bernard and associates conducted a double-blind, placebo-controlled trial of intravenous ibuprofen (10 mg/kg; maximum dose, 800 mg) given every 6 hours for eight doses in 455 patients with a diagnosis of sepsis.[158] The ibuprofen-treated group did not experience any increased incidence of renal dysfunction, gastrointestinal bleeding, or other adverse effects. Short-term treatment with ibuprofen did not significantly affect the duration of shock or the 30-day survival rate. However, ibuprofen did produce significant declines in urinary 6-keto-$PGF_{1\alpha}$ and TXB_2 excretion, temperature, heart rate, oxygen consumption, and lactic acidosis. In a subsequent analysis of a subset of hypothermic septic patients in this study, ibuprofen treatment was demonstrated to improve 30-day survival.[159]

In contrast to studies with eicosanoid inhibitors, certain eicosanoids may have beneficial hemodynamic or anti-inflammatory effects. Liposomal encapsulated PGE_1 was shown to reduce hypoxemia and to improve lung compliance and survival in a study of 25 ARDS patients.[160] However, in a subsequent phase III clinical trial with a total of 350 ARDS patients, intravenous liposomal PGE_1 was shown to improve indices of oxygenation but did not decrease the duration of mechanical ventilation or improve 28-day survival.[161] Aerosolized PGI_2 has also been tested in ARDS patients. The effect of PGI_2 was similar to that of inhaled nitric oxide, in that it induced pulmonary vasodilatation and improved ventilation perfusion.[162-164] This treatment approach also prevented hypoxemia in ARDS patients with respiratory failure caused by pneumonia.[165]

These studies provide the impetus for more extensive studies of eicosanoids and eicosanoid-altering drugs in trauma, sepsis, and ARDS. Also, the new generation of COX-2 inhibitors, with fewer side effects than traditional NSAIDs in critically ill patients, remains to be tested. Experimentally, combinations of drugs have been more effective than single-drug treatments.[166-171] Of particular interest, in view of the demonstrated increase of lipoxygenase products in patients with ARDS, is the potential application of lipoxygenase inhibitors or leukotriene receptor antagonists. The potential beneficial effect of certain eicosanoids (e.g., PGI_2) in ARDS suggests that complete inhibition of eicosanoid synthesis may not be desirable. Finally, the new and evolving concept that specific eicosanoids play pivotal roles in inflammation resolution[59,67] may direct future therapeutic interventions.

ACKNOWLEDGMENTS

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ANNOTATED REFERENCES

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This review covers previous studies and recent experimental approaches for immunologic therapies for sepsis. Problems associated with entry criteria and definitions of sepsis are discussed, as are future recommendations.

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The effect of ibuprofen on sepsis severity was examined in a large randomized, double-blinded, placebo-controlled trial. Ibuprofen reduced eicosanoid synthesis, fever, tachycardia, oxygen consumption, and lactic acidosis but did not prevent shock or improve survival.

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This study provides evidence for a third distinct cyclooxygenase isoenzyme, COX-3, which is inhibited by acetaminophen. Inhibition of COX-3 may be a mechanism whereby drugs decrease pain and fever.

Lawrence T, Willoughby DA, Gilroy DW: Anti-inflammatory lipid mediators and insights into the resolution of inflammation. Nat Rev Immunol 2002;2:787-795.

This review examines lipid mediators that switch off inflammation. Endogenous mediators such as lipoxins and cyclopentenone prostaglandins suppress inflammatory gene expression, cell trafficking, inflammatory cell apoptosis, and phagocytosis, which are determinants of successful resolution of inflammation.

Chapter 42
NITRIC OXIDE

Sabah Hussain

KEY POINTS

1. **Nitric oxide (NO) has both direct and indirect modes of action.** Direct actions usually occur at relatively low levels of NO and include reaction with transition metals, including iron and copper. Activation of guanylate cyclase by NO is a prime example of a direct NO action. Indirect actions involve the reaction of NO with oxygen radicals and the formation of reactive nitrogen species, including the highly reactive peroxynitrite.
2. **NO is synthesized by three isoforms of nitric oxide synthase (NOS).** Neuronal NOS is constitutively expressed in central neurons, skeletal muscles, pulmonary epithelial cells, and nerve fibers supplying the lungs and intestinal system. Endothelial NOS is constitutively expressed mainly in endothelial cells. Inducible NOS has limited expression in normal cells; however, its expression is highly induced in response to proinflammatory cytokines and bacterial lipopolysaccharides.
3. **Activity of the human inducible NOS promoter** is less responsive to proinflammatory cytokines than is that of the murine promoter. Induction of inducible NOS expression in human cells is dependent on multiple transcription factors, including nuclear factor kappa-B and activator protein-1, and interferon regulatory factors.
4. **The gene of human neuronal NOS** is very complex, and both tissue-specific promoter activities and tissue-specific alternative splicing regulate its expression. Changes in gene expression of endothelial NOS have been documented in response to inflammatory mediators, changes in tissue PO_2, and alterations in regional blood flow.
5. **NOS activity can be inhibited in vivo** by many commercially available compounds, the majority of which are non–isoform selective. This category of nonselective inhibitors includes L-arginine analogs, aminoguanidine, and thiourea compounds. Highly selective inhibitors of inducible NOS have recently become available, including 1400W, GW273639, and GW274150.
6. **In normal vessels,** constitutive NO production by endothelial NOS localized in endothelial cells provides an important dilator mechanism that opposes the local myogenic response. This effect is mediated by activation of soluble guanylate cyclase and increased production of cyclic guanosine monophosphate in vascular smooth muscles. Inhibition of endothelial NO release induces a reduction in blood flow in various organs as a result of unmasking of the local myogenic tone.
7. **Basal NO production by endothelial cells** is sensitive to changes in shear stress and promotes higher local blood flow during increased metabolic demands (active hyperemia) and in response to transient interruptions of blood flow (reactive hyperemia).
8. **In septic patients,** many reports have documented high levels of plasma NO in adult patients with septic shock or severe sepsis and in pediatric patients with severe sepsis. The rise in plasma NO levels correlates negatively with patient survival. The exact isoform responsible for increased vascular NO production in septic humans remains to be documented.
9. **Infusion of nonselective NOS inhibitors in septic patients** restores arterial pressure and peripheral vascular resistance but significantly reduces cardiac output in septic patients. In one clinical trial, infusion of a nonselective NOS inhibitor in septic patients augmented mortality and resulted in early termination of the trial, leading to the conclusion that selective inhibitors of inducible NOS rather than nonselective NOS inhibitors should be administered to septic patients.
10. **Augmented NO production** has been documented in the livers of animals with severe sepsis or in hepatocytes exposed to proinflammatory cytokines. Administration of nonselective NOS inhibitors worsened liver injury in septic animals due to inhibition of constitutive endothelial NOS activity in hepatocytes and hepatic endothelial cells. Contradictory results have been reported in terms of whether inducible NOS plays a detrimental or a beneficial role in preventing hepatic injury in septic animals.

Nitric oxide (NO) may be the most intensively studied molecule over the past 20 years, by virtue of its functional centrality in almost every mammalian biologic system. It is most closely associated with the cardiovascular system, although thousands of publications have implicated NO in the

regulation of many other physiologic processes as well. Detailing all the biologic functions of NO is beyond the scope of this chapter. What is presented is a brief discussion of the basic chemistry of NO, the structure and biochemical characteristics of the enzymes that synthesize it, how they are regulated, and NO's role in regulating vascular tone and hepatic function under normal conditions and in humans with severe sepsis or inflammatory liver injury.

BASIC CHEMISTRY

NO is a signaling and effector molecule with a wide range of biologic functions, including the regulation of blood pressure, neurotransmission, and tissue metabolism. Although it is considered a free radical, NO is not highly reactive per se. It mediates biologic functions through direct and indirect effects. Direct effects are mediated by physiologic (nonmolar) concentrations that help maintain homeostasis in most systems. Direct actions include reactions with transition metal centers (particularly iron and copper) in proteins, with the result being either protein activation or inhibition.[1] However, the most well-known direct effect of NO is its activation of soluble guanylate cyclase, which results in an increase in intracellular cyclic guanosine monophosphate (cGMP), an important regulator of smooth muscle contractility, platelet aggregation, and leukocyte adhesion.[2]

Direct effects of NO also include its reaction with cysteine redox centers, a process known as S-nitrosylation.[1] Several proteins have recently been identified as undergoing S-nitrosylation by NO, resulting in either activation or inhibition of activity. These proteins include nuclear factor kappa-B (NF-κB), Ca^{++}-dependent K^+ channels, ryanodine receptors, and caspase-3. Finally, NO also diffuses into red blood cells and reacts with oxyhemoglobin, forming NO_2 and methemoglobin.

Indirect effects of NO are mediated through its interactions with O_2 and O_2^- and are usually elicited by relatively high (micromolar) concentrations of NO. In aqueous solutions, NO reacts with O_2 to form NO_2 and N_2O_3 (a potent S-nitrosylating agent), a reaction that is biologically relevant only at high concentrations of NO.[3] The most important indirect effect of NO is its near diffusion-limited reaction with O_2^- anions to generate peroxynitrite ($ONOO^-$), a highly reactive radical with a very short in vivo half-life (1 sec).[4] Peroxynitrite rapidly dissociates to peroxynitrous acid or a carbonate adduct, which in turn rapidly generates carbonate and NO_2 radicals.[4] Peroxynitrite is a major contributor to cellular oxidative stress as a result of enhancement of thiol oxidation and lipid peroxidation and inhibition and inactivation of major antioxidant defenses such as reduced gluathione and superoxide dismutases (SODs).[5] It also targets specific tyrosine residues in several proteins and generates 3-nitrotyrosine. The range of tyrosine-nitrated proteins so affected includes those involved in apoptosis, glycolysis, mitochondrial respiration, structural support, and antioxidant defenses.[6] Tyrosine nitration of even a single residue, as in the case of Mn-SOD, may result in drastic inhibition of protein activity.

Formation of 3-nitrotyrosine has also been linked to several human pathologies, including acute lung injury and severe sepsis. It should be emphasized that the formation of peroxynitrite is usually restricted to specific conditions in which the local levels of both NO and O_2^- are substantially elevated. Under normal conditions, however, O_2^- anions are converted to H_2O_2 by SODs without significant peroxynitrite formation. It is also noteworthy that despite the possibility of peroxynitrite formation under special circumstances, physiologic NO production is considered an antioxidant pathway because of the direct antioxidant actions of NO, which consist of reduction of toxic oxidants such as ferryl cations, inhibition of Fe^{+++}-catalyzed generation of hydroxyl radicals, and termination of lipid peroxidation.[7] Indirect antioxidant actions of NO include the induction of ferritin synthesis, which helps reduce free Fe^{++} levels. In addition, NO promotes the expression of heme oxygenase I, an important antioxidant enzyme by virtue of its products, carbon monoxide and bilirubin.[8] Finally, NO induces the expression of extracellular SOD, a key antioxidant enzyme responsible for dismutation of O_2^- anions in the vascular system.[9]

NITRIC OXIDE SYNTHASES

NO is produced by NO synthases (NOSs) from the terminal guanidine nitrogen of L-arginine through a reaction that requires two molecules of O_2 and 1.5 mol of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH). Three distinct isoforms of NOS have been identified, each of which is a product of different genes and has different localization, regulation, catalytic properties, and inhibitor sensitivities. These isoforms are neuronal NOS (nNOS), which is expressed predominantly in neuronal tissue; inducible NOS (iNOS), which is inducible in a wide range of cells; and endothelial NOS (eNOS), which is expressed mainly in endothelial cells. NOS isoforms have also been classified on the basis of their constitutive (eNOS and nNOS) or inducible (iNOS) expression and their Ca^{++} dependence (eNOS and nNOS) or independence (iNOS). The nNOS gene (chromosome 12) has a complex structural organization with 29 exons and 28 introns and codes for a 1434–amino acid protein, whereas both the iNOS (chromosome 17) and eNOS (chromosome 7) genes consist of 26 exons and 25 introns, coding for 1153 and 1203 amino acids, respectively.[10]

All NOS isoforms consist of two domains—an N-terminal oxygenase domain that binds to heme, tetrahydrobiopterin (BH_4), and L-arginine, and a C-terminal reductase domain that binds to flavins (flavin adenine dinucleotide [FAD], flavin mononucleotide [FMN]) and NADPH (Fig. 42-1). NOSs are active only when they are homodimers, and they require an electron transfer from NADPH, which is catalyzed by bound FMN and FAD. BH_4 is required for dimerization, for coupling of NADPH oxidation to NO synthesis, and for protection against oxidation and autoinactivation. NOS proteins undergo autoinhibition when NO reacts with Fe^{++} atoms of the NOS-bound heme group, resulting in inhibition of NOS activity. The nNOS isoform is the most susceptible of the three to autoinhibition, with 95% of its activity being inhibited by self-derived NO.[11]

REGULATION OF NITRIC OXIDE SYNTHASES

The rate of NO production by NOS isoforms is regulated at several levels, including transcriptional and post-transcriptional regulation of NOS expression and pharmacologic regulation of NOS protein activity and localization.

TRANSCRIPTIONAL REGULATION

Human promoters of the three NOS isoforms have been cloned and characterized. With respect to iNOS, it has been well established that stimuli such as bacterial lipopolysaccharide

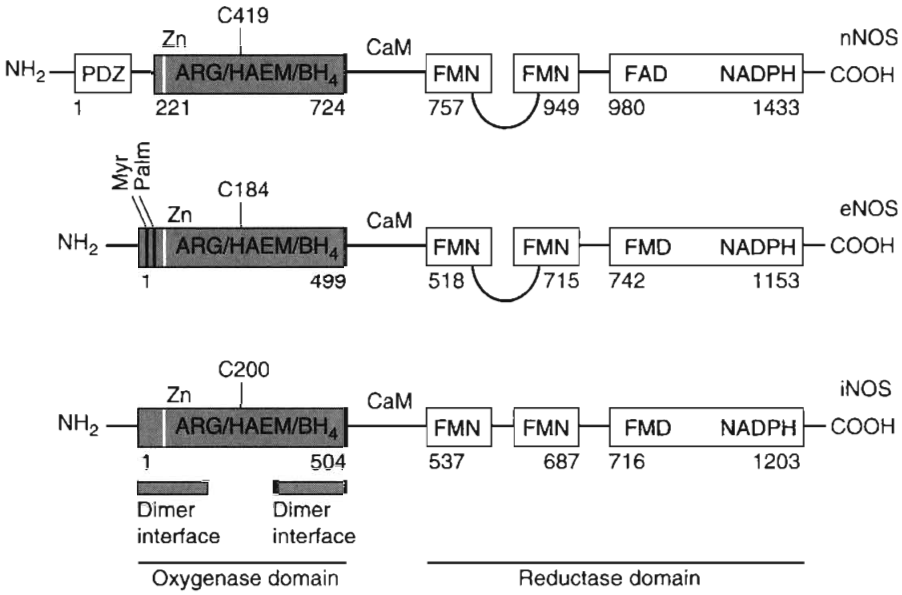

FIGURE 42–1. Domain structure of human neuronal nitric oxide synthase (nNOS), endothelial nitric oxide synthase (eNOS), and inducible nitric oxide synthase (iNOS). Oxygenase, reductase, and PDZ domains are denoted by solid boxes, and the amino acid residue number at the start or end of each domain is shown. The cysteine residue, which ligates the heme and the calmodulin binding site, is indicated for each isoform. Myristoylation (Myr) and palmitoylation (Palm) sites on eNOS are shown, as is the location of the zinc-ligating cysteines (Zn). The autoinhibitory loop within the flavin mononucleotide (FMN) regions of nNOS and eNOS is also shown, and gray bars indicate the dimer interface in the oxygenase domain. ARG, arginine; BH_4, tetrahydrobiopterin; NADPH, reduced form of nicotinamide adenine dinucleotide phosphate. (Adapted from Alderton WK, Cooper CE, Knowles RG: Nitric oxide synthases: Structure, function and inhibition. Biochem J 2001;357:593-615.)

(LPS) and cytokines, including tumor necrosis factor (TNF), interleukin (IL)-1, and interferon (IFN)-γ, are capable of inducing iNOS messenger RNA (mRNA) and protein in many human cells, including macrophages, hepatocytes, smooth muscles, and chondrocytes. In normal humans, iNOS mRNA expression is present in a few cell types, for example, airway epithelial cells. Cloning and expression of 8.3 and 16 kilobases (kb) of the human iNOS promoter revealed the following characteristics[12,13]: (1) Human promoter activity is only modestly induced in response to exposure of cultured cells to an LPS and cytokine mixture, compared with murine iNOS promoter activity. This difference has been attributed to the presence of multiple inactivating nucleotide substitutions in the enhancing elements responsible for LPS- and cytokine-induced expression in the human iNOS promoter. (2) Sequences conferring LPS and cytokine inducibility of the human iNOS promoter reside at upstream locations from the transcription initiation site (>4 kb). (3) Multiple transcription factors are involved in activating the human iNOS promoter, including the NF-κB family of transcription factors, activator protein-1 transcription factors, STAT-1α (signal transducer and activator of transcription) and INF regulatory factor-1. (4) Synergism between these transcription factors is required for enhancing iNOS promoter activity.

The expression of iNOS is also regulated by changes in mRNA stability and protein translation. The presence of several ATTTA sequence motifs (involved in protein-mRNA interactions) at the 3′ untranslated region (UTR) of human iNOS mRNA suggests that its stability may undergo significant regulation. Expression of iNOS mRNA is also regulated by alternative splicing within both 5′ UTR and the coding sequence.[14]

The human eNOS promoter possesses several binding sites for Sp1, GATA, activator proteins (AP-1, AP-2), $E_2$6 transformation specific (ETS), NF-κB, nuclear factor-1, NF-IL-6, shear stress, cyclic adenosine monophosphate response, acute-phase response, and IFN-induced transcription factors.[15] In vivo analysis of transgenic mice expressing 5200 base pairs of murine eNOS promoter elicited a robust expression in large and medium blood vessels, whereas small arterioles, capillaries, and venules showed very little transcriptional activity. In addition, many stimuli, including estrogens, angiotensin II, proinflammatory cytokines, and hypoxia, alter eNOS mRNA expression through changes in its half-life.

The nNOS gene is the most complex human gene yet described in terms of promoter diversity and alternative splicing. Wang and colleagues described nine unique exon 1 variants of nNOS (exons 1a through 1i) that are associated with transcript initiation in various tissues.[16] Exons 1a, 1b, and 1c are abundantly expressed in skeletal muscles, whereas exons 1f, 1g, and 1i are present mainly in the brain. All nine exons are expressed in the testis. Analysis of alternative splicing of nNOS mRNA uncovered two main variants, nNOSβ and nNOSγ, which have 136- and 125-kDa molecular masses and are capable of producing 80% and 3% of nNOSα activity, respectively. Another splice variant of nNOS is nNOSμ, which has an additional 34 amino acids inserted between exons 16 and 17. It is abundantly expressed in skeletal muscle and in penile and urethral tissues.[17] This variant has similar enzyme kinetics to those of nNOSα.[17]

POST-TRANSLATIONAL REGULATION

One of the most important regulators of NOS activity is calmodulin binding, which increases the rate of electron transfer from NADPH to the flavins and heme group. It is triggered by a rise in intracellular Ca^{++} and is inhibited by a motif of 40 to 50 amino acids localized in the FMN binding site. The absence of this motif in iNOS results in tight binding of calmodulin to the iNOS protein, rendering its activity insensitive to intracellular Ca^{++} fluxes (hence the term Ca^{++}- and calmodulin-independent). NOS activity is also regulated through interactions with specific proteins such as protein inhibitor of nNOS, which inhibits nNOS activity by preventing monomer dimerization.[18]

Another regulator of NOS activity is heat shock protein 90, which interacts directly with eNOS and augments its activity by promoting calmodulin binding.[19] Other eNOS protein modifications include dual acetylation by myristate and palmitate, which are required for localization of eNOS at the caveolae. Myristoylation is an irreversible process that involves a single N-terminus glycine, whereas palmitoylation is reversible and develops at Cys-5 and Cys-26 and is modulated by intracellular Ca^{++} levels.

NOS expression is also regulated when iNOS selectively interacts with two separate proteins, kalirin and a 110-kDa NOS-associated protein (NAP110).[20,21] Kalirin associates with iNOS in vitro and in vivo and inhibits its activity by preventing monomer dimerization. Similarly, NAP110 selectively interacts with the N-terminal portion of iNOS and inhibits its activity by about 90% in cultured cells.[21]

Finally, NOS activities are also mediated by phosphorylation of serine, threonine, and tyrosine residues. Increased shear stress and activation of protein kinase B induces eNOS phosphorylation at Ser-1177, which in turn activates this enzyme.[22] By contrast, phosphorylation of eNOS at Thr-495 inhibits its activity.[23] The nNOS protein is phosphorylated by Ca^{++} calmodulin-dependent kinases at Ser-847, thereby reducing nNOS activity.[24] There are also published reports of tyrosine phosphorylation of iNOS, which results in its activation.[25]

PHARMACOLOGIC REGULATION

Various biologic roles of NO have been uncovered as a result of the availability of pharmacologic inhibitors. However, many investigators have not been sufficiently careful in verifying the selectivity of these inhibitors, and a few have assigned in vivo isoform selectivity to inhibitors for which only in vitro selectivity has been established. Many NOS inhibitors, including L-arginine analogs such as N^G-monomethyl L-arginine (LNMMA), N^G-nitro-L-arginine (L-NA) and its methyl ester (L-NAME), thiocitrullines, 1400W, aminoguanidine, S-ethylisothiourea, N^5-iminoethyl-L-ornithine (L-NIO), N^6-iminoethyl-L-lysine (L-NIL), GW273629, and GW274150, bind NOSs at L-arginine binding sites and inhibit substrate binding. All these inhibitors require active enzyme activity and the presence of NADPH for their binding.[26] Aminoguanidine also inhibits NOS activity by forming complex covalent bonds with NOS proteins without interfering with NOS dimerization.[27]

Another class of inhibitors, including 4-amino BH_4 and BH_2, inhibit NOS activity by targeting the BH_4 binding site, whereas 7-nitroindazole and its related compounds compete for binding at both the L-arginine and BH_4 binding sites.[28] Additionally, the antifungal imidazoles hinder iNOS activity by binding to the heme group and competing with calmodulin binding.

Table 42-1 lists the selectivity and effective concentrations of various NOS inhibitors measured in vitro. Inhibitors with 10- to 50-fold selectivity are considered partially selective inhibitors. For example, S-ethyl- and S-methyl-L-thiocitrullines and ARL17477 are considered partially selective nNOS inhibitors. L-NIO and L-NIL are considered partially selective iNOS inhibitors. Recently, highly selective iNOS inhibitors have become available, such as 1400W, GW273639, and GW274150, which have enabled investigators to evaluate the functional roles of iNOS in a variety of physiologic contexts. It should be emphasized, though, that aminoguanidine, the most widely used iNOS inhibitor, has only about a 10-fold selectivity for iNOS relative to eNOS and has virtually no selectivity relative to nNOS. This inhibitor also attenuates catalase, diamine oxidase, and polyamine metabolism.

BIOLOGIC FUNCTIONS OF NITRIC OXIDE

NORMAL VASCULAR TONE

Vasodilatation is the earliest discovered and most widely studied action of NO in the cardiovascular system. In a 1980 landmark study, Furchgott and Zawadzki described the obligatory role of endothelium-derived relaxing factor in inducing vascular smooth muscle relaxation of large conduit vessels.[29] Two studies in 1986 and 1988 identified endothelium-derived relaxing factor as NO and proposed the presence of an NO synthesizing protein in endothelial cells.[2,30] The most important NOS isoform in the regulation of normal vascular tone is certainly eNOS. Although the nNOS isoform is expressed in perivascular nerves, cardiac conduction pathways, and myocardial sarcoplasmic reticulum, it is less important than eNOS in regulating vascular tone.

It is well established that eNOS-derived NO production by the endothelial cells is activated very rapidly by longitudinal shear forces acting on the endothelium and generated by blood flow and by the pulsatile stretch of the vasculature. This flow-dependent NO release provides a crucial mechanism for the dynamic coupling of tissue metabolic demands and upstream vascular resistance and has been documented in conduit arteries, resistance arteries, arterioles, and venules.[31] Because shear stress in blood vessels is determined by flow velocity, flow pulsatility, blood viscosity, and vessel diameter, these variables have significant effects on endothelial NO release both in vitro and in vivo (Fig. 42-2). Basal endothelial NO release in normal vessels is in dynamic equilibrium with the local constrictor provided by the intrinsic myogenic tone of smooth muscles and by sympathetic vasoconstrictor drive. When eNOS-derived NO synthesis is inhibited in vivo, the local myogenic tone becomes unmasked and causes a reduction in vessel diameter and a rise in vascular resistance in almost all vascular beds.[32] The dilator effect of NO on smooth muscles is triggered by soluble guanylate cyclase activation, which results in increased production of the second messenger cGMP. In turn, cGMP activates two cGMP-dependent protein kinases (PKGI and II), which regulate smooth muscle intracellular Ca^{++} levels and hence contractility by increasing Ca^{++} sequestration in and inhibiting Ca^{++} release from the sarcoplasmic reticulum.[33] In certain vascular beds, NO evokes smooth muscle relaxation by hyperpolarizing membrane potential, an effect that is mediated by the activation of Ca^{++}-dependent K^+ channels. Finally, NO-mediated smooth muscle relaxation can also be the result of a prejunctional effect on adrenergic nerve fibers, leading to inhibition of local catecholamine release.[34]

Increased shear stress also up-regulates eNOS expression when maintained for relatively long periods. Indeed, significant induction of eNOS mRNA and protein has been documented in cultured endothelial cell preparations in which shear stress was artificially maintained and in in vivo settings in which organ blood flow and shear stress were chronically elevated in response to exercise training or the result of arteriovenous fistulas.[35]

Vascular NO production is also acutely activated in response to agonist stimulation of endothelial membrane receptors by acetylcholine, adenosine triphosphate, bradykinin, and substance P. These agonists are synthesized and released by endothelial cells in response to shear stress and mechanical perturbations and act in an autocrine fashion to stimulate their prospective receptors. Activation of these receptors elicits a rise in intracellular Ca^{++} concentrations and thereby activates eNOS. Agonist-induced endothelial NO release, especially by adenosine triphosphate and bradykinin, provides another mechanism through which tissue metabolic demands are matched to local blood flow, as in human heart and forearm vasculatures.[36]

TABLE 42–1. SELECTIVITY OF NITRIC OXIDE SYNTHASE INHIBITORS

Inhibitor	IC_{50} (μM)			Selectivity (Fold)		
	iNOS	*nNOS*	*eNOS*	*iNOS*	*nNOS*	*eNOS*
L-NA*	3.1	0.29	0.35	0.09	0.11	1.2
LNMMA	6.6	4.9	3.5	0.7	0.5	0.7
7-NI*	9.7	8.3	11.8	0.9	1.2	1.4
ARL17477	0.33	0.07	1.6	0.2	5.0	23†
AG*	31	170	330	5.5	11†	1.9
L-NIL	1.6	37	49	23†	49†	1.3
1400W	0.23	7.3	1000	32†	>4000‡	>130‡
GW273629	8.0	630	1000	78‡	>125‡	>1.6
GW274150	1.4	145	466	104‡	333‡	3.2

Results shown are for human NOS isoforms expressed in a baculovirus expression system. Activity assays were performed on cell lysates in the presence of 30 μM at 37°C for 15 minutes. NOS inhibitors were pre-exposed to inhibitors for a 15-minute period.
* Data obtained from J. Dawson and R. G. Knowles, unpublished results.
† Partially selective.
‡ Highly selective.
AG, aminoguanidine; eNOS, endothelial NOS; iNOS, inducible NOS; L-NA, N^G-nitro-L-arginine; L-NIL, N^6-iminoethyl-L-lysine; LNMMA, N^G-monomethyl-L-arginine; nNOS, neuronal NOS; NOS, nitric oxide synthase.
Adapted from Alderton WK, Cooper CE, Knowles RG: Nitric oxide synthases: Structure, function and inhibition. Biochem J 2001;357:593-615. Data from Young et al, except as otherwise noted.

In addition to the regulation of basal blood flow, endothelial NO contributes to the vasodilatory response to elevated metabolic demands (active hyperemia). The degree of this contribution, however, differs among vasculatures. For instance, Hussain and coworkers reported that endothelial NO contributes between 20% and 40% of the total active hyperemia of the in situ diaphragm in dogs,[37] whereas up to 50% of human myocardial active hyperemia induced by cardiac pacing was mediated by endothelial NO release.[38] Endothelial NO also participates in the reactive hyperemic response, which is the dilatation that follows transient vascular occlusion. This contribution is much more pronounced in tissues with high metabolic demands and manifests as prolongation of reactive hyperemia duration, with no influence on peak reactive hyperemic flow.[39] Another vascular phenomenon that is partly regulated by endothelial NO is autoregulation, defined as the ability of tissues to maintain their perfusion independent of changes in arterial pressure. It has been reported that inhibition of endothelial NO production and the subsequent augmentation of local myogenic tone lead to an improvement in flow autoregulation. However, this improvement is dependent on local metabolic rate and is more pronounced in tissues with relatively low metabolic rates, such as the mesenteric vasculature, than in tissues with high metabolic rates, such as the heart, kidneys, and brain; in the latter tissues, NOS inhibition only lowers blood flow levels, with no effect on the autoregulatory range.[40]

In addition to its role in the regulation of blood flow, NO has important functional significance for tissue metabolism, by virtue of its effect on mitochondrial respiration. It has been well established that NO donors or endogenous NO production inhibits, albeit reversibly, the activities of cytochrome

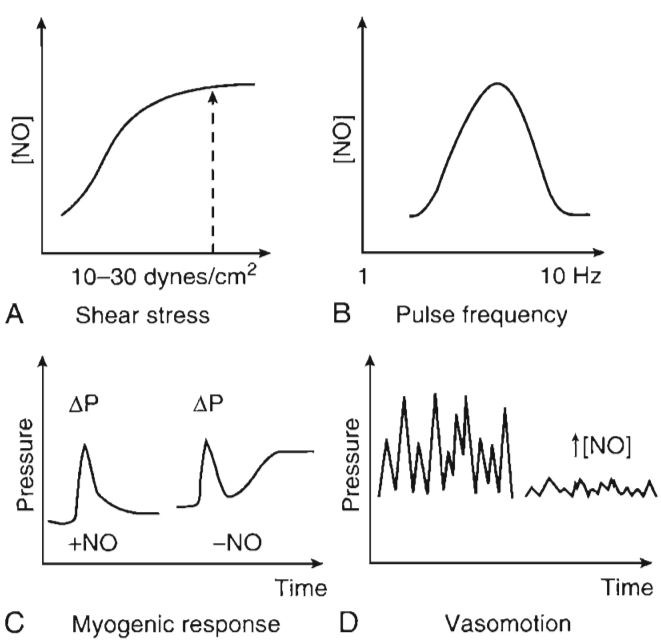

FIGURE 42–2. Key mechanisms involved in the regulation of perfusion by nitric oxide (NO). *A*, Endothelial NO production increases monotonically with time-averaged shear stress, reaching a plateau at 10 to 30 dynes/cm². *B*, NO release from the endothelium is sensitive to flow pulsatility, being maximal at pulse frequencies of about 5 Hz. *C*, In isolated vessels, acute increases in transmural pressure (ΔP) promote a myogenic constrictor response, normally attenuated by NO. Loss of NO activity also elevates basal constrictor tone. *D*, The amplitude of spontaneous oscillations in vascular caliber (vasomotion) is damped by NO. (Adapted from Griffith TM: Role of nitric oxide in the regulation of blood flow. In Ignarro LJ [ed]: nitric oxide Biology and Pathobiology. San Diego, Academic Press, 2000, pp 483-502.)

oxidase (the terminal enzyme of the mitochondrial respiratory chain) and aconitase (an important enzyme in the citric acid cycle).[41,42] Removal of this inhibition has been proposed as the mechanism behind the rise in whole body or organ oxygen consumption when NOS inhibitors are infused in vivo.[43]

Another vascular function of NO is the prevention of platelet aggregation. Many reports have confirmed that NO stimulates cGMP production inside the platelets and inhibits agonist-induced platelet aggregation through the regulation of intracellular Ca^{++} levels.[44] In addition, endothelial NO production has an important antiatherosclerotic function and protects against the early phase of atherosclerosis by inhibiting leukocyte adhesion to and migration through the endothelial cells. Both effects are achieved by reducing the expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and P-selectin.[45] The late stages of atherosclerosis are also inhibited by NO as a result of attenuation of endothelial permeability, reduction of lipoprotein influx into the vascular wall, and inhibition of oxidation of low-density lipoproteins.[46]

VASCULAR FAILURE DUE TO SEPSIS

The cardiovascular abnormalities associated with severe sepsis are characterized by low peripheral vascular resistance, hypotension, high cardiac output, maldistribution of blood flow, increased microvascular permeability, disseminated intravascular coagulation, and microthrombosis.[47] Many factors have been implicated in these dysfunctions, such as proinflammatory cytokines (TNF, IL-1, IFN-γ), reactive oxygen species, and prostaglandins that disrupt the normal balance between vasodilators (NO and prostacyclin) and vasoconstrictors (endothelins, catecholamines, angiotensin II). Numerous studies have also implicated excessive NO production by iNOS in the vascular dysfunction accompanying sepsis. The majority of these studies used models in which *Escherichia coli* LPS was administered as a bolus dose in mice or rats. In these models, arterial pressure declined within minutes of LPS injection, followed by partial recovery, then a sustained decline in pressure 3 to 4 hours later. It has now been well established that plasma concentrations of NO and its related products (NO_2^- and NO_3^-) rise severalfold in a progressive fashion a few hours after LPS injection. Moreover, many authors have documented iNOS mRNA and protein in endothelial cells, smooth muscles, cardiac myocytes, skeletal muscles, hepatocytes, and renal cells in LPS-injected rodents.[48] However, it should be emphasized that LPS rodent models of sepsis have limited clinical relevance, primarily because both rats and mice are less sensitive to LPS than humans are; thus, relatively large doses of LPS are required to elicit sepsis in these animals. A less dramatic rise or no change in NO production has been reported in rodent peritonitis models and in nonrodent models of sepsis. For instance, no significant changes in plasma NO levels were observed after short (<5 hours) or prolonged (9 to 18 hours) periods of endotoxemia in pigs. Moreover, only a 50% rise in plasma NO concentration was reported in endotoxemic dogs.[49]

Studies of humans with severe sepsis have also shown a significant increase in vascular NO production, but to a much lower degree than that observed in LPS rodent models. Ochoa and associates were the first to report that plasma NO_2^- and NO_3^- levels were higher in hyperdynamic septic patients than in trauma patients.[50] This finding was confirmed by Arnalich and colleagues, who also found that plasma NO_2^- and NO_3^- levels were higher in patients with septic shock than in those with only severe sepsis.[51] Moreover, plasma NO_x (combined NO, NO_2^-, and NO_3^-) concentrations were significantly greater in patients who died of postoperative sepsis compared with septic patients who survived.[52] In 53 pediatric patients with severe sepsis, Doughty and coworkers reported that plasma NO_2^- and NO_3^- concentrations measured on day 1 of admission predicted persistent failure of three or more organs and sequential organ failure, but not mortality.[53] This has prodded investigators to question whether the rise in plasma NO_x levels in septic patients is the result of iNOS expression or poor renal excretion of NO_x compounds. This question has not yet been answered; however, evidence is emerging that iNOS mRNA and protein are induced in many cells of septic patients, including neutrophils, alveolar macrophages, and skeletal muscles.[54-56] Whether this expression is sufficient to cause an increase in circulating plasma NO_x levels remains unclear.

Despite extensive documentation of elevated NO production in the vessels of septic animals and humans, the contribution of individual NOS isoforms to the pathogenesis of sepsis-induced vascular failure remains the focus of many investigators. In early studies published in 1990, the administration of nonselective NOS inhibitors (LNMMA, L-NA, L-NAME) in rodent LPS models of sepsis reversed early hypotension and improved vascular reactivity to vasoactive agents.[57,58] The initial euphoria triggered by these observations was dampened when severe reduction in cardiac output; worsening of cardiac function; exacerbated microvascular leakage; amplification of inflammation in the liver, kidney, and intestine; and augmented animal mortality were observed after several hours of LNMMA, L-NA, or L-NAME infusion in septic rodents. These findings led to the conclusion that nonselective NOS inhibitors are not beneficial for septic animals because they inhibit important homeostatic functions of eNOS. Subsequent studies using highly selective iNOS inhibitors revealed that selective elimination of iNOS activity in various animal models of sepsis reverses hypotension, restores vascular reactivity, improves myocardial function, attenuates acute lung injury, and partially restores mitochondrial function.[59-61]

Petros and coworkers were the first to report, in 1991, that the injection of nonselective NOS inhibitors (LNMMA and L-NAME) in septic human patients restored arterial pressure and peripheral vascular resistance.[62] Schilling and colleagues confirmed these findings but also reported that these inhibitors reduced cardiac output to 66% of initial values.[63] Restoration of vascular response to vasoactive agents, restoration of arterial pressure, and a significant decline in cardiac index have also been observed after L-NA injection in septic patients (Fig. 42-3).[64,65] Three subsequent prospective, uncontrolled trials used continuous infusion of either L-NAME (1 to 3 mg/kg/h for 12 to 24 hours) or LNMMA (up to 20 mg/kg/h for 8 hours) and reported sustained elevation of arterial pressure and peripheral vascular resistance, coupled with a significant decline in cardiac output.[66-68] Despite the restoration of arterial pressure, the effect of NOS inhibition on the outcome of septic patients is still being debated. A phase III prospective, randomized, double-blinded, placebo-controlled trial was conducted to treat septic patients with LNMMA, along with dobutamine to maintain cardiac output. This trial was recently terminated because of a statistically significant higher mortality in the treatment group.[69]

In addition to nonselective NOS inhibitors, investigators have used methylene blue (inhibitor of soluble guanylate cyclase) to counteract the effects of excessive NO production. Short-term infusion and bolus injection of this compound in septic patients raised mean arterial pressure by 10 mm Hg without affecting cardiac output.[70,71] Neither patient mortality nor the possibility that methylene blue might have effects other than inhibition of soluble guanylate cyclase was addressed.

In summary, it is apparent from animal and human studies that the use of nonselective NOS inhibitors to treat vascular failure due to sepsis is not warranted because of eNOS inhibition and elimination of the possible beneficial effects of iNOS, which include anti-inflammatory and anti–platelet aggregation effects. Future trials using highly selective iNOS inhibitors in patients with sepsis should aid in elucidating the extent to which overproduction of NO by this isoform contributes to sepsis-induced vascular failure.

LIVER FUNCTION

Under normal conditions, the eNOS isoform is the main source of NO in hepatic cells and is involved in the regulation of hepatic blood flow and the prevention of leukocyte infiltration and platelet adhesion.[72] Hepatic nNOS expression is limited to the nerve fibers supplying large hepatic vessels. All human liver cells are capable of expressing iNOS when exposed to LPS; cytokines such as TNF, IL-1β, and IFN; activators of protein kinase C; arachidonic acid metabolites; and platelet-activating factor.[73] Hepatic iNOS expression is strongly inhibited by glucocorticoids, NO or NO donors, and hepatocyte, epidermal, and transforming growth factors.[74] Hepatocyte NO synthesis is involved in many processes, such as protein synthesis, glucose synthesis from pyruvate and lactate, glucagon-stimulated glycogenolysis, and activity of cytochrome P_{450} enzymes, which are involved in drug metabolism.[75]

INFLAMMATORY LIVER INJURY

The involvement of NO in hepatic dysfunction has been investigated extensively in various models of liver injury. In LPS-induced models of sepsis, liver injury is characterized by the presence of neutrophil, lymphocyte, and macrophage infiltration and by hypertrophy, vacuolization, and chromosomal margination of hepatocytes. Moreover, elevated serum levels of aspartate transaminase (AST) and alanine transaminase (ALT) have been used extensively as an index of hepatic injury. It has been well established that in vivo LPS injection elicits a substantial rise in hepatic NO production, iNOS mRNA, and protein induction in hepatocytes and endothelial, Kupffer, and bile duct cells.[76]

Early studies in which nonselective NOS inhibitors (LNMMA and L-NAME) were used revealed that inhibition of all NOS isoforms worsens hepatic injury, causes a further rise in serum AST and ALT levels, increases hepatocyte necrosis and leukocyte infiltration, and enhances lipid peroxidation and oxidative DNA damage.[77] These changes have been attributed to interference with hepatic microcirculation and a severe reduction in sinusoidal blood flow as a result of the elimination of endothelial eNOS production. Similar worsening of liver injury with the use of nonspecific NOS inhibitors has been reported in hemorrhagic shock-induced hepatocyte injury[78] and alcoholic hepatitis.[79] Although these findings confirm a beneficial role for eNOS, the nature of iNOS involvement in liver injury is controversial, with deleterious, beneficial, or minimal roles being proposed.

Authors who have compared the in vivo effects of nonselective versus highly selective iNOS inhibitors in LPS models have concluded that iNOS promotes liver injury through the formation of peroxynitrite.[80] This is supported by Szabo and colleagues, who used S-methylisothiourea to inhibit iNOS activity and reported significant attenuation in serum AST, ALT, and bilirubin levels in septic mice.[81] By comparison, MacMicking and associates reported that the degree of LPS-induced liver injury in iNOS knockout mice was similar to that elicited in wild-type mice, suggesting that iNOS is not a major contributor to this injury.[82] It should be emphasized, however, that the degree of liver dysfunction in this study was mild, because relatively low doses of LPS were used. Alternatively, several authors have concluded that iNOS activity protects liver cells against injury and oxidative stress elicited by exposure to LPS or proinflammatory cytokines.

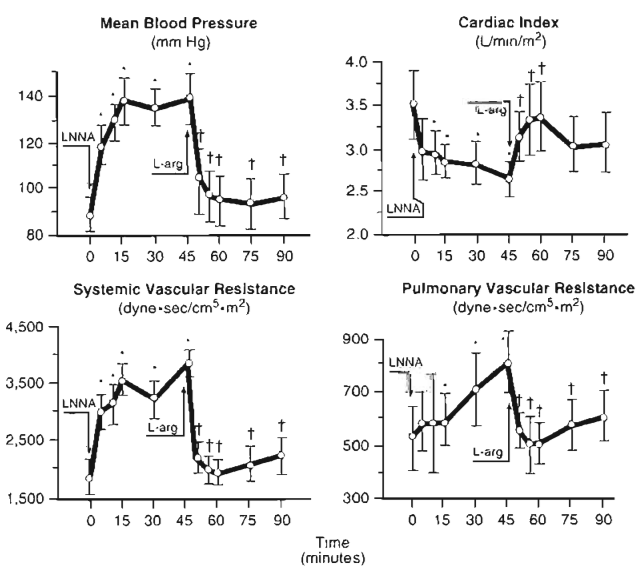

FIGURE 42–3. Hemodynamic changes induced by intravenous administration of Ng-nitro-L-arginine (LNNA) at minute 0 and L-arginine (L-arg) at minute 45 (mean ± standard error of the mean). *$P < 0.05$ for the comparison with minute 0; †$P < 0.05$ for the comparison with minute 45. (Adapted from Lorente JA, Landin L, De Pablo R, et al: L-Arginine pathway in the sepsis syndrome. Crit Care Med 1993;21:1287-1295.)

This proposal is supported by the observation that when iNOS mRNA was selectively expressed in the liver of transgenic mice, LPS-induced liver injury was attenuated by more than 50%, and the rise in plasma TNF and IL-1β levels was reduced as a result of NF-κB inhibition by iNOS activity.[83]

One possible mechanism by which iNOS activity may attenuate liver injury is through the inhibition of apoptosis. Ou and coworkers confirmed that continuous infusion of nonspecific NOS inhibitors into the portal vein significantly reduced serum AST and ALT levels and attenuated hepatic neutrophil infiltration 16 hours after LPS injection.[84] By comparison, selective iNOS inhibition with L-N-(1-iminoethyl)lysine did not alter AST and ALT levels or leukocyte infiltration; rather, it induced apoptosis of hepatocytes and endothelial cells, suggesting that hepatic iNOS activity may play an important antiapoptotic role. In summary, the contradictory conclusions regarding the role of iNOS in inflammation-induced liver injury are likely due to differences in the degree of liver damage, the rate of NO production, iNOS cellular localization, and the redox status of hepatic cells in various models of sepsis. Moreover, differences in the type, isoform selectivity, dosage, route, and timing of administration of NOS inhibitors should be taken into consideration when the role of iNOS is evaluated.

ANNOTATED REFERENCES

Aulak KS, Miyagi M, Yan L, et al: Proteomic method identifies proteins nitrated in vivo during inflammatory challenge. Proc Natl Acad Sci U S A 2001;98:12056-12061.

A proteomic approach was used for the first time to identify tyrosine-nitrated proteins in the lung and liver of septic animals. This study showed that nitration of tyrosine residues occurs in a wide variety of proteins, including glycolytic enzymes, protein involved in the regulation of apoptosis, and several important mitochondrial enzymes.

Furchgott RF, Zawadzki JW: The obligatory rule of endothelial cells in the relaxation of vascular smooth muscle by acetylcholine. Nature 1980;286:373-376.

This landmark study described the presence of endothelium-derived relaxing factor (EDRF), which is an important regulator of smooth muscle relaxation. In 1998, the first author was awarded the Nobel Prize for medicine for his discovery that EDRF is actually NO.

Jaffrey SR, Snyder SH: PIN: An associated protein inhibitor of neuronal nitric oxide synthase. Science 1996;274:774-777.

Protein inhibitor of nNOS (PIN), a subunit of the molecular motor dynein, was found to inhibit the activity of nNOS by preventing the dimerization of NOS monomers. The existence and tissue distribution of PIN were described for the first time.

Kilbourn RG, Gross SS, Adams J, et al: L-N^G-Methylarginine inhibits tumor necrosis factor–induced hypotension: Implications for the involvement of nitric oxide. Proc Natl Acad Sci U S A 1990;87:3629-3632.

This was one of the earliest studies to suggest that excessive NO production contributes to sepsis-induced hypotension. The authors found that infusion of TNF in dogs elicits systemic hypotension and that treatment with the NOS inhibitor L-NG-methylarginine reverses it.

Petros AJ, Bennett D, Vallance P: Effect of nitric oxide synthase inhibitors on hypotension in patients with septic shock. Lancet 1991;338:1557-1558.

The effect of NOS inhibition on the hemodynamics of patients with septic shock was described for the first time. In two septic patients whose blood pressure could not be restored by conventional therapy, administration of NG-monomethyl-l-arginine resulted in significant increases in blood pressure and systemic vascular resistance.

Chapter 43

CARBON MONOXIDE AND HEME OXYGENASE-1

Augustine M. K. Choi • Jigme Sethi

KEY POINTS

1. Heme oxygenase-1 (HO-1) is a unique enzyme with **dual roles in the cell—heme catabolism** and potent **cytoprotection**—and with antioxidant, antiapoptotic, antiproliferative, and anti-inflammatory activities.
2. HO-1 is **vigorously induced by** hypoxia, hyperoxia, heat shock, and a plethora of **oxidative and inflammatory stimuli.**
3. Increased activity of **HO-1** has been demonstrated to be **strongly protective** in a variety of models of oxidative stress and inflammation, including **acute lung injury, acute liver injury, acute renal failure, and cardiac xenotransplantation.**
4. All the **byproducts** of the reaction catalyzed by HO-1 **(ferritin, carbon monoxide) have major antioxidant and cytoprotective properties.**
5. **Carbon monoxide** has vasodilatory and bronchodilatory properties, functions as a neurotransmitter, and inhibits platelet and monocyte activation. It also demonstrates the cytoprotective properties attributed to HO-1 and **may be the major effector of the beneficial effects of HO-1 induction.**
6. **Carbon monoxide binds to heme proteins** such as **cytochrome P_{450},** which it inactivates, and **soluble guanylate cyclase,** which it activates, thus modulating cellular function.
7. **Carbon monoxide** also **can modulate signaling through the mitogen-activated protein kinase pathways,** thereby down-regulating inflammation.
8. **These beneficial effects of exogenous inhaled carbon monoxide** are noted at doses that are only a fraction of toxic levels—as low as 100 to 250 parts per million.

HISTORICAL PERSPECTIVE

Humans, like other obligate aerobes, are dependent on oxygen as the "molecule of life," but at a price—the potential for oxidative damage caused by free oxygen radicals. The introduction of molecular oxygen into the atmosphere forced adaptive changes in all existing forms of life, specifically to guard against oxidative damage. One such adaptation was the chelation of free iron, another essential molecule, into protoporphyrin complexes to prevent precipitation of the relatively insoluble oxidized ferric iron and the generation of toxic oxidant radicals by the reduction of ferric to ferrous iron. Recycling this sequestered iron between substrates in numerous biologic processes required the controlled catabolism of these protoporphyrin-iron, or heme, moieties. Thus it was no surprise when Tenhunen and associates identified heme oxygenase (HO) as the enzyme responsible for this reaction.[1] This enzyme uses the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) and three molecules of oxygen to cleave the alpha-methenyl bridges between pyrroles I and II of the heme porphyrin ring, producing biliverdin and liberating free iron and carbon monoxide (CO) in equimolar amounts (Fig. 43-1).[2] The free iron thus released is liberated for the synthesis of other iron-containing proteins or sequestered for transport or storage in transferrin or apoferritin, respectively. Understandably, initial research focused on this important but less than exciting role of HO in heme catabolism, until Applegate and colleagues showed that HO could be vigorously induced not just by its substrate heme but also by a variety of agents that shared the ability to generate reactive oxygen species (ROS) in the cell.[3] Examples of such agents are lipopolysaccharide (LPS), phorbol esters, sodium arsenite, sulfhydryl reagents, hydrogen peroxide, and heavy metals, as well as hyperthermia, hyperoxia, heat shock, and ultraviolet radiation. This extraordinary diversity of inducers for an enzyme that seemingly functioned only in heme turnover was very surprising and fueled speculation that it also served a powerful role in protecting the cell against oxidative stress. The seminal observation, by Nath and coworkers in 1992,[4] that prior induction of HO could protect rats from renal failure caused by glycerol-induced rhabdomyolysis triggered a wave of research into the role of HO in oxidant-mediated cellular and tissue injury. This enzyme has now been firmly established as a crucial and potent cytoprotective molecule with strong anti-inflammatory, antiapoptotic, and antiproliferative properties. Just how remarkable this enzyme really is, is evident from its ubiquitous distribution in nature, not merely in mammalian and lower eukaryotic systems but also in plants, algae, fungi, and bacteria. It has been extraordinarily conserved through evolution, with approximately 80% identity between rat and human HO isoforms and nearly 70% homology between human HO-1 and that derived from the pathogen *Corynebacterium diphtheriae.*[5] Not surprisingly, targeted deletions of the HO-1 gene in mice result in HO-1 null mice that usually do not survive to term.[6] No known mutant forms of HO have been discovered, despite the near universal distribution of this enzyme in nature.

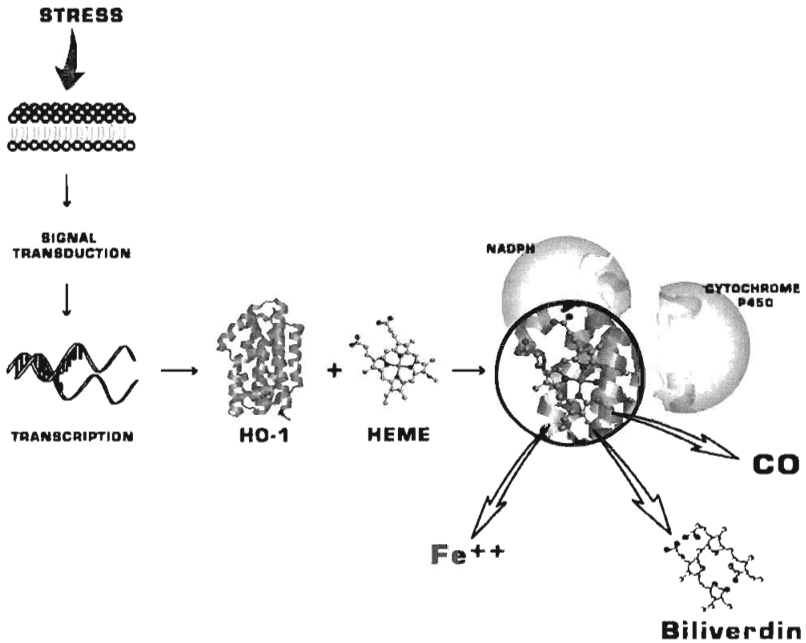

FIGURE 43–1. Reaction catalyzed by heme oxygenase-1. (See color section in this text.) (From Otterbein LE, et al: Heme oxygenase-1: Unleashing the protective properties of heme. Trends Immunol 2003;24:449-455.)

ENZYME STRUCTURE AND FUNCTION

Crystal analyses of the HO structure reveal the heme pocket to be sandwiched between two helices—the proximal and distal helices; histidine residues at positions 25 and 132 are critical for heme binding to each of these helices, respectively (Fig. 43-2).[7] The distal helix is most closely associated with heme and has the highest sequence identity between HO proteins derived from various species. Laboratory mutations that distort the structure of the distal helix decrease the efficiency of catalysis,[7] indicating that the distal helix might serve as a fingerprint motif for the HO proteins. There are several unique aspects of the HO protein that further its physiologic role. First, HO has an affinity for oxygen that is 30 to 90 times that of myoglobin, ensuring a steady supply of oxygen for substrate catalysis.[8] Second, the bound heme serves both as a cofactor for the enzyme and as its substrate.[9]

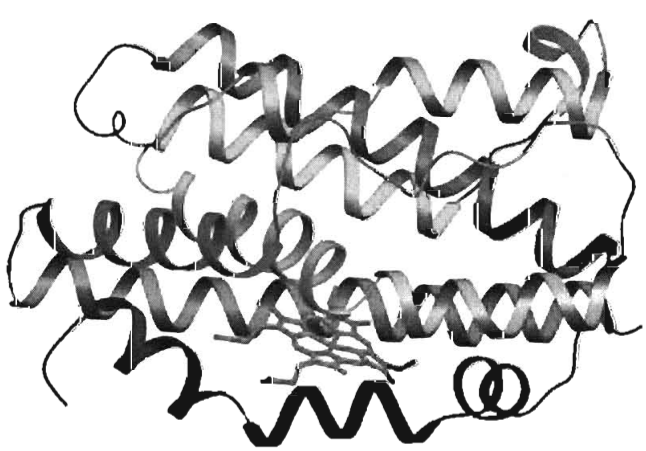

FIGURE 43–2. Structure of human heme oxygenase-1. The N-terminus is blue and the C-terminus is red, with green in the middle. The position of the heme ring is shown in pink. (See color section in this text.) (From Schuller DJ, et al: Crystal structure of human heme oxygenase-1. Nat Struct Biol 1999;6:860-867.)

Third, HO-1 is devoid of cysteine residues, making it insensitive to inactivation by reactive nitrogen and oxygen species, a critical property for a protein that serves as an antioxidant defense.

GENE STRUCTURE AND REGULATION

There are three distinct isoforms of human HO, coded for by three distinct genes.[10,11] HO-1 (inducible) and HO-2 (constitutionally expressed) share 42% identical residues; HO-3 is 90% homologous with HO-2 but is not known to be functional.[11] HO-1 is widely distributed throughout the body; HO-2 is highly concentrated in the brain and testes; and HO-3 is localized to the prostate, liver, and kidney. Whereas HO-1 is induced to serve a protective role in pathophysiologic states, HO-2 may have a more routine physiologic function, such as control of blood pressure or neurotransmission (see later).[12]

The structure of the mouse HO-1 gene is best characterized, and the deduced amino acid sequence of mouse HO-1 exhibits 93.4% and 82.3% homology with rat and human sequences, respectively. It has five exons, the relative positions of which are similar in all three species.

Heme-dependent stimulation of HO activity can be inhibited by prior treatment with the RNA synthesis inhibitor actinomycin D, suggesting that enzymatic activation is regulated at the level of gene transcription.[13] This appears to be true not just for heme but for most other inducing agents as well, although it has been suggested that increased expression of HO-1 by nitric oxide may, in part, be due to increased HO-1 messenger RNA (mRNA) stability.[14] This increased stability has also been invoked as the mechanism for hypoxic induction of HO-1 in human skin fibroblasts.[15] The *cis*-acting DNA elements of the gene that interact with their cognate-inducing proteins are becoming better understood through experiments that mutate the potential binding sites and observe the effects on the induction of the HO-1 protein by various inducers. In the case of the mouse gene,

the regulatory elements in the 5′ flanking region are arranged into three distinct areas: the proximal promoter region and two distal enhancers, DE 1 and 2, located 4 and 10 kilobase pairs upstream of the transcription initiation site, respectively.[16,17]

Although the promoter region has motifs that are variations of well-known transcription factor binding sites, the functionality of these transcription binding sites is not clearly understood.[18] However, the human gene promoter region, but not that of the mouse or rat, has a $(GT)_n$ repeat that is highly polymorphic, called a microsatellite polymorphism, with n varying from 15 to 40. These repeats may serve to modulate promoter activity or induction. In fact, promoter activity may decrease with increasing n.[19] Cigarette smokers with long repeats ($n > 31$) have a greater risk of developing emphysema than do those with shorter repeats ($n < 31$), perhaps because reduced HO-1 expression may be unable to protect against the oxidative stress of smoking.[19]

The dominant functional sequence motif in the enhancers is the stress response element (StRE). It is 10 base pairs in length; occurs repeatedly in the two distal enhancers; and, at least in the mouse, is required for the induction of HO-1 by all agents tested, except for hypoxia. In particular, induction by heme requires the entire 10 base pairs of the StRE.[20] Most likely, the DNA binding transcription factors v-Maf, NF-E2, and Nrf 1 and 2 are all involved in mediating the response to heme.[21] To respond to hypoxia, however, the hypoxia-inducible factor (HIF-1) that activates transcription of erythropoietin and vascular endothelial growth factor must bind to distinct hypoxia response elements that reside in DE 2.[22]

The first three residues of the StRE are the antioxidant-electrophile response elements, necessary for induction by oxidants and electrophiles.[23] The StRE also contains the heptad that recognizes the fos/jun (activator protein-1 [AP-1]) family of DNA-binding, transcription-activating proteins. Mutation of this site results in loss of activation by heavy metals, hydrogen peroxide, arsenite, and LPS.[17,24] Many potent antioxidant chemicals, including pyrrolidine dithiocarbamate and diphenylene iodonium, also activate HO-1 by activating AP-1 binding.[25] Another pathway of HO-1 activation during oxidative stress involves thioredoxin, a protein that keeps disulfide bonds in the reduced state, protecting intracellular proteins against oxidation.[26] Thioredoxin is induced by oxidative stress, translocates into the nucleus, and binds to intranuclear redox factor 1, which in turn reduces and activates the DNA binding activity of AP-1. This can lead to HO-1 induction.[27]

A unique situation pertains to the activation of HO-1 by interleukin (IL)-6 or interferon, both of which use the JAK-STAT pathway to induce gene transcription. When IL-6 binds to a surface receptor, a JAK factor is activated, which in turn phosphorylates and dimerizes a STAT factor, which then binds to the IL-6 response element in the PE locus of the mouse HO-1 gene.[28] In some unknown manner, a protein bound to the StREs located 4 kilobase pairs away is also needed for IL-6 induction of HO-1.[29] The mechanism of this "cooperativity" is not fully understood.

Hyperoxia also strongly induces HO-1 via the IL-6 response element.[30] Because IL-6 mRNA is induced by hyperoxia in 4 to 8 hours, well before the peak induction of HO-1 at 24 to 48 hours, it may simply be that IL-6 acts on the IL-6 response element to induce HO-1. However, both c-jun and c-fos, components of the AP-1 transcription factor, are induced by hyperoxia and could directly induce STAT binding to DNA via this site.

When organisms are exposed to hyperthermia or heat shock, a specific family of heat shock proteins is induced that confers cytoprotection against the oxidative and inflammatory stress resulting from hyperthermia. HO-1 is also known as heat shock protein 32, because it is involved in the heat shock response. Although the rat HO-1 gene is induced by heat shock, mediated by two heat shock elements in the PE region, human HO-1 heat shock induction is observed only in HeLa cells, skin fibroblasts, and the Hep3B hepatoma cell line. This is because the single heat shock element in the human HO-1 gene is constitutively repressed in vivo by a flanking sequence and the silencing action of $(GT)_n$ repeats.[31] A similar phenomenon of HO-1 repression has been demonstrated in cultured human astrocytes and coronary artery endothelial cells in response to hypoxia,[32] the significance of which is unknown. It has been suggested, however, that hypoxic repression of HO-1 may benefit some hypoxic cell types by conserving energy (given the high utilization of molecular oxygen by this enzyme), thereby protecting mitochondrial cytochrome oxidase against inhibition by CO.[33]

HO-1 AND CELLULAR PROTECTION

ANTIOXIDANT PROPERTIES

The realization that the wide variety of inducers of HO-1 all serve to generate oxidant stress led investigators to explore the potential beneficial effects of HO-1 induction in disease models characterized by overwhelming oxidant injury. One such condition, acute lung injury, involves widespread inflammatory damage to the alveoli of the lung caused by infectious pathogens, inhaled environmental toxins, trauma to nonpulmonary organs, blood transfusions, noxious gases, near drowning, or drug exposure. It is well known that many injurious agents, such as LPS derived from Gram-negative bacteria; drugs, such as bleomycin; exposure to 100% oxygen; or even host-derived tumor necrosis factor (TNF) all lead to the generation of ROS, generated from the oxidative burst of infiltrating inflammatory cells. These ROS are thought to initiate the damage to the alveolar epithelium in acute lung injury. Similarly, acute renal failure can result from many different insults, including glycerol-induced acute rhabdomyolysis, in which free heme is the nephrotoxic agent, or exposure to the nephrotoxic agent cisplatin. Again, ROS mediate the extensive tissue injury that occurs in this condition. Not surprisingly, HO-1 is intensely up-regulated in inflamed tissues in both these conditions.

Acute Lung Injury

Rats exposed to greater than 95% oxygen or sublethal injections of LPS develop acute lung injury that is remarkably similar to the human disease. Lung edema and particularly pleural effusions develop within 48 to 60 hours of exposure to greater than 95% oxygen, and rats uniformly die after 60 to 72 hours of continuous exposure. Intraperitoneal injections of LPS stimulate intense neutrophilic infiltration of the alveoli, together with hemorrhagic edema. Increased immunohistochemical staining for HO-1 protein is seen diffusely throughout the alveolar and bronchiolar epithelium and the infiltrating cells, accompanied by marked increases in HO-1 activity in the lung homogenates.[24,34]

The functional significance of this induction of HO-1 has been elucidated by experiments in which rats were pretreated with inhibitors of HO-1 activity. Pretreatment with tin protoporphyrin (SnPP) abrogated the induction of lung HO-1 in LPS-treated rats and increased susceptibility to a lethal dose of LPS; conversely, pretreatment with hemoglobin (a potent inducer of HO-1) conferred marked protection against neutrophilic alveolitis and hemorrhagic edema resulting from sublethal doses of LPS.[35] When an adenoviral vector containing the coding region of the HO-1 gene was instilled into rat lungs, it was taken up by the bronchiolar epithelium and resulted in increased protein expression of HO-1 in this region. These rats, when subsequently exposed to hyperoxia, exhibited a greater than 90% reduction in pleural effusions and survived longer than their control counterparts, which had received instillations of the adenoviral vector without the HO-1 gene insert.[36]

Acute Renal Failure

In models of acute renal failure, increased HO-1 mRNA and protein expression are noted along the tubules,[4,37] whereas in acute renal transplant rejection, the staining is localized to the infiltrating inflammatory cells.[38] As with acute lung injury, pretreatment with SnPP led to increased renal injury and death in rats undergoing rhabdomyolysis-initiated, heme-mediated acute renal failure, whereas prior treatment with hemoglobin unequivocally reduced mortality and renal damage in the same model.[4] A similar result was seen in cisplatin-induced acute renal injury,[37] implying that the benefit of HO-1 induction goes beyond protection against heme-induced injury alone.

These fundamental observations of the beneficial effects of HO-1 induction in states of oxidant injury have been extended with the availability of the HO-1$^{-/-}$ knockout mouse. (Normally, HO-1 knockout mice die in utero, so in vitro fertilization techniques were used to salvage the homozygous knockout mice.) As expected, fibroblasts derived from these mice were more sensitive to oxidant injury, and the mice exhibited increased mortality and increased liver damage resulting from LPS administration.[39] In the model of glycerol-induced rhabdomyolysis and acute renal failure, knockout mice demonstrated 100% mortality and increased tubular injury compared with their wild-type controls.[40] Similarly, administration of cisplatin to HO-1$^{-/-}$ mice resulted in more severe nephron damage than that seen in HO-1$^{+/+}$ mice.[41]

Acute Liver Injury

There is a unique topographic distribution of HO in the liver: HO-1 is prominent in Kupffer cells, and HO-2 predominates in hepatocytes.[42] This could explain the ability of HO-1, via CO, to regulate both biliary flow[43] and sinusoidal pressure (see later). Once again, it appears that ischemic stress, which liberates oxidant radicals, can be ameliorated by the induction of HO-1. Partial ligation of the portal vein in rats with portal hypertension strongly induced HO-1 in the liver.[44] Mice deficient in HO-1 demonstrated increased susceptibility to injury by endotoxin,[6] and in a model of compensated hemorrhagic shock, blockade of HO-1 was shown to increase centrilobular necrosis.[45]

Effects in the Brain

Mice lacking the HO-2 gene suffer a larger brain infarct than do controls after temporary occlusion of the middle cerebral artery, but this effect is not seen with deletion of HO-1.[46] Inhibition of HO with SnPP increases the size of the infarct in wild-type mice, again suggesting a role for HO-2 in cerebral protection against transient ischemia.[47] HO protects neurons from hydrogen peroxide–mediated injury and limits neuronal apoptosis in cell culture, indicating the potential to limit neuronal cell death in the ischemic penumbra.[47]

Oxidative stress plays a central role in the pathogenesis of Alzheimer's disease and Parkinson's disease. HO-1 protein is greatly increased in the senile plaques and neurofibrillary tangles that are characteristic of Alzheimer's disease.[48] *Tau* protein, which forms the neurofibrillary tangles, is greatly reduced in cells that overexpress HO-1.[49] Amyloid precursor protein, which is believed to be the neurotoxic agent in Alzheimer's disease, may bind to and inhibit HO, leading to more oxidative neurotoxicity,[50] but HO-1 induction can reduce both the protein and the cytotoxicity from hydrogen peroxide in neuronal cells.[51] It appears that subjects who develop Alzheimer's disease have lower levels of protective HO-1 in plasma and cerebrospinal fluid and lower lymphocyte HO-1 mRNA than do healthy elderly controls.[52] HO-1 immunoreactivity is also enhanced in the substantia nigra of patients with Parkinson's disease[48] and even in mouse brains infected with the scrapie prion,[53] which induces HO-1.[54]

Atherosclerosis

HO-1 can be induced in both endothelial and vascular smooth muscle cells by proatherogenic stimuli, such as oxidized low-density lipoprotein (LDL), lipid metabolites, shear stress, and angiotension II, among others.[55] HO-1 is highly up-regulated in the endothelium and in the foam cells of intimal lesions from humans and apolipoprotein E–deficient mice.[56] The induction of HO-1 reduces atherosclerotic lesions in LDL receptor knockout mice.[57] HO-1 can also protect against atherosclerosis by producing CO, which is known to inhibit platelet aggregation.

Clearly, these observations implicate HO-1 as a potent antioxidant protein, but the beneficial effects of its induction seem to extend beyond this antioxidant role. Astonishingly, accumulating evidence suggests that this protein can also function in an antiapoptotic role, as a regulator of cell growth and proliferation, and as an anti-inflammatory agent; it may even modulate the immune system.

ANTIAPOPTOTIC PROPERTIES

Apoptosis, or programmed noninflammatory cell death, plays an important role in human disease. For example, in acute lung injury in both humans and rodents, soluble Fas ligand mediates the apoptotic cell death of distal airway epithelium, which expresses the receptor for this so-called death ligand. Soluble Fas ligand is present in the bronchoalveolar lavage fluid from humans with early acute lung injury, but not in those at risk for the development of this disease; high levels of this ligand are associated with increased mortality.[58] Overexpression of HO-1 has been shown to protect both cultured fibroblasts from TNF-induced apoptosis[59] and bovine aortic endothelial cells from peroxynitrite-mediated apoptotic cell death.[60] Exogenous transfer of adenoviral vector–encoded HO-1 into mouse lungs attenuates the degree of hyperoxia-induced lung cell apoptosis in vivo.[61]

Bleomycin, a chemotherapeutic agent, causes acute pulmonary inflammation in humans, but when given to mice,

it results in lung fibrosis that is used as a model of the human disease idiopathic pulmonary fibrosis. Cellular apoptosis in the lung is a characteristic feature of this model, so a recent report that adenoviral-mediated overexpression of HO-1 in the lungs protected against pulmonary fibrosis caused by bleomycin is not surprising.[62]

CELL GROWTH AND PROLIFERATION

In vitro, HO-1 modulates cell growth. If pulmonary epithelial cells grown in culture are transfected with adenoviral vectors encoding the HO-1 gene, the resulting overexpression of HO-1 protein is associated with decreased cell proliferation, increased numbers of cells in the G_0/G_1 phase of the cell cycle, and reduced entry into the S phase, compared with cells transfected with the adenoviral vector alone, without the HO-1 insert. Cells that overexpress HO-1 are blocked in the G_2/M phase and are unable to progress through the cell cycle, despite serum stimulation. When SnPP is added, these effects are reversed, proving that growth arrest results from the actions of HO-1.[63] Similar growth slowing is seen in vascular smooth muscle cells transfected with HO-1,[64] and because pulmonary hypertension is associated with pronounced hypertrophy of smooth muscle in the media of the pulmonary arteries, this might well be the mechanism by which chemical preinduction of HO-1 protects rats against pulmonary hypertension from chronic hypoxia.[65] Transgenic mice overexpressing HO-1 in the lungs also develop less pulmonary hypertension in response to hypoxia.[66] HO-1 appears to regulate vascular remodeling in systemic vessels as well. In vivo, induction of HO-1 by hemin reduces neointimal thickness and medial wall thickness in the balloon-injured carotid arteries of rats.[67]

Not surprisingly, this antigrowth effect of HO-1 is applicable to tumor biology as well. A549 pulmonary epithelial cells injected into immunodeficient mice form tumors that grow rapidly. If, however, the cells are made to overexpress HO-1 before transfer to the mice, the tumors formed are half the size, and survival is improved by greater than 90%.[68] Expression of HO-1 in oral squamous cell carcinoma may be a marker for a low risk of regional lymph node metastases.[69]

THE IMMUNE SYSTEM

Increases in HO-1 protein are seen in alveolar macrophages obtained by sputum induction in humans with asthma, but not in healthy subjects.[70] In mice that develop an asthmatic phenotype brought about by prior sensitization and then challenge with inhaled ovalbumin aerosols, HO-1 induction in lung tissue can be readily demonstrated.[71] Higher HO-1 expression is seen in alveolar macrophages from humans who have acute or chronic graft rejection after lung allotransplantation, compared with those without overt rejection.[72] HO-1 is induced in the transplanted kidney after the development of acute rejection,[73] and adenoviral transfer of HO-1 dramatically protects rat liver transplants against rejection,[74] perhaps by modulating the T helper 1–T helper 2 cytokine balance.[75] HO-1 induction can protect islet cell transplants from apoptosis[76] and ameliorate the severity of graft-versus-host disease.[77] Dramatic proof of the immunomodulatory role of HO-1 comes from a mouse-to-rat cardiac xenotransplantation model.[78] Normally, mouse hearts survive indefinitely when they are transplanted under the skin of immunosuppressed rats, but pretreatment with SnPP to block HO-1 leads to rapid rejection. Transplantation of mouse hearts from HO-$1^{-/-}$ knockout mice also leads to rapid rejection. Together, these experiments prove that despite immunosuppression, HO-1 is necessary for xenograft survival.

ANTI-INFLAMMATORY EFFECTS

The mitogen-activated protein kinases (MAPKs) constitute hierarchic phosphorylation cascades responsible for transducing inflammatory signals from the cell surface to the nucleus, resulting in cellular activation and the production of cytokines that amplify inflammation. Thus, for example, when human neutrophils are stimulated by the peptide nFMLP, the ERK family of MAPKs transduces the inflammatory signals to the nucleus, resulting in a broad array of activation responses, including calcium influx, superoxide production, granule release, and chemotaxis. Similarly, LPS stimulates the p38 MAPK, resulting in TNF release. In vivo, selective chemical inhibition of p38 abrogates TNF release, and hence acute lung injury, in a rat model of pancreatitis-associated lung injury. Phosphorylation of the ERK 1/2 kinase cascade results in induction of the transcription factors AP-1 and nuclear factor kappa-B, both of which induce the expression adhesion molecules on endothelium and induce the production of IL-8 from endothelial cells.

HO-1 can modulate inflammation by changing signal transduction through the ubiquitous MAPK pathways. For example, HO-1 suppresses the phosphorylation of ERK 1/2 by TNF in rat pulmonary artery endothelial cells, providing a mechanism for the down-regulation of TNF-induced inflammation.[79] Stimulation of macrophages with LPS causes them to produce TNF, but if the macrophages are treated to overexpress HO-1 before stimulation with LPS, the production of TNF declines and the production of IL-10 (an anti-inflammatory cytokine) increases. Again, in a lethal endotoxic shock mouse model, the protective effects of IL-10 require the induction of HO-1.[80] On an organ system level, this translates to reduced inflammation and injury. For example, in a model of pleural inflammation, HO-1 up-regulation reduced inflammatory exudates and cellular infiltration, and these effects were reversed by HO-1 inhibition.[81] The protective effect of HO-1 in changing the T helper 1–T helper 2 balance in organ transplantation was alluded to earlier.

ISCHEMIA-REPERFUSION INJURY

HO-1 mRNA, protein, and activity are strongly induced in models of ischemia-reperfusion injury, both in the rat kidney[82] and in ischemic myocardium.[83] Preinduction of HO-1 can result in ischemic conditioning, ameliorating the injury caused by subsequent ischemia and reperfusion, as noted in guinea pig lung transplants[84] and in rats undergoing liver transplantation.[85]

MEDIATORS AND END PRODUCTS OF HO-1 INDUCTION

The heme moiety, despite being the cofactor for numerous enzymes and a critical component of hemoglobin, is highly toxic and can cause renal injury, as noted earlier. In addition, free heme is a potent pro-oxidant molecule, capable of oxidizing

and damaging almost all the constituents of a cell, such as the lipid membranes, mitochondria, cytoskeleton, and even nucleus.[86] It would be reasonable to suppose that all the protective effects of HO-1 induction could be explained by the degradation of this toxic free heme moiety, but a closer look at the products of the enzymatic reaction catalyzed by HO-1 shows that they too may subserve antioxidant functions directly.

FERRITIN

Ferritin, which stores free iron, has been suggested to mediate the beneficial effects of HO-1. Ferrous iron, if left free in the cytoplasm, can donate an electron to hydrogen peroxide and thus generate, via the Fenton reaction, the highly reactive hydroxyl radical. Free iron can also stimulate lipid peroxidation. However, induction of HO-1 is associated with a simultaneous increase in ferritin, which immediately sequesters the free heme and thus resolves the paradox whereby an antioxidant protein such as HO-1 generates a potentially toxic free iron radical. For example, heme-mediated induction of HO-1 results in increased transcription of ferritin,[87] and in human skin fibroblasts, oxidative injury produced by ultraviolet radiation results in HO-1–dependent induction of ferritin and thereby protection from oxidative injury.[88] In addition, HO-1 can repress the expression of a highly active ferrous iron–adenosine triphosphatase transporter involved in iron efflux from cells.[89] This transporter is colocalized with HO-1 in the microsomal fraction of the cell, and it is notable that mice with a genomic deletion of HO-1 display increased tissue accumulation of iron. This coregulation of ferritin, the iron transporter, and HO-1 may partially explain the protective effects of HO-1 induction, but in an elegant experiment, Otterbein and colleagues provided evidence of additional mechanisms.[90] In their experiments, rats pretreated with both heme to induce HO-1 and with desferrioxamine to bind ferritin were fully protected against LPS-mediated lethal endotoxic shock; conversely, pretreatment of rats with inorganic iron alone, to induce ferritin but not HO-1, could not protect the animals against endotoxic shock. Exogenous apoferritin did not confer any protection in this model.[90]

CARBON MONOXIDE

A wealth of evidence now suggest that CO, the final byproduct of the heme catabolism pathway, is the main mediator of the cytoprotection exhibited by HO-1 induction. Sjostrand first discovered endogenous production of this gas in 1949,[91] 19 years before the discovery of HO itself. This gas was known to be a poison, with the initial description of CO poisoning attributed to Aristotle. In 1857, Bernard first noted its high affinity for hemoglobin. The toxicity of this gas in exogenously inhaled concentrations results from its ability to impair the oxygen-carrying capacity of hemoglobin in two ways. First, it binds to hemoglobin with an affinity 245 times that of oxygen (at pH 7.4), competitively inhibiting oxygen binding. Second, it causes an allosteric conformational change, from sigmoid to hyperbolic, in the hemoglobin molecule, such that the oxygen molecules bound to hemoglobin are less easily released, effectively left-shifting the hemoglobin dissociation curve and reducing tissue oxygen extraction from hemoglobin. It also binds to and inactivates the reduced form of cytochrome a_3, impairing tissue respiration.

CO is a colorless and odorless gas. Its solubility in water is about 30% less than that of oxygen (O_2). Given this low solubility and its high affinity for heme moieties, CO may be shuttled from heme moiety to moiety, based on the reaction constants within the different heme groups. Because O_2 also binds to heme moieties, it competes with these reactions; the relationship is defined in terms of the Warburg coefficient (K),

$$K = (n/1 - n)\ (CO/O_2),$$

where n is the fraction of heme moiety bound to CO. Thus, the Warburg coefficient is the ratio of the concentration of CO to that of O_2 required for 50% saturation of the heme compound (i.e., when n = 0.5). Because the Warburg coefficient is 0.4 for myoglobin, it follows that CO binds readily to myoglobin and that hemoglobin shuttles its CO content to myoglobin when the O_2 concentration in muscle drops to low levels during exercise.[92,93] In the case of cytochrome a_3, however, for which K ranges from 5 to 15, it does so only when present in high concentrations (estimated at >20%)[94] or in the presence of severe O_2 depletion (e.g., in the mitochondria of asphyxiated tissues). As excellently reviewed by Piantadosi,[95] CO *has* been shown to bind to cytochrome *a*, a_3 in vivo (e.g., in the brains of rats perfused with perfluorocarbons instead of blood, while exposed to CO).[96] Despite the fact that these ratios are defined from in vitro experiments, they help explain how a gas that is apparently toxic can be readily formed endogenously and how the reaction was retained through millions of years of evolution, without adverse effects to the organism.

CO is produced endogenously at a rate of about 0.42 ± 0.07 mL/h, or approximately 10 mL/day.[97] Nearly all the CO produced endogenously results from the catabolism of heme—about 85% from the erythron, and the remainder from nonhemoglobin heme. Minute amounts can be generated by NADPH- or iron ascorbate–dependent lipid peroxidation.[98] The cytochrome P_{450} system can metabolize dihalomethanes to CO in vivo,[99] which may be significant in cases of toxic inhalation of these compounds. The majority of CO produced in the body is excreted by exhalation, although, intriguingly, CO can also be oxidized to carbon dioxide by cytochrome a_3, the cellular target of CO.[100] The importance of this reaction as a pathway of elimination of CO from the body is unknown.

The first suggestion that CO could exert physiologic effects came in 1991, around the time that gaseous nitric oxide (NO) was recognized as a physiologic effector molecule.[101] Experiments in which exogenous CO has the same effects as up-regulation of HO-1, or in which CO can "rescue" the effects of HO-1 blockade, provide evidence for its role as a mediator of HO-1 cytoprotection. For example, pretreatment of rats with 250 parts per million (ppm) of CO protects against hyperoxia (Fig. 43-3) and LPS-induced injury in a manner comparable to overexpression of HO-1.[61] Likewise, CO inhibits lung cell apoptosis in hyperoxia-injured animals.[61] Exogenous CO in the same low doses can protect against TNF-induced apoptosis to the same extent as overexpression of HO-1.[59,102] In vitro, low-dose CO reduces TNF-induced ERK 1/2 phosphorylation in rat pulmonary artery endothelial cells in the same manner as does overexpression of HO-1.[79] In this system, p38 phosphorylation is increased by HO-1 overexpression and by CO, while the other MAPK pathway, JNK, is unaffected. This argues against these effects being the result of the general cellular toxicity of CO. Exposure of

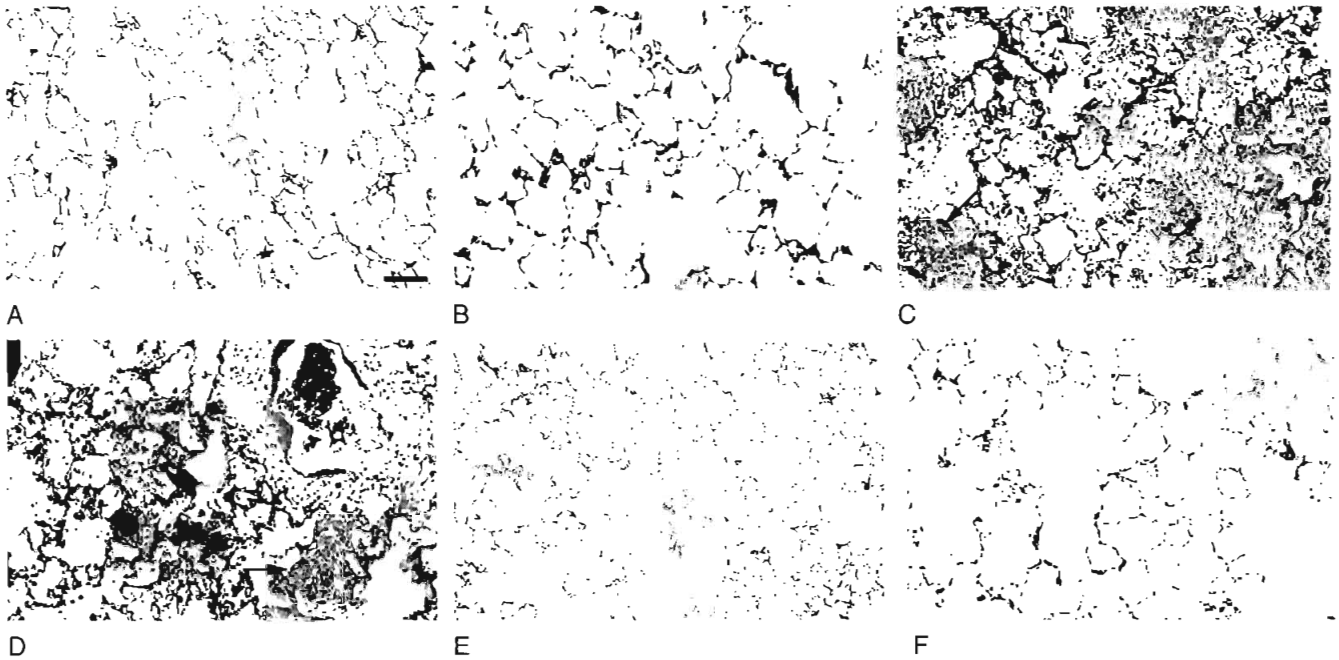

FIGURE 43–3. Protective effect of exogenous carbon monoxide (CO; 250 ppm) on hyperoxia-induced lung injury in rats. Histologic sections of rat lungs: *A*, normoxia control; *B*, CO control (256 ppm × 56 h); *C* and *D*, hyperoxia (× 56 h); *E* and *F*, hyperoxia (250 ppm CO × 56 h). (See color section in this text.) (From Otterbein LE, Mantell LL, Choi AM: Carbon monoxide provides protection against hyperoxic lung injury. Am J Physiol 1999;276:L688-L694.)

LPS-stimulated macrophages to low-dose CO results in the same constellation of reduced TNF generation and enhanced IL-10 production as seen with overexpression of HO-1 in these cells.[103] Low-dose CO retards the growth of tumors in vivo, just as is noted with HO-1 overexpression in A549 tumor cells injected into mice.[68] In mice sensitized and then challenged with aeroallergen, inhaled CO can selectively reduce the production of the eosinophil chemoattractant IL-5 and, consequently, eosinophil accumulation in the lung.[104] In the mouse-to-rat cardiac xenotransplantation model described earlier, treatment of both donor and recipient with exogenous CO results in indefinite survival of the xenotransplant, even in the face of inhibition of HO-1 by SnPP, exemplifying the ability of CO to substitute for HO-1.[105] Similar to the effects of HO-1 induction in preventing neointimal hyperplasia after balloon injury in rat carotid arteries, inhalation of low-dose CO for just 1 hour also virtually ablates neointimal hyperplasia (Fig. 43-4).[106]

Clearly, CO must be a major effector of the protection imparted by HO-1 induction. Nevertheless, CO has other physiologic roles of its own that might protect the body in a variety of disease states.

Vasodilator. Exogenous CO in high concentrations (10%) causes a reversible increase in coronary blood flow in isolated perfused rat hearts.[107] Although this may be an effect of hypoxia rather than a physiologic effect of CO, direct relaxation of vascular smooth muscle by CO has been shown in isolated porcine coronary arteries and veins[108] and in rabbit[109] and rat[110] aortas. In isolated perfused rat livers, inhibition of HO activity increased hepatic vascular resistance, but this effect was reversed by exogenous low-dose CO (1 μM).[111] CO generated by the induction of HO-1 lowers blood pressure in spontaneously hypertensive rats,[112] whereas inhibition of HO-1 raises blood pressure and total peripheral resistance in rats.[113] In the kidney, CO can attenuate the effect of vasoconstrictors on renal arterioles, and CO can reverse phenylephrine-induced vasoconstriction in rat tail arteries.[114] Some of the vasodilator effects of CO may be mediated centrally, through the nucleus tractus solitarius.

Bronchodilator. Exogenous CO can reverse the bronchoconstriction due to histamine in anesthetized, ventilated guinea pigs, albeit at a high concentration (100%).[115] Inhibition of HO-1 with ZnPP also inhibits hypoxia-associated bronchoconstriction in vivo.[116] Recently, even low-dose exogenous CO has been shown to reverse the bronchoconstriction produced by methacholine in ventilated mice[117] and in guinea pig tracheal muscle ex vivo.[118]

Inhibitor of Platelet Function. CO inhibits the activation and aggregation responses of platelets,[119] which might explain the cardioprotective effect of CO in the mouse-to-rat xenotransplant described earlier. The surviving transplants had markedly reduced vascular thromboses.[105]

Neurotransmitter. In the myenteric plexus of the intestine, CO exhibits effects identical to those of NO, another gas molecule that functions as a neurotransmitter. Intestines of HO-2–deficient mice have impaired relaxation, and HO inhibitors cause intestinal contractions in NO synthase–deficient mice.[120] In the brain, intraventricular injection of HO inhibitors blocks the production of adrenocorticotropic hormone in response to electroshock; this action appears to be localized to the brain, not the pituitary.[121] There is evidence too that CO functions in long-term potentiation in the hippocampus,[122,123] and chemical inhibition of HO-1 activity can block glutamate receptor activation in the rat nucleus tractus solitarius.[124] In endotoxin-induced injury, CO inhibits the release of vasopressin.[125] CO regulates the nerve output of the carotid body, suppressing sensory discharge under basal conditions. During hypoxia, sensory discharge from the carotid body increases because of reduced CO generation.[126] Taken together, these effects are remarkably similar to those of the other diatomic gaseous neurotransmitter, NO.

Mechanism of Action. In the body, CO undergoes two types of reactions that have special significance (Fig. 43-5).

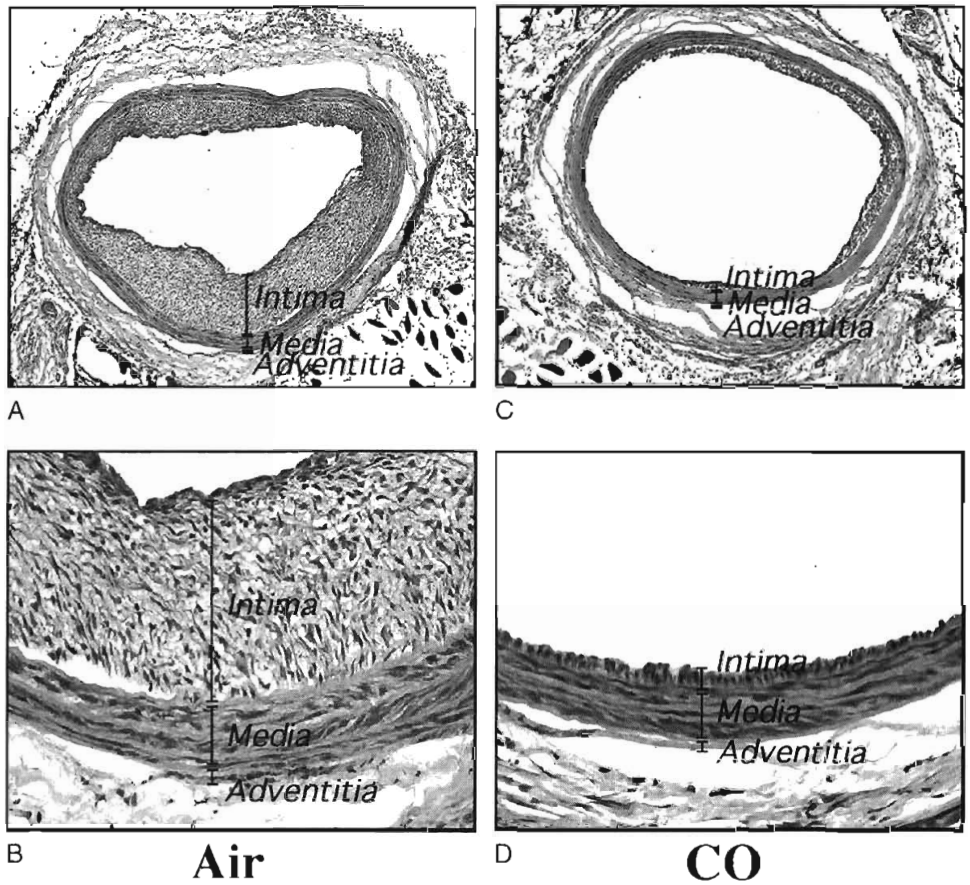

FIGURE 43–4. Pretreatment with exogenous carbon monoxide (CO; 250 ppm) greatly reduces the intimal proliferation after balloon injury in rat arteries. Rats were exposed to air (*A* and *B*) or exogenous CO for 1 h (*C* and *D*). Magnification is ×10 in the upper panels (*A* and *C*) and ×50 in the lower panels (*B* and *D*). (From Otterbein LE, Zuckerbraun BS, Haga M, et al: Carbon monoxide suppresses arteriosclerotic lesions associated with chronic graft rejection and with balloon injury. Nat Med 2003;9: 183-190.)

There are undoubtedly other reactions that may account for some of the biologic properties of CO, but these are not yet well delineated.

First, CO readily reacts with transitional metals to form metal carbonyls, and these may act as stores of CO in the body. Under some conditions, such as exposure to light, interaction with other ligands, or interaction with molecular oxygen, these metal carbonyls may gradually release CO. Motterlini and coworkers recently demonstrated the ability of synthetic metal carbonyls to deliver CO in vivo, and the actions of these chemicals mimic those of endogenously produced CO.[127]

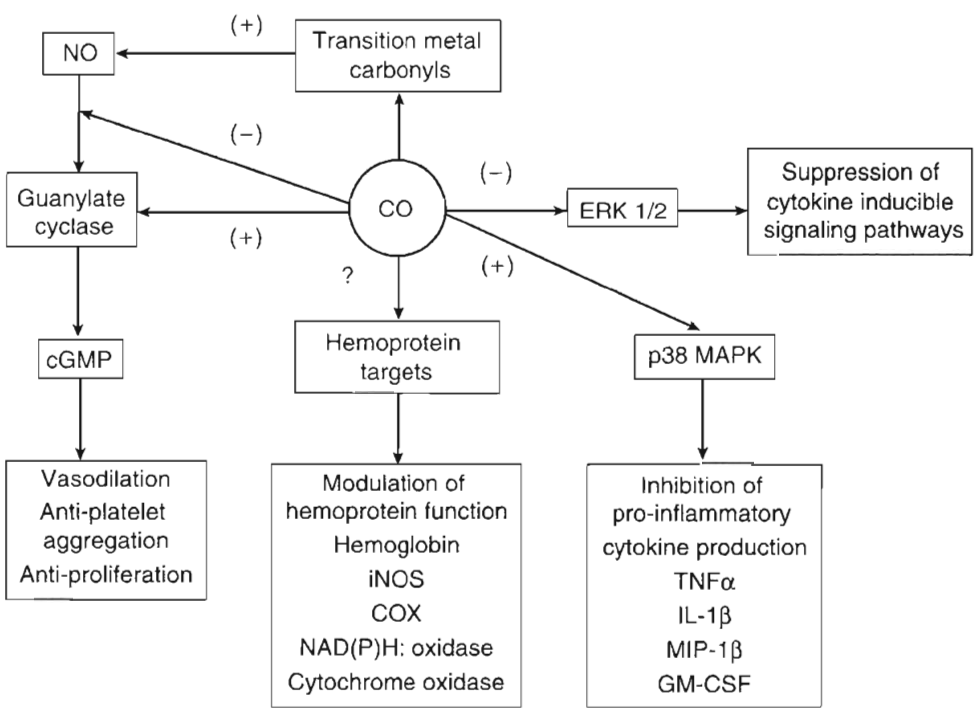

FIGURE 43–5. Mechanism of action of carbon monoxide (CO). cGMP, cyclic guanosine monophosphate; COX, cyclooxygenase; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; iNOS, inducible nitric oxide synthase; MAPK, mitogen-activated protein kinase; NO, nitric oxide; TNF, tumor necrosis factor. (Adapted from Slebos DJ, Ryter SW, Choi AMK: Heme oxygenase-1 and carbon monoxide in pulmonary medicine. Respir Res 2003;4:7.)

Second, CO binds to the ferrous heme moieties of hemoproteins but does not bind to ferric heme, unlike NO, which binds in both redox configurations. NO has an extremely high affinity for ferrous heme in comparison to CO, but the dissociation constant for CO bound to ferrous heme is much longer than that for NO,[128] resulting in the gradual dissociation of NO from ferrous hemoproteins in the presence of CO.[129] Thus, CO could exert some of its effects indirectly, through NO. Such effects have been described in the endothelium. For example, nitrotyrosine levels (the "footprint" or "signature" of NO release) increase in aortic endothelium within 1 hour of ventilating rats with 50 ppm of CO,[129] and cultured endothelial cells release peroxynitrite upon exposure to 100 ppm of CO.[130]

The binding of CO to the hemoprotein cytochrome P_{450} (Warburg coefficient = 1) inactivates the enzyme, decreasing the metabolism of drugs such as barbiturates. Inactivation of cytochrome P_{450}–dependent synthesis of endogenous vasoconstrictors has been proposed to explain the vasodilatation induced by CO, but it is unclear whether oxygen concentrations are low enough in organs such as the liver to allow such reactions to proceed physiologically.

The binding of CO to the heme moiety of soluble guanylate cyclase (sGC), and the consequent activation of sGC, is a major mechanism by which CO exerts many biologic effects. The effects of CO on platelets and neutrophils, and the vasodilating effects of CO described earlier, are all mediated by sGC and can be abrogated by chemical inhibition of sGC. In the brain, HO-1 and HO-2 are colocalized with sGC, suggesting that many of the putative neurotransmitter effects of CO are also sGC mediated. CO exerts these effects even though it is, at best, a weak activator of sGC and produces a minimum of the conformational change that activates sGC, at least in comparison to the tremendously more potent NO. Curiously, a synthetic compound, YC-1, has been discovered that increases the activation of sGC by CO by an astounding 4000%, secondary to stabilization of the conformational change that accompanies sGC activation.[131] Similar endogenous compounds may bring about more marked activation of sGC by CO than is seen in vitro.

Another interesting feature of the relatively weak interaction between CO and sGC explains how CO can either facilitate or antagonize the activation of sGC by NO. In the absence of NO, CO would activate sGC. Low concentrations of CO bound to sGC might actually inhibit NO binding and thereby inhibit activation of sGC by NO. In high concentrations, it is possible that CO would act much like an NO and amplify the effect of NO on sGC activation. For example, transgenic mice that have HO-1 overexpression targeted specifically to the endothelium actually show a significant *increase* in blood pressure, and aortic rings from these mice demonstrate impaired vasodilatation in response to NO, despite intact sGC activity. Because nitrovasodilatory activity is restored by the inhibition of CO, it appears that, in this context, CO is acting as a partial antagonist of NO.[132] This concentration-dependent ability of CO to function as a potentiator or partial inhibitor of NO-mediated sGC activation has been demonstrated in vitro.[133]

Not all the biologic activity of CO can be attributed to hemoprotein binding, however. The effect of exogenous low dose CO on the MAPKs is not mediated by sGC, and the kinases do not have heme groups. The TNF-mediated ERK 1/2 phosphorylation in rat pulmonary artery endothelial cells, described earlier, is also inhibited by n-acetylcysteine, a scavenger of oxidant species, suggesting that CO can exert indirect effects on the MAPK system by reducing free radical generation.[79] Similarly, CO can block vasoconstriction in rat tail arteries by both stimulating sGC and increasing the open probability of large-conductance, calcium-activated potassium channels.[114] Piglet pial arterioles vasodilate in response to infusions of heme, which stimulate HO-1 and lead to the local production of CO. These effects are blocked by HO-1 inhibition, as well as by blockade of the calcium-activated potassium channels described earlier. It is postulated that there is an interaction between CO and the histidine residues of the channel.[134]

CONCLUSION

Heme oxygenase's rise to fame—from a lowly enzyme serving to "recycle" hemoglobin to one of the most powerful cytoprotective proteins in nature—makes for fascinating reading. Equally exciting is the saga of carbon monoxide, as investigators around the world struggle to rehabilitate its image from poisonous gas to astoundingly multifunctional physiologic mediator. But these two biologic entities also underline how the relentless process of scientific discovery can overturn entrenched paradigms. HO was discovered in 1968, but it took another 23 years for its role beyond heme catabolism to be uncovered. And if not for the discovery of the remarkable physiologic role of NO, research into CO may have been stalled by those convinced only of its poisonous properties.

Although knowledge of the physiologic role of this HO-1–CO system is burgeoning, some experiments suggest that much more research is required before it can be fully understood and its power harnessed in pharmacology. For example, in contrast with the beneficial effects of HO-1 induction in protecting against heme- or cisplatin-induced renal failure, HO-1 is up-regulated in experimental gentamicin nephrotoxicity, but in this case, inhibition of the enzyme by SnPP does not modify the resulting renal injury.[37] Although moderate overexpression of HO-1 in fibroblasts confers protection against hyperoxic injury, higher levels of HO-1 overexpression lead to increased susceptibility to hyperoxia, suggesting a dosing threshold.[135] Similarly, CO in low concentrations (100 ppm) can generate oxidant radicals in vascular endothelium. Clearly, the preponderance of evidence favors the view that HO-1 and CO are vital to the organism's defense against injury, but much still needs to be learned. With more research into dosing and delivery, inhaled low-dose CO may well become a pharmacologic agent in the not-so-distant future.

ANNOTATED REFERENCES

Applegate LA, Luscher P, Tyrrell RM: Induction of heme oxygenase: A general response to oxidant stress in cultured mammalian cells. Cancer Res 1991;51:974-978.

In this seminal paper, the authors detected increases in HO-1 mRNA in a human fibroblast cell line in response to a variety of oxidants and agents that alter cellular glutathione levels. This induction of HO-1 by oxidants led the authors to propose a secondary cytoprotective role for this enzyme, previously thought to function only in heme catabolism.

Nath KA, Balla G, Vercellotti GM, et al: Induction of heme oxygenase is a rapid, protective response in rhabdomyolysis in the rat. J Clin Invest 1992;90:267-270.

This paper provided the first in vivo evidence of the protective effect of HO-1 induction against acute renal failure in a rat rhabdomyolysis model. Conversely, chemical inhibition of HO-1 exacerbated kidney dysfunction.

Otterbein L, Chin BY, Otterbein SL, et al: Mechanism of hemoglobin-induced protection against endotoxemia in rats: A ferritin-independent pathway. Am J Physiol 1997;272:L268-L275.

In this elegant study, the authors studied whether the protective effect of HO-1 on LPS-induced multiorgan failure in rats was mediated by ferritin. Rats pretreated with hemoglobin and desferoxamine (which induced HO-1 but blocked ferritin) were protected against LPS-induced organ failure and death, whereas rats pretreated with iron dextran (which induced ferritin but not HO-1) died.

Otterbein LE, Mantell LL, Choi AM: Carbon monoxide provides protection against hyperoxic lung injury. Am J Physiol 1999;276:L688-L694.

In this paper, the authors showed that exogenous gaseous CO in low doses (50 to 500 ppm) markedly attenuates the acute lung injury, inflammatory cell infiltration, cellular apoptosis, and pleural effusions that result when rats are exposed to hyperoxia. Survival was also improved, and this benefit was evident even when endogenous HO-1 was chemically inhibited, proving that CO may mediate or replace the benefits of HO-1 induction in oxidant-induced tissue injury.

Sato K, Balla J, Otterbein L, et al: Carbon monoxide generated by heme oxygenase-1 suppresses the rejection of mouse-to-rat cardiac transplants. J Immunol 2001;166:4185-4194.

It was known that HO-1 expression in the graft vasculature was critical to the survival of mouse-to-rat cardiac transplants by preventing platelet aggregation, endothelial cell apoptosis, and vascular thrombosis. In this study, HO-1 was chemically inhibited, but exogenous CO restored long-term graft survival, replicating the effects of HO-1 induction.

Chapter 44

MOLECULAR AND BIOCHEMICAL MONITORING

J. Perren Cobb • T. Philip Chung

KEY POINTS

1. The term **molecular monitoring** refers to the evaluation of patient status and disease using measurement methods derived from applied molecular biology.
2. The term **biochemical monitoring** usually refers to the use of sensitive protein detection methods to measure biomarkers to aid in establishing a diagnosis and prognosis.
3. Molecular biologic techniques, recently expanded by **technologic breakthroughs that span the entire genome**, promise to transform diagnostics in all fields of medicine, especially critical care.
4. The **sequences of the human and mouse genomes have been reported**, and efforts are under way to make the sequencing of each person's genome practical by means of readily available, high-throughput, automated DNA sequencing.
5. There are common, heritable genetic variations that contribute to susceptibility or resistance to disease. These common variants most frequently take the form of **single-nucleotide polymorphisms.**
6. The term **transcriptome** refers to the complete set of messenger RNAs (mRNAs) encoded by the genome for a particular cell type.
7. By varying the source of the target mRNA, investigators can compare relative levels of mRNA abundance using **DNA microarrays**, in practice generating a genome-wide expression profile—the *transcriptome*—for the cell or tissue of interest.
8. The term ***proteome*** was coined to describe the set of proteins encoded by the genome, and it defines the entire protein complement in a given cell or tissue.
9. The technology necessary to make protein "chips"—the tools needed to readily generate **genome-wide "snapshots" of the proteome**—is still emerging, some 5 years behind its DNA microarray cousin.
10. **The analytic process of classification** refers to the ability to distinguish between samples based on inherent, measurable features. Ideally, these features are easily quantitated, stable, and widely divergent between classes.
11. The overarching strategy for **molecular classification** includes the description of informational features in a training data set associated with the phenotype of interest—in essence, defining a molecular profile of the phenotype. Application of these features to unknown samples in a test data set determines the accuracy with which the features can classify unknown samples.
12. Although comprehensive reviews of **gene association studies** indicate that the majority of reported associations are not robust, meta-analysis indicates that larger, appropriately powered studies will likely find many single-nucleotide polymorphisms that are convincingly informational.
13. **Microarray gene expression analysis** has been used experimentally in the field of cancer to classify samples, addressing important clinical issues such as response to chemotherapy and propensity to metastasize. It is logical to assume that these same techniques will be widely applicable to many complex human diseases, including critical illness and injury.
14. Circulating leukocyte mRNA and protein abundance is a dynamic that varies as patients move along various **clinical trajectories (phenotypes) during sepsis**. Preliminary data in animals and human patients suggest that these trajectories can be characterized, monitored, and ultimately used to recognize infection in patients in whom sepsis is particularly difficult to diagnose. Important clinical advances in sepsis diagnostics are anticipated.

This chapter describes the current state of molecular monitoring and highlights recent advances in high-throughput genomic technology. The latter, when coupled with robust computational approaches, promises to yield more accurate diagnoses, improved understanding of underlying molecular mechanisms, and better therapeutic targets. Because of its central role as a determinant of organ dysfunction and mortality in ICUs, monitoring of systemic inflammation and infection is used as a case example.

MOLECULAR AND BIOCHEMICAL MONITORING IN CRITICAL CARE

The term *molecular monitoring* refers to the evaluation of patient status and disease using measurement methods derived from applied molecular biology. This is different

from simply monitoring molecules (e.g., serum electrolytes, urinalysis, complete blood counts), as reviewed elsewhere. The term initially was used to describe the detection of minimal disease or tumor recurrence in patients with cancer using sensitive DNA or RNA detection methods[1,2]; more recently, applications in infectious disease have been reported.[3-5] These techniques are based on the polymerase chain reaction, an in vitro technique introduced in 1985 that can amplify by several orders of magnitude the abundance of a short stretch of DNA (typically <3000 base pairs) using a thermostable polymerase and sequence-specific primers. RNA can be used as the polymerase template for the chain reaction if reverse transcriptase is applied first to convert the RNA to DNA; this is called reverse transcription polymerase chain reaction. A more detailed description of these standard molecular techniques is beyond the scope of this chapter; interested readers are referred to several recent reviews for additional information (see also Chapter 28).[6-8]

The term *biochemical monitoring* usually refers to the use of sensitive protein-detection methods to measure biomarkers that can aid in diagnosis and prognosis (e.g., prostate-specific antigen).[9] There has been great interest in the past decade in pursuing markers for a number of conditions, including acute cardiac injury and sepsis. Regarding the former, the success of monitoring troponin I has revolutionized the workup and diagnosis of acute myocardial syndromes (see Chapter 95 for additional information).[10,11] The search for an accurate marker of sepsis, however, has largely failed, as evidenced by the report of a recent consensus conference.[12] Although the reasons for this failure are complex and incompletely understood, several lessons have been learned. The first is that a set of rigorous, specific, objective, measurable diagnostic criteria to use as a "gold standard" significantly aids the search for biochemical markers. This is characteristic of acute myocardial infarction but remains elusive for sepsis. Second, whereas acute myocardial syndromes involve a single, relatively homogeneous type of specialized tissue (myocardial cells) in a critical mass that carries out two readily observed functions (contraction and relaxation), sepsis involves an overwhelmingly complex interaction of multiple cell types (infecting agent, leukocytes, endothelial cells) in multiple compartments (blood, spleen, liver) that are in constant flux. In this context, the lack of success in the field of sepsis can be more readily understood. Examples of marker proteins that continue to generate interest are interleukin-6 and procalcitonin. Both reportedly serve as markers of systemic inflammation and the severity of the host response to sepsis.[12] However, insufficient and conflicting data confound the discussions supporting their use as sepsis biomarkers. It is to this end that molecular biologic techniques, recently expanded by technologic breakthroughs that span the entire genome, promise to transform diagnostics in all fields of medicine, especially critical care.

MONITORING IN THE GENOMIC ERA

It remains exceedingly difficult to gauge the clinical trajectory and response to therapy in any given patient. There are a host of probabilistic tools available (e.g., Acute Physiology and Chronic Health Evaluation [APACHE] III), based on clinical examination and physiologic parameters. What the current tools lack is an ability to measure or gauge a heritable predisposition to a given clinical trajectory and a patient's response to current therapy. Today, however, it is possible to both gauge heredity and measure the response to therapy at the molecular, whole-genome level. The biologic assumptions underlying these efforts are that (1) predisposition is determined to a greater or lesser degree by our genetics, and (2) response to therapy can be measured, predicted, and individualized at the level of RNA and protein. The promise of molecular monitoring is that it will be possible in the near future to get preliminary data when patients are admitted and, with a few repeated measures, to answer the questions "what is going on?" and "how are they going to do?" This will be important to families in terms of offering hope (or not) for the patient's recovery. It will be important to physicians because it will provide guidance for optimal and individualized therapy for the critically ill or injured.

THE GENOME (DNA)

The sequence of the human genome has been reported,[13-15] and efforts are under way to make the sequencing of each person's genome practical by means of readily available, high-throughput, automated DNA sequencing (e.g., dideoxynucleotide chain termination, or Sanger, method). Despite the overwhelming similarity in sequences among individuals (99.9%), there are common, heritable genetic variations that contribute to susceptibility or resistance to disease. These common variants most frequently take the form of single-nucleotide polymorphisms. Technically, single-nucleotide polymorphisms refer to DNA sequence variations that are present in at least 1% of the population. It is important to recognize that the approximately 10 million single-nucleotide polymorphisms in the human genome occur frequently because they have been conserved in our species, ostensibly because they provide an adaptive advantage to the organism under specific circumstances. Thus, single-nucleotide polymorphisms do not cause disease but likely influence the risk of developing a disease or the outcome from a disease (e.g., death from sepsis). Single-nucleotide and other polymorphisms exist in nonrandom patterns, or haplotypes (variant alleles located together along portions of individual chromosomes). In light of recent reports,[16,17] it has been argued that accurate characterization of genotype-phenotype associations will require the definition of haplotypes rather than the examination of individual single-nucleotide polymorphisms.[18] Thus, many in the field of functional genomics are awaiting the results of the HapMap (www.hapmap.org) efforts and are simply collecting DNA samples from at-risk patients for later analysis.[19] It is expected that successful mapping of human haplotypes will provide a critical resource for biomedical researchers who study health, disease, and variations in drug response based on genotypic differences (pharmacogenomics).

THE TRANSCRIPTOME (mRNA)

The term *transcriptome* refers to the complete set of messenger RNAs (mRNAs) encoded by the genome for a particular cell type. Unlike the genome, the transcriptome and the proteome (see later) are dynamic, characteristic of a particular cell type in a particular cell state at a specific time. For example, changes in the relative abundance of RNA and protein are what cause the dramatic changes induced by pregnancy, not the underlying maternal DNA "blueprint" that has been present since conception. Until recently, polymerase chain

reaction technology was the mainstay for detecting RNA. In particular, real-time polymerase chain reaction is a popular method of quantitating changes in relative mRNA abundance between samples, usually on the order of a handful of genes. Although most genes have coding sequences that are hundreds of nucleotides in length, only a relatively short sequence (<100 nucleotides) is required to uniquely identify each gene. Advances in robotic and miniaturization technology have made it possible to study simultaneously the relative abundance of several thousand RNA species. Developers exploited these advances by fashioning glass slides ("chips") with minute quantities of short, gene-specific nucleotides. These gene-specific "probe" nucleotides—ideally, one for each gene in the genome—are arrayed on the chip surface to produce a DNA *microarray*. From cells or tissue of interest, mRNA can be isolated and labeled to produce "target" nucleotides. Hybridization of the microarray probes with the complementary-labeled targets results in the formation of a labeled heteroduplex. With the aid of a laser scanner and computational software, the relative degree of label signal intensity, correlating to the relative mRNA abundance for each gene, can be calculated. By varying the source of the target mRNA, investigators can compare relative levels of mRNA abundance, in practice, generating an expression profile—the *transcriptome*—for the cell or tissue of interest. It is now possible to profile the entire human and mouse transcriptomes using the latest-generation microarrays.

THE PROTEOME (PROTEIN)

The term *proteome* was coined to describe the set of proteins encoded by the genome, and it defines the entire protein complement in a given cell or tissue.[20] Comprehensive mechanistic insight into cellular behavior depends on detailed knowledge of protein interactions. Thus, although gene expression "snapshots" have been enormously helpful in providing our first glimpses of molecular systems, genome-wide proteomics will be required to take our understanding to the next level and facilitate the application of systems analysis. Unlike their oligonucleotide counterparts, peptides are more difficult to study for several reasons (see the accompanying box).[21-24] As a result, the technology necessary to make protein "chips"—the tools needed to readily generate genome-wide "snapshots" of the proteome—is still emerging, some 5 years behind its DNA microarray cousin. Thus, even though there are technologic hurdles to overcome, the promise of the proteome continues to engage the imagination of investigators and speculators alike, especially for clinical diagnostics and drug development.

To monitor and later identify different proteins in a given sample, they must be separated into relatively homogeneous fractions. Two-dimensional gel electrophoresis and mass spectrometry are mainstay technologies for proteomics.[21,23-26] Two recent advances are discussed here: two-dimensional differential gel electrophoresis and isotopic-coded affinity tagging. Single-dimensional gel electrophoresis has been used for decades to separate and study small numbers of proteins (e.g., Western immunoblot analysis). The technique exploits the negatively charged nature of proteins, which move in an electric field toward the cathode, with the rate of movement determined largely by size. Two-dimensional gel electrophoresis separates in the first dimension based on isoelectric point, and then orthogonally based on size. Fluorescent two-dimensional differential gel electrophoresis is a new multiplexed method that enables the comparison of up to three experimental conditions in the same physical gel.[27] Two-dimensional differential gel electrophoresis is used to determine changes in the level of protein expression from arrays of approximately 2000 proteins (i.e., ~2000 gel spots are usually observed from plasma). The resulting differential protein expression profiles can be interpreted with greater confidence, with far fewer replicates, than with conventional two-dimensional gels. This methodology has been successfully applied in diverse systems.[28-33] The advantages of this method are that it is quantitative and allows image analysis; the disadvantage is that it poorly resolves proteins that are very high or low molecular weight, very alkaline, or hydrophobic.[34]

Isotopic-coded affinity tagging is a complementary technique that has significant advantages over two-dimensional differential gel electrophoresis for the identification of membrane proteins, proteins of lower abundance, and highly basic proteins (pI > 10).[24,35,36] Its disadvantages are that it poorly resolves proteins that are cysteine-poor and very acidic.[34] Typically, both two-dimensional differential gel electrophoresis and isotopic-coded affinity tagging are linked to subsequent analysis and identification by mass spectrometry, which measures mass-to-charge ratios of ionized analytes in the gas phase.[37] Mass spectrometry has demonstrated an ability to identify molecular signatures of peptides ("peptide-mass fingerprinting") that are diagnostic in cancer case-control studies.[22,38,39] It is expected that the proven utility of proteomics in cancer will be extended to the field of critical illness and injury, analogous to efforts in transcriptomics using DNA microarrays. Again, the expectation is that genes and pathways that are useful for diagnostics, this time at the protein level, will provide important molecular insight into regulation of the host response to critical illness and injury.

CLASSIFICATION USING MOLECULAR PROFILES

The analytic process of classification refers to the ability to distinguish between samples based on inherent, measurable features. Ideally, these features are easily quantitated, stable, and widely divergent between classes. The clinical application of classification strategies spans diagnosis, prognosis, and gauging the response to therapy. Although traditional statistics provides many robust classification tools using high-dimensional data in the fields of physics and economics, the application of classification strategies to functional genomic data is as new as the technology itself; both are evolving rapidly. Moreover, direct application of traditional computational strategies to high-dimensional biologic data can be hazardous, given that these strategies were not designed to account for the many limitations of biologic systems, such as nongaussian distributions and saturation (nonlinear) properties of probe-target interactions (microarray hybridizations). Despite these limitations, however, the power of molecular classification using genome, transcriptome, and proteome data is evident, as described later. The overarching strategy involves the description of informational features in a training data set associated with the phenotype of interest—in essence, defining a molecular profile of the phenotype. Application of these features to samples in a test data set determines the accuracy with which the features can classify unknown samples. The test data samples can be added to the training data set, typically

improving the predictive ability of the model; then, new unknowns are tested in an iterative manner. Classification is based on recognition of a defined "fingerprint" characteristic of a particular phenotype; it is not necessary to know the identity or function of the features or genes that determine it. Application of these classification strategies in the ICU promises improved diagnostics and prognostics based on real-time monitoring of changes in relative RNA or protein abundance, in the context of predisposition data from DNA sequences (single-nucleotide polymorphisms). A more detailed description of the computational strategies used to analyze data from high-throughput technologies can be found in several recent reviews.[40-46]

CLASSIFICATION USING DNA SEQUENCE VARIATIONS

There is an established association between genetics and predisposition to infection, although the mechanisms are unknown. In a seminal paper, Sorensen and colleagues calculated the heritable predisposition for early death from several complex diseases in adoptees compared with their biologic or adoptive parents.[47] These investigators found that premature death in adults has a strong genetic correlation, especially death from infectious causes, suggesting a significant underlying genetic basis. The search for genetic clues to this predisposition for critical illness from infection and other causes has been accelerated dramatically by sequencing of the human and mouse genomes and identification of informational single-nucleotide polymorphisms.[13,48] A number of reports suggest a role for single-nucleotide polymorphisms as markers of sepsis severity and outcome after injury (reviewed in reference 49). For example, association studies have linked single-nucleotide polymorphisms in innate immunity genes (e.g., Toll-like receptors, CD14), cytokine genes (e.g., tumor necrosis factor, interleukin-1 beta), and endothelial genes (plasminogen activator inhibitor-1) with important clinical phenotypes, such as increased disease susceptibility and poor outcome.[49] The exact role of any given single-nucleotide polymorphism in determining outcome in critical illness and injury, however, remains controversial, primarily because of inadequate study design (underpowered studies).[17,50] Although comprehensive reviews of association studies indicate that the majority of reported associations are not robust (<5% were consistently replicated when three or more reports existed),[16] meta-analysis indicates that larger, appropriately powered studies will likely find many single-nucleotide polymorphisms that are convincingly informational.[17] Even when confirmed, these associations are unlikely to be causal, and additional research will be required to determine the reason for the association and its molecular link to disease pathophysiology.

CLASSIFICATION USING RELATIVE RNA ABUNDANCE

Microarrays have been touted as the divining rods of the 21st century,[51] given that transcriptome characterization using DNA microarrays has the potential to revolutionize molecular diagnostics. Notably, microarray analysis has been used experimentally in the field of cancer to classify samples, addressing important clinical issues such as response to chemotherapy and propensity to metastasize.[52] It has been suggested that expression profile typing for some tumors may be significantly better than traditional diagnostic methods. With the appropriate confirmatory studies and attention to study design, it is expected that gene expression profiles will move from the bench to clinical reality shortly.[53] These studies can also be designed to couple sample classification (diagnosis, recovery trajectory, and response to therapy) with a study of gene function, discovery, interaction, and coregulation—in other words, making genomics "functional." It is logical to assume that these same techniques will be widely applicable to many complex human diseases, including critical illness and injury.[54-56]

To illustrate the power of this approach for cells of the immune system, Figure 44-1 depicts the classification of gene expression profiles of normal blood leukocytes, isolated T cells, and isolated monocytes. What differences in gene expression contribute to the differences observed among T cells, monocytes, and mixed cell populations? Shown at the right in Figure 44-1 is one version of the transforming growth factor-beta signaling pathway, arbitrarily chosen from one of the pathway discovery tools for microarray data, GenMAPP (www.genmapp.org). These data are consistent with a recent report indicating that human leukocyte expression profiles are cell specific.[57] Once a robust training data set has been collected describing the responses of isolated leukocytes in critically ill or injured patients, gene expression profiles will likely be monitored in the ICU to classify response to therapy and gauge clinical trajectories.[58]

CLASSIFICATION USING RELATIVE PROTEIN ABUNDANCE

Although DNA microarrays provide a molecular fingerprint that is useful in understanding the regulation of gene transcription, less than half the changes at the mRNA level are translated into changes at the protein level in the majority of systems. Thus, analyses of both the circulating transcriptome and proteome are indicated. Moreover, full mechanistic insight requires that changes in the transcriptome be linked to changes in the proteome, because the correlation between changes in relative mRNA and protein abundance varies, depending on the cellular role of the pathways studied.[59-61] This is irrelevant to the use of gene expression profiles for class prediction or modeling of gene coregulation, but it *is* relevant to understanding the biology of the host response. For example, close correlation was found between mRNA and protein abundance ratios for glycolysis genes in yeast, whereas abundance ratios for mitochondrial and protein synthesis genes were discordant, suggesting novel regulatory mechanisms.[61]

There are approximately 500 known (annotated) proteins in the circulating plasma proteome in humans.[22] Ideally, it would be desirable to employ "protein chips" in tandem studies to discover genome-wide protein expression profiles to complement our gene expression profiles. The combined data would allow us to find not only informational changes in blood that correlate with clinical trajectory and phenotype but also key regulatory information regarding control of gene and protein expression. However, this is not yet possible, because genome-wide proteomic technology is years behind transcriptomic technology. Despite the technologic challenges, however, recent reports highlight the potential of high-throughput proteomics. For example, simultaneous comparison of the proteome and transcriptome of human

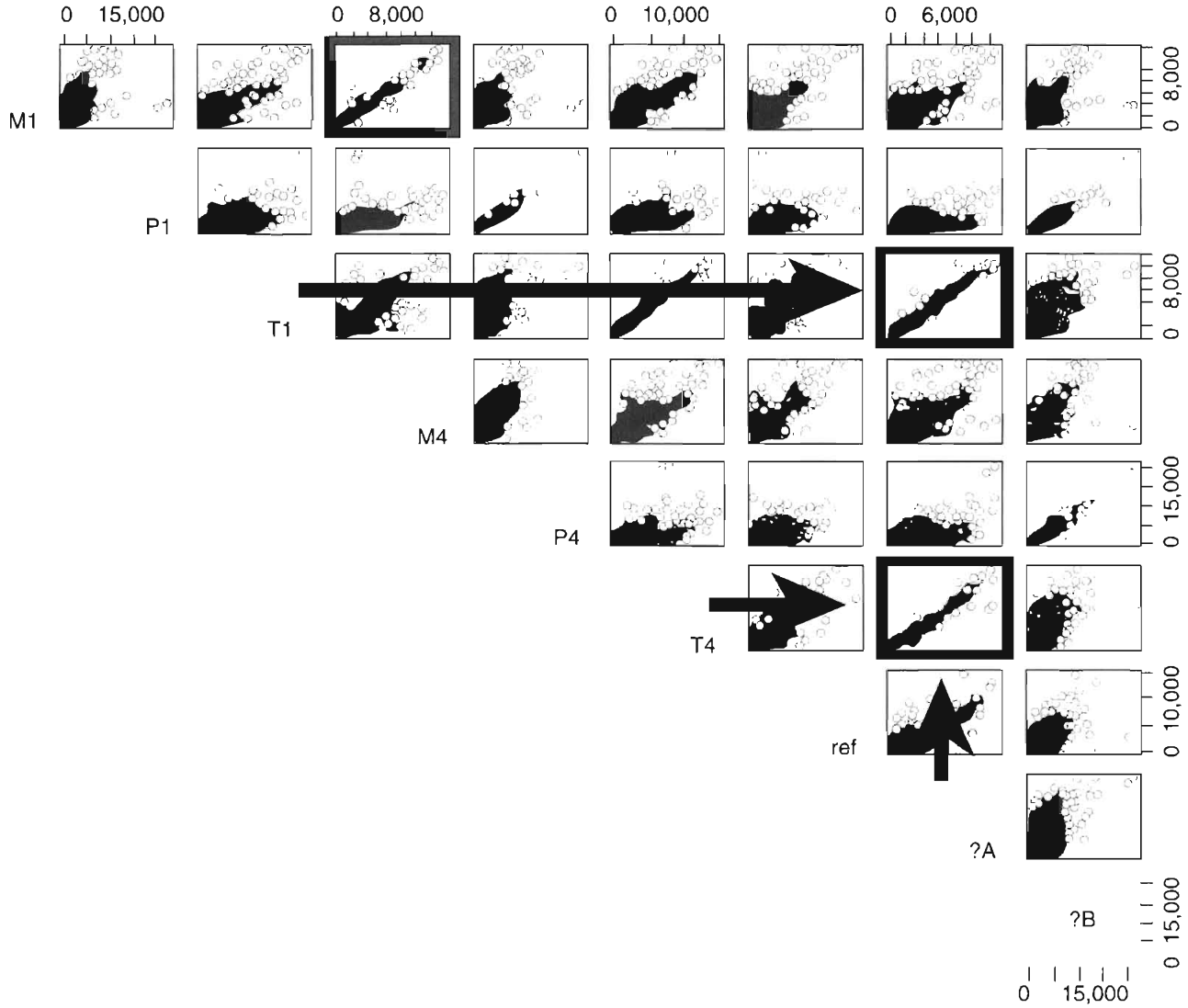

FIGURE 44–1. (A) Human transcriptome profiles of circulating T lymphocytes (T), monocytes (M), and mixed blood leukocytes (P) from normal volunteers (#1 and #4), compared with reference human RNA and two unknown samples (?A and ?B). At left, pair-wise comparisons of U95Av2 GeneChip expression signal for approximately 12,000 genes and expressed sequence tags show good pair-wise correlations between profiles of like cell types but not between different cell types in the same individual (e.g., compare good M1 to M4 correlation [yellow box] with poor M1 to T1 or P1 correlations). Moreover, assigning a cell type to the unknown samples A and B is easily accomplished, as shown by the orange arrows (?A to T cells, and ?B to mixed leukocytes). At right, the GenMAPP transforming growth factor-beta (TGF-β) pathway indicates differences in gene expression among T cell (red), monocyte (green), and PAXgene (blue). This program allows one to visually compare apparent levels of gene expression by color-coding genes that have increased expression in a given data set. In this example comparing blood leukocyte, isolated T cell, and isolated monocyte GeneChip signals, apparent gene expression for the type III TGF-β receptor (betaglycan) was greatest in T cells (red box); stress-induced protein 1 (SIP1) and c-FOS were greatest in monocytes (green boxes); and STAT3 was greatest in blood (mixed) leukocytes (blue box). The other genes shown (uncolored) were not changed. Thus, this figure indicates that apparent gene expression for the type III accessory receptor for TGF-β was greater in T cells, whereas apparent gene expression for SIP1 repressor and c-FOS cofactor was higher in monocytes. In contrast, there was higher apparent gene expression in blood (mixed) leukocytes only for the STAT3 cofactor. (See color section of this text.)

Continued on next page

neutrophils stimulated with lipopolysaccharide ex vivo indicated that isolated neutrophils have a much more complex and dynamic transcriptional response than previously appreciated.[60] Importantly, this study also highlighted the poor concordance between mRNA transcription and protein translation in a human neutrophil model of innate immune activation.

THE PROMISE OF MOLECULAR MONITORING IN THE ICU: SEPSIS

MH is a 74-year-old woman with a 3-day history of progressive dyspnea associated with crampy abdominal pain, nausea, and vomiting. Her past medical history is significant for childhood tuberculosis (left pneumonectomy) and dysfunctional uterine bleeding (open hysterectomy 3 years previously). In the triage area, her whole-body computed tomography scan was most consistent with partial small bowel obstruction and a mild basilar infiltrate in the remaining lung. The absence of a uterus and left lung was confirmed. Her peripheral leukocyte count was 11,000; the gene expression profile was consistent with inflammation. Plasma markers of infection were absent. She was admitted to the hospital with a working diagnosis of partial small bowel obstruction and treated with i.v. fluid hydration and nasogastric tube decompression. Her symptoms and signs of abdominal distention improved. On hospital day 2, however,

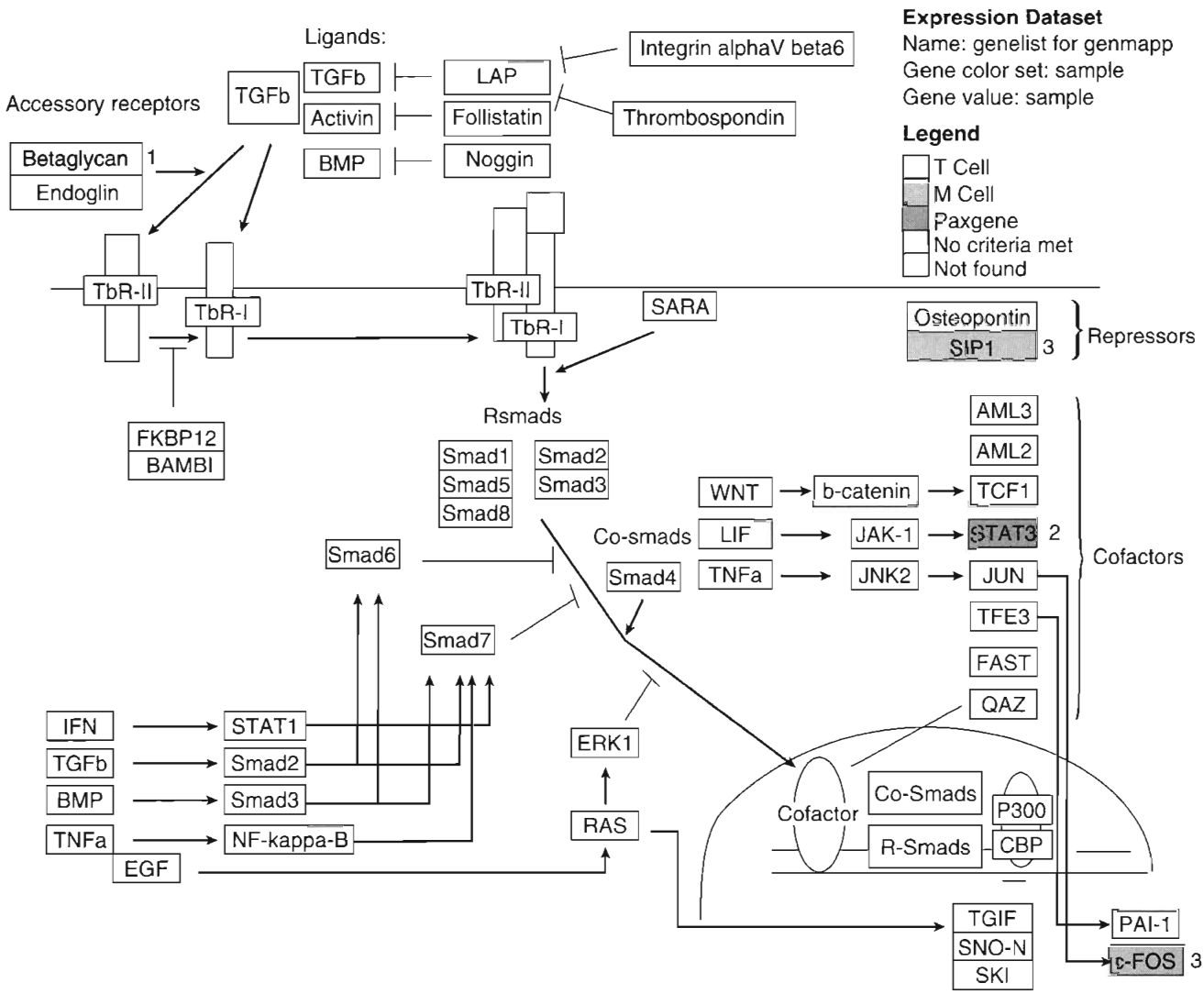

FIGURE 44–1—cont'd. (B)

her respiratory insufficiency worsened, requiring endotracheal tube insertion, mechanical ventilatory support, and admission to the ICU. Repeat leukocyte studies showed that her count had fallen to 6000, but the circulating gene expression patterns remained consistent with inflammation, and plasma markers of systemic infection were absent. On hospital day 5, the leukocyte count rose to 9000, and the pattern of sepsis molecular markers changed, indicating an expression profile consistent with Gram-positive infection. A diagnosis of Gram-positive bacterial pneumonia was made, and the patient was started on a narrow-spectrum antibiotic to treat Gram-positive organisms. The patient's abdominal examination and scans improved, and she was extubated with signs of resolving bowel obstruction and pneumonia on day 9.

As noted earlier, sepsis in the ICU presents several common diagnostic dilemmas. The hypothetical case just presented provides an example of how the advanced molecular diagnostics described herein will help discriminate between systemic infection and inflammation in the future. The assumption is that circulating leukocyte mRNA and protein abundance is a dynamic that varies as patients move along various clinical trajectories (phenotypes) during sepsis. We also anticipate that these trajectories can be characterized, monitored, and ultimately used to recognize infection in patients in whom sepsis is particularly difficult to diagnose.[55] The promise of this line of investigation is that these patterns of change in gene expression and protein abundance will become, in effect, new genomic "vital signs."[62] The human tissue that is most easily accessible for such longitudinal profiling is peripheral (circulating) blood. Further, it has been hypothesized that this systematic approach, using genome-wide gene and protein expression profiling, can be used to identify molecular classification schemes that provide novel insight into the adaptive response to inflammation and infection.[54,55]

Sepsis is particularly appropriate for this type of diagnostic approach. Although still controversial, modifications of sepsis criteria continue to be useful, as evidenced by a recent randomized, prospective, controlled clinical trial testing the only agent reported to increase the survival of patients with severe sepsis.[63] The authors of that study noted that the resulting pool of "septic" patients had a wide range of clinical features and were heterogeneous with regard to a number of biochemical inflammatory classifiers, including serum plasma D-dimer, interleukin-6, and protein C. More important, the inability to reliably distinguish between different degrees of septic injury continues to frustrate

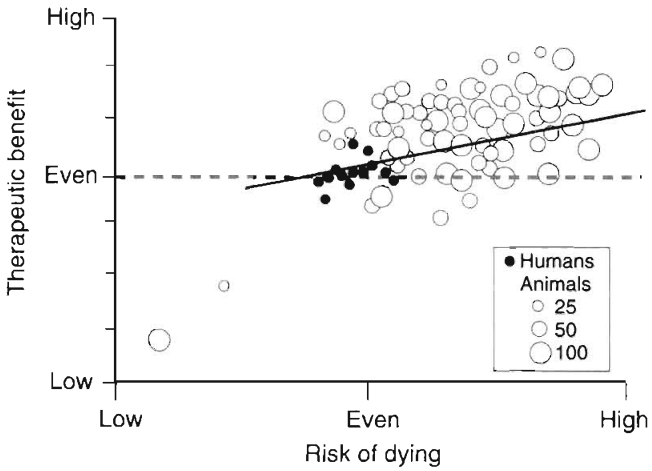

FIGURE 44–2. Relationship between the effect of anti-inflammatory treatment and the odds of the control group dying in animal and human sepsis trials. There is a significant correlation between the severity of illness and the likelihood of beneficial effect with treatment. Note that current enrollment in human studies centers around the point where therapies have no effect in animal models (in other words, the results of preclinical trials suggest that the human studies are unlikely to show benefit, given the current odds of dying in the human control groups). These data suggest that the ability to identify subpopulations of sicker patients would probably increase the likelihood of efficacy of anti-inflammatory agents. The technology needed to better classify septic patients is described in the text. (From Minneci PC, Deans KJ, Banks SM, et al: Should we continue to target the platelet-activating factor pathway in septic patients? Crit Care Med 2004;32:585-588.)

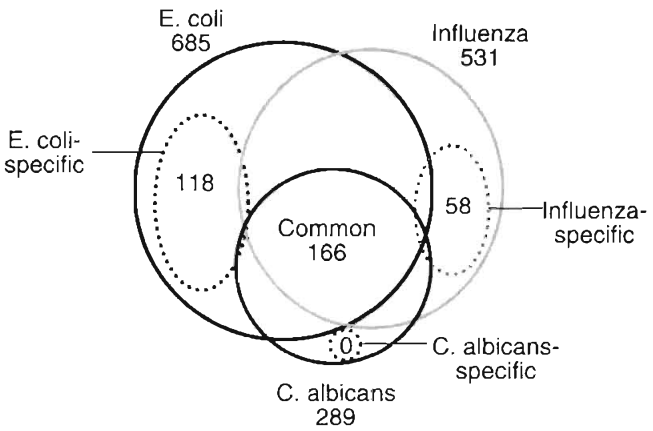

FIGURE 44–3. Overlapping sets of genes identified by DNA microarray analysis applied to human dendritic cells stimulated ex vivo with *Escherichia coli*, influenza virus, or *Candida albicans*.[67] Note that there were 166 genes in common, suggesting that there are both generic and stimulus-specific genes activated by infectious or inflammatory stimuli.

investigators and slow the development of sepsis therapeutics. For example, the efficacy of anti-inflammatory agents in treating sepsis is dependent on the severity of illness, with sicker patients and animals appearing to benefit the most from anti-inflammatory agents (Fig. 44-2).[64,65] Moreover, investigators must not only identify the infectious organism (e.g., Gram-positive bacteria versus fungi) to optimize outcome but also distinguish temporally among potential host responses to the invading organism, including the systemic inflammatory versus counterregulatory anti-inflammatory response syndromes. These tasks remain exceedingly difficult, despite ongoing improvements in diagnostic technology, and are still based largely on history, physical examination, and the results of common laboratory tests. As an example, recent evidence indicates that patients with ventilator-associated pneumonia are frequently misdiagnosed, based on an examination of postmortem specimens, radiographic findings, and clinical criteria.[66] Clearly, the ability to classify patients rapidly based on presence of infection, type of organism, and temporal phase of the host's adaptive response would increase the likelihood of therapeutic success. Thus, new strategies and tools are needed to correctly identify those who are most ill with sepsis, and thereby those who are most likely to benefit in clinical trials of sepsis therapeutics.

Recent reports using DNA microarray analysis indicate that inflammatory and infectious insults produce distinct molecular signatures. For example, microarray analysis of dendritic cells stimulated ex vivo exhibit both common and pathogen-specific immune responses.[67] Specifically, there were 166 genes expressed in response to bacterial, fungal, and viral stimulation, consistent with a common cluster of genes expressed in response to infection (Fig. 44-3).[67] Interestingly, yeasts were found to respond similarly to diverse insults, expressing a so-called common stress response cluster.[68] In another study, gene expression profiles of human whole blood stimulated ex vivo with heat-killed *Staphylococcus aureus* or *Escherichia coli* lipopolysaccharide had both generic and bacteria-specific features.[69] It follows, then, that it may be possible to define clusters of mammalian genes that are commonly up-regulated or, conversely, down-regulated in response to sepsis—what could be called a "common sepsis response" cluster.[70] Finally, recent data from animal models of abdominal and pulmonary sepsis suggest that measurements of RNA relative abundance in blood can be used to predict not only whether a mouse is infected but also the type of infecting organism.[70,71] It is expected that proteomic data will be equally or even more revealing.[72] These preliminary data suggest that important advances in sepsis diagnostics can be anticipated in the near future based on analysis of blood transcriptomes and proteomes.

CONCLUSION

Critically ill and injured patients have suffered from clinicians' inability to accurately classify and gauge clinical trajectory and response to therapy. Coincident with the sequencing of the human and mouse genomes, the technology has become available to move critical care monitoring and diagnostics into the genomic era. This will be characterized by the appearance of novel tools capable of profiling DNA, RNA, and protein in a search for molecular fingerprints associated with clinically important phenotypes and, more important, individualized response to therapy. To realize the full potential of this technology, support for ongoing, large-scale, collaborative research projects using genomic and proteomic technology to define the immunoinflammatory phenotypes in response to critical illness and injury will be essential.* As described earlier, diagnosing sepsis and

*These include National Institutes of Health research projects currently funded by the National Institute of General Medical Sciences (http://www.nigms.nih.gov/funding/gluegrants.html); National Heart, Lung, and Blood Institute (http://www.nhlbi.nih.gov/resources/pga/); and National Institute of Allergy and Infectious Diseases (http://www.immunetolerance.org/ and http://www.septicshock.org/).

Technical Challenges to Monitoring the Proteome

At least 35% of proteins exist in multiple isoforms, secondary to alternative splicing and post-translational modification, a "seemingly infinite universe of post-transcriptional complexities."[22]

Proteomic analysis is substrate limited, as there is no means to amplify product (i.e., there is no polymerase chain reaction–equivalent for proteins).

Protein concentrations cover a huge dynamic range (10^6 in cells and 10^9 in plasma), yet current proteomic technology can measure changes over a range of only three to four orders of magnitude.

Only a portion of a given proteome (i.e., a subproteome) can be interrogated at one time, owing to limited substrate in the sample and limited dynamic range of the technology. Therefore, subtraction and enrichment strategies, and their limitations, are commonly encountered.

Current proteomic technology is primarily qualitative and inherently more complex than DNA or RNA technology, resulting in lower throughput.

monitoring the response to antibiotic therapy are prime examples. Annotated databases linking these data, with free access to the public, are sorely needed. Using gene and protein expression profile analysis, novel strategies for sepsis recognition, pathogen identification, and modeling of the leukocyte response are being tested. Industry reports suggest that the results of such tests will soon be available in hours, as opposed to the several days currently required. In the absence of new therapies, such a strategy will be essential to improving outcomes among the critically ill and injured.

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This landmark twin study made the association between genotype and risk of death from infection.

Chapter 45
GENETICS OF CRITICAL ILLNESS

Richard G. Wunderink

KEY POINTS

1. **Association studies**, comparing the frequency of polymorphisms in patients with a disease or a complication to that in a control population, are most likely to determine the genetic components of complex critical illnesses.
2. **The risk of dying from infection is familial**, and a good family history of infection should be obtained in all patients.
3. **The genetic predisposition to a disease**, such as septic shock, **may be different from the genetic predisposition to a specific manifestation**, such as acute respiratory distress syndrome or disseminated intravascular coagulation.
4. **Large databases and multivariate analyses are required** to tease out the relative contributions of genetic factors to infection, within the context of underlying diseases, the variable pathogenicity of microorganisms, treatment factors, and so forth.
5. **Establishing the genetic risk of developing a disease** will be clinically relevant when the genetic variability allows risk stratification of patients and leads to differences in management, and when diagnostic or screening tests are readily available.
6. The great hope of **pharmacogenomics**—use of genetic information to individualize drug therapy—is not only to identify the right dose of medication to use safely but also to individualize the choice of drug in specific circumstances and specific patients.

Understanding the genetic variability in the response to critical illness, with its implications for individualization of therapy, is likely to be a focus of research in the next few decades. Recent technologic advances have made routine genotyping in a clinically relevant time frame feasible. Unfortunately, knowledge about the clinical implications of individual genetic variation on the course or risk of critical illness lags far behind.

Genetic variability is likely to affect many aspects of the care of critically ill patients. The initial focus is on three main areas—the host immune response to infection, the risk of coagulation or thrombosis, and the effects on drug metabolism. Although research interest in other areas will undoubtedly develop, these three topics illustrate the importance of unraveling the role of genetic variability in the outcome of critical illness.

GENETIC PRINCIPLES

Variability is incredibly common in the human genome. A variant allele occurs in approximately 1 of every 300 to 500 bases in human DNA. Although new mutations can cause isolated disease, the majority of genetic variation is in the form of polymorphisms. Polymorphisms are allelic variations that exist stably in a population at a frequency (generally ≥1%) that cannot be accounted for by new mutations alone. The implication is that these mutations do not confer a strong selective disadvantage and may even be associated with a beneficial effect in specific circumstances.

Genetic polymorphisms can occur in a variety of forms. The most common is a single-nucleotide polymorphism (SNP), which is a variation in a single nucleotide. This can be a substitution of one base for another, a deletion, or an addition of a base pair. Larger sections of the chromosome can also be deleted. Variable tandem repeats are sections of the chromosome (minisatellites) that contain multiple copies of a segment of DNA. These usually occur in the large stretches of the chromosome that do not encode a gene. Multiple two, three, or four base pair repeats (microsatellites) are also common. The number of repeats in these microsatellites is highly variable, a fact that is useful in forensic medicine. Large chromosomal mutations can be seen in critically ill patients and are common causes of neonatal ICU admissions.

The area where a SNP occurs determines the resultant effect. If a mutation occurs in an exon of the gene, an abnormal protein is more likely. Because of the redundancy of codons coding for specific amino acids, the polymorphic allele may not result in a different amino acid sequence—a silent mutation. Association of disease or disease severity with a silent mutation most likely indicates that it is a marker for a different functional polymorphism. Mutations that change the codon to one that signals the end of gene transcription can occur but are rare, because of their generally deleterious effect. The area of chromosome before the first gene sequence, called the promoter region, is critical in initiating gene transcription. Mutations in the promoter region are therefore more likely to affect the amount of gene product produced as a result of differential binding of nuclear transcription factors, such as nuclear factor kappa-B. The variable amount of messenger RNA (mRNA) still codes for a normal protein. Mutations in introns, areas within the gene that code for sections of mRNA but are clipped off before translation into the final protein, are less likely to result in a functional difference in the amount of protein or a structural difference in the protein itself. However, a biologic effect from polymorphisms in these areas is possible.

Genetic Terminology

Allele: One of the variant forms of a gene at a particular locus, or location, on a chromosome.
Codon: Three bases in a DNA or RNA sequence that specify a single amino acid.
Exon: Region of a gene that contains the code for producing the gene's protein. Each exon codes for a specific portion of the complete protein.
Haplotype: Set of genetic markers on the same chromosome linked closely enough to be inherited as a unit.
Heterozygous: Possessing two different forms of a particular gene, one inherited from each parent.
Homozygous: Possessing two identical forms of a particular gene, one inherited from each parent.
Intron: Noncoding sequence of DNA that is initially copied into RNA but is cut out of the final RNA transcript.
Linkage: Association of genes or markers that lie near one another on a chromosome. Linked genes and markers tend to be inherited together.
Linkage disequilibrium: Two alleles at different loci that occur together in an individual more often than would be predicted by random chance.
Locus: Place on a chromosome where a specific gene is located—a kind of address for the gene. (The plural is loci.)
Lod score: Statistical estimate of whether two loci are likely to lie near each other on a chromosome and are therefore likely to be inherited together. A lod score of three or more generally indicates that the two loci are close.
Marker: Segment of DNA with an identifiable physical location on a chromosome whose inheritance can be followed. Because DNA segments that lie near each other on a chromosome tend to be inherited together, markers are an indirect way of tracking the inheritance pattern of genes that have not yet been identified but whose approximate locations are known.
Microsatellite: Repetitive DNA sequence with a repeat unit of 2 to 4 base pairs.
Minisatellite: Repetitive DNA sequence with a repeat unit of 5 to 30 base pairs.
Penetrance: The frequency of expression of genotype.
Polymorphism: A common variation in the sequence of DNA among individuals.
Promoter: The part of a gene that contains the information to turn the gene on or off. The process of transcription is initiated at the promoter.
Single-nucleotide polymorphism (SNP): Common but minute variations that occur in human DNA at a frequency of 1 every 1000 bases. (SNP is pronounced "snip.")
Variable number tandem repeats: Generic term for mini- and microsatellites. Often used as genetic markers to track inheritance in families.

From http://www.genome.gov/glossary.cfm.

Micro- and minisatellites can cause disease, such as the fragile X syndrome and Huntington's disease, but they are more likely to be markers for other functional polymorphisms.

DEMONSTRATION OF GENETIC RISK

A variety of methods are available for demonstrating the genetic component of critical illness. The two main methods are linkage analysis and association studies. Each type of analysis is appropriate or advantageous in different situations (Fig. 45-1).

LINKAGE ANALYSIS

Traditional family studies and pedigrees are powerful techniques to find rare mutations that consistently result in clinical disease (high penetrance). This type of genetic pattern is usually studied with linkage analysis. Linkage analysis involves genotyping specimens for multiple polymorphisms to determine which polymorphic alleles are transmitted together in affected individuals. The strength of the association can be described by the lod (logarithm of the odds) score—an estimate of whether the observed data are due to linkage or to random variation. Generally, a lod score of three or more is evidence of linkage between the marker and the causative gene.

Linkage analysis is less helpful in illnesses requiring ICU care because of the impact of environmental exposure, the frequent variability in gene penetrance, and the multiple-loci nature of complex illnesses. For these and other reasons, critical illness does not appear to occur in a familial pattern. Therefore, the only way linkage studies can be performed is to compare unrelated affected and unaffected individuals. The additional variability introduced by this factor precludes finding all but the strongest associations. Newer molecular technologies, including the use of gene array chips, hold great promise for future studies but are still both difficult to interpret and very expensive.

ASSOCIATION STUDIES

The most common type of study supporting a role for genetic variability in the complex diseases affecting the critically ill is the association study. Association studies essentially look for a different frequency of specific alleles in patients with a disease or complication compared with the frequency in a control population.

Association studies have a variety of problems.[1] The initial assumption of the association study is that the gene of interest is involved in the illness being studied. A strong physiologic rationale for the candidate gene is required to ensure that associations are not spurious. Association studies therefore are dependent on basic research and animal studies to identify

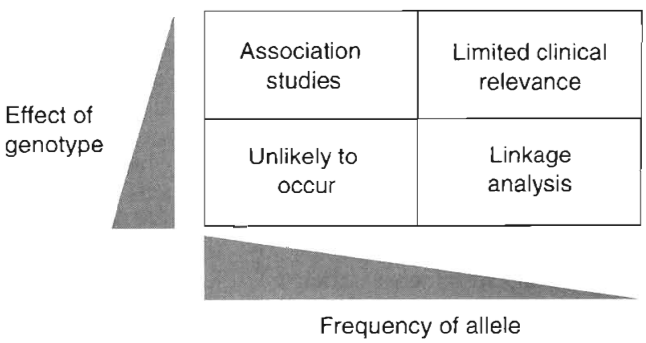

FIGURE 45–1. Approaches to determining genetic predisposition.

appropriate or novel candidate genes. Gene expression arrays are increasingly important as a method to identify unknown genes or genes with previously unrecognized importance.

In addition, the specific polymorphism studied may not be the causative locus. Genes are not inherited independently; they are inherited as whole chromosomes. Multiple mutations may occur in the gene of interest or in adjacent genes on the same chromosome, each of which may or may not affect either the actual protein structure or the amount of protein produced. For example, at least 10 mutations occur in the tumor necrosis factor (TNF) promoter region, several of which are known to affect the TNF response to a standard stimulus. Many of these mutations are in linkage disequilibrium with each other. An association between a specific mutation and an outcome, predisposition, or even physiologic response does not prove that the mutation causes the response. Therefore, any polymorphism associated with a clinical condition or outcome should be considered a marker for genetic risk until more extensive studies confirm that the mutation leads to a change in biologic function and that the change induced produces the outcome observed.

For complex diseases, the mutation must be common enough to affect a significant portion of the population. Although rare mutations can cause unique infection syndromes, such as disseminated bacille Calmette-Guérin infection after immunization, the majority of patients with a common infection such as community-acquired pneumonia are unlikely to carry these rare mutations. The known genetic mutations that have an impact on immunity, such as immunoglobulin deficiencies or cilia dysfunction, clearly do not explain the majority of cases of pneumonia or sepsis. Therefore, most association studies have examined polymorphisms.

Complex medical illnesses, such as those that present to the ICU, are likely to be polygenic, with multiple genes on different chromosomes interacting to cause the effect. Teasing out these interactions with association studies is difficult and requires large populations. Many published association studies are underpowered.

The appropriate comparison population is critical to association studies.[2] Ethnicity, age, gender, and exposure are important factors, but they do not guarantee a valid control group. Choosing the appropriate control population for critically ill patients is even more difficult and controversial. The appropriate controls for the development of an illness may be different from the controls for a specific manifestation once that illness has occurred. Simple tests, such as Hardy-Weinberg equilibrium (i.e., the genotype frequencies should equal that predicted by allele frequencies in the population), in the control population are needed to ensure selection bias. Newer statistical techniques of genomic controls may help exclude a spurious association based on nonrandom sampling.

Specific phenotypes are also difficult to define for the critically ill. The physiologic response to sepsis may be different based on whether the cause is Gram-negative bacteria, Gram-positive bacteria, fungi, or viruses; however, the distinction is often difficult to make clinically. Similarly, the risk for simple deep venous thrombosis may be different from that for pulmonary emboli, even though they are combined in many clinical studies. Many studies have focused on more objective outcomes, such as death, septic shock, or bacteremia, because of the difficulties in defining other phenotypic presentations.

Finally, environmental or nongenetic host factors complicate the interpretation of association studies. The host response (and therefore the genes involved) is very different for *Mycoplasma* pneumonia than for pneumococcal pneumonia. The effect of active alcohol ingestion can lead to a phenotypic change (increased risk of septic shock, neutropenia, or acute respiratory distress syndrome [ARDS]) that is not genetically based. Therefore, association studies should include multivariate analysis, with inclusion of known clinical risk factors (as well as other genetic risks) as part of the analysis.

The statistical analysis of association studies is not necessarily less complex than that of linkage analysis. Many studies examine several SNPs in the same population. The usual statistical correction for multiple comparisons may be too conservative and is probably inappropriate, because it assumes the comparison of independent factors when, in fact, multiple SNPs in the same or adjacent genes do not sort independently. Haplotype analysis may overcome this statistical issue, but it introduces greater complexity in other ways.

Despite these limitations, association studies are presently the most commonly used genetic study for complex multifactorial diseases, and most of the subsequent information presented in this chapter is derived from association studies. The genetic influence on complex illnesses continues to be a difficult area of research. Knowledge of the role of genetics in critical illness will continue to expand, and any discussion of specific genetic factors will likely be quickly outdated. However, reviewing the data currently available illustrates some of the principles that are important in evaluating future studies of genetic risk.

GENETIC INFLUENCE ON THE HOST IMMUNE RESPONSE

The strongest support for the role of genetics in infection is the adoptee study by Sorenson and colleagues.[3] They linked cause of death in adoptees to cause of death in both the natural parents and the adoptive parents. The risk of dying of infection if either natural parent died of infection by age 50 years was nearly six times greater than if neither died of infection. The increased risk exceeded the genetic risk of early death from cardiovascular disease or cancer (Fig. 45-2). In addition, the excess genetic risk for death from infection

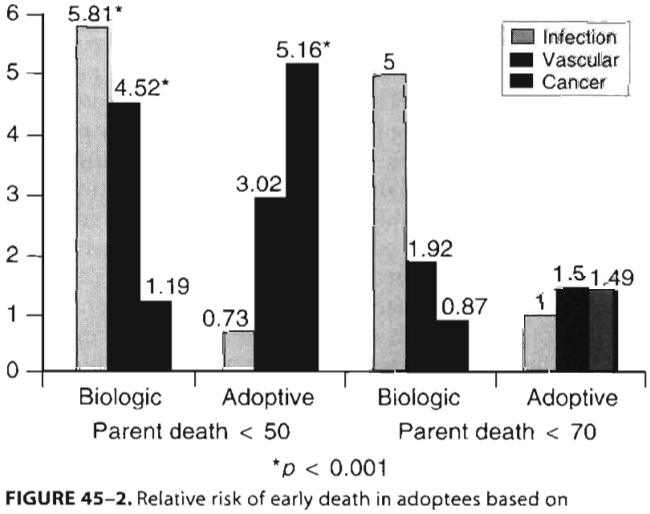

FIGURE 45–2. Relative risk of early death in adoptees based on identical cause of death in either natural or adoptive parents. (From Sorensen TI, Nielsen GG, Andersen PK, et al: Genetic and environmental influences on premature death in adult adoptees. N Engl J Med 1988;318:727-732.)

extended to parental death any time in the first 70 years of life. Despite well-documented genetic factors, familial risk of death from cardiovascular disease and malignancy is negligible when parental death occurs between ages 50 and 70 years.

Although these findings strongly support the role of genetic factors in infectious mortality, neither the type of infection nor the specific genetic factors can be determined from this type of study. Epidemiologic data suggest that pneumonia and bacteremia are the major causes of septic deaths in the United States. More unusual causes of severe sepsis, such as meningitis and endocarditis, also have high fatality rates. Although some of the earliest and strongest evidence for a genetic influence on response to infectious disease came from malaria studies, many studies of genetic risk focus on severe sepsis, pneumonia, and meningitis.

Ethnic and racial differences in mortality from infectious diseases have been known for centuries and provide additional evidence of the influence of genetic factors. Even accounting for socioeconomic differences, racial differences in death rates from pneumonia are consistently found. However, the type and degree of differences are not consistent. In many past studies, African Americans had higher mortality rates than white Americans, and Asian Americans had lower rates. However, recent data demonstrate that, for bacteremic pneumococcal pneumonia, mortality rates for Asian Americans are significantly greater than those for black and white Americans.[4] Several explanations for these contradictory findings are possible. For instance, different genetic backgrounds may be more important for bacteremic pneumococcal pneumonia than for pneumonia in general. However, the more likely explanation is that different subpopulations with different genetic backgrounds were sampled and that the statistical lumping of ethnically diverse populations into broad "races" confuses the issue. Other studies have demonstrated that the risk of death from pneumonia varies widely among different ethnic groups categorized as Hispanic American or Asian American. This variability within demographic groups actually supports the importance of genetic factors in the outcome of severe infection.

Because the genetic risk for severe infection likely involves multiple gene loci (many of which demonstrate variable penetrance), and because there is clearly a major environmental component (i.e., exposure to an infectious agent), several authors have suggested that family studies of infection cannot be done. However, classic family studies, such as triad studies (sampling the affected child and both parents), are possible if a careful and comprehensive family history is obtained.[5] Figure. 45-3 illustrates a family pedigree demonstrating a type of familial infection syndrome. Certain key features allow the recognition of a genetic predisposition to infection. Index cases of death from infection at an age younger than age 50 to 60 years, especially when no underlying systemic disease confuses the issue, are critical to recognize. Awareness that the genetic risk for infection may be generic in terms of site, such that different family members may be affected by a variety of infections, is also important.

From a practical standpoint, one of the more important reasons to take a complete and comprehensive family history is to increase suspicion of the myriad rare genetic causes of altered immunity. Although too extensive to discuss in this chapter, genetic defects in neutrophil or lymphocyte function, immunoglobulin deficiencies, cilia dysfunction, and the like can be seen (rarely) in the critically ill. In adults, the first manifestation is unlikely to be a critical illness; however,

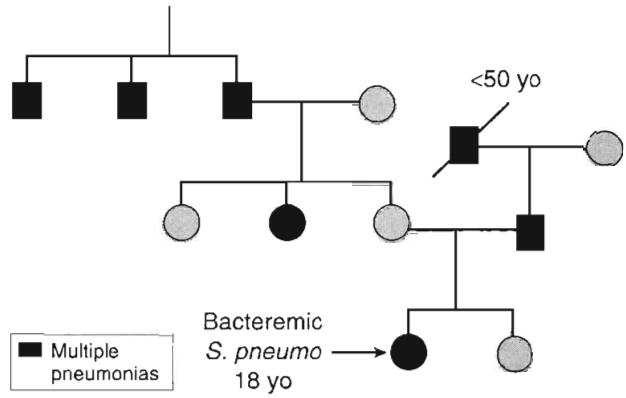

FIGURE 45–3. Pedigree of familial infection syndrome.

this may be the initial presentation in neonatal and pediatric ICUs. Simply because of their higher frequency, polymorphisms in the innate response are likely to affect a greater proportion of the critically ill.[6]

INNATE IMMUNE RESPONSE

Because of the rapidity and severity of onset, the types of illness precipitating ICU admission, especially infection, likely involve the innate immune response more often than the acquired immune response. The three main components of the innate immune response are pattern recognition molecules, inflammatory response mediators, and the important counterregulatory anti-inflammatory response mediators.

Pattern Recognition Molecules

Key to the innate immune response is the recognition of invading microorganisms. Pattern recognition molecules are inherited through the germ line; therefore, though common to all cells, their number is more limited than the remarkable diversity of receptors possible on individual lymphocytes involved in the acquired immune response. Because of this limited repertoire, pattern recognition receptors are usually focused on highly conserved structures present in large classes of microorganisms. These pathogen-associated molecular patterns are unique to microbial pathogens, without human homologues. In addition, the structures recognized are usually essential for either survival or pathogenicity of the microorganism.

Pattern recognition molecules can be secreted into the circulation and function by binding to microorganisms and facilitating recognition by phagocytes or the complement system. Mannose-binding lectin not only activates the complement system when bound to bacteria but also regulates inflammatory mediators. Several mutations in the gene or promoter region can lead to little or no serum mannose-binding lectin. The incidence of homozygous variant coding alleles appears to be almost twice as common in pneumococcal bacteremia as in noninvasive disease.[7] Mannose-binding lectin is phylogenetically related to surfactant proteins, rare mutations of which have also been associated with infection and lung disease.

Lipopolysaccharide-binding protein is another secreted pattern recognition molecule. Rare alleles of lipopolysaccharide-binding protein have been found to be increased in septic patients, and all septic patients homozygous for these alleles died.[8] No associations between sepsis and polymorphisms

in the related bactericidal permeability increasing protein gene were found in the same population. Interestingly, the frequency of rare alleles was more common in males in one study; in another, it was more common in African Americans of both genders. The site may therefore be a marker for an as yet unidentified adjacent SNP that is important in sepsis. Support for this possibility comes from the finding that the originally described restriction length polymorphism cleavage site is actually at an adjacent nucleotide, resulting in a silent mutation.[9]

Pattern recognition molecules can also be located on cell surfaces, where they function either by mediating uptake into lysosomes for destruction and antigen processing or by activating signaling pathways to induce the expression of a variety of host response genes, especially inflammatory cytokines. Toll-like receptors (TLRs) are important examples. At least 10 different TLRs exist, with different affinities for various microorganisms. TLR4 appears to be essential for the recognition of endotoxin, whereas TLR2 is more important for the recognition of Gram-positive bacteria. Two polymorphisms, TLR4 Asp299Gly and Thr399Ile, were examined in a French cohort of 91 patients with septic shock and 73 healthy controls.[10] Both polymorphisms were uncommon, but carriage of 299Gly was found only in the shock cohort. This SNP did not appear to increase the risk or severity of meningococcal meningitis.

Increased levels of soluble CD14, a component of the endotoxin-lipopolysaccharide recognition pathway, may be an important risk factor for septic shock. A polymorphism at the −159 site has been associated with higher circulating levels of soluble CD14 and greater TNF production in peripheral blood mononuclear cells after stimulation with lipopolysaccharide or *Escherichia coli*. The CD14 −159 TT genotype was more common in patients with septic shock than in controls (71% versus 48%; $P = 0.008$).[11] In addition, mortality from shock was significantly higher in patients who carried a T allele.

Theoretically, functional polymorphisms in pattern recognition receptors should increase susceptibility to infection, but so far, the majority of data has found associations with indices of severity. This may be a function of study design. One of the few longitudinal studies in this literature found that TLR4 mutations increased the risk of serious bacterial infections.[12] The greatest risk appeared to be in patients with the 299Gly mutation in the absence of the 399Ile mutation. Although susceptibility to infection was not the primary focus of this particular study, longitudinal studies are a better design than cross-sectional studies to demonstrate such susceptibility.

Proinflammatory Mediators

Not surprisingly, much of the initial research into the role of genetic variability in infectious disease focused on the gene for TNF, a key mediator initiating the inflammatory cascade.[13-16] The TNF locus, especially the promoter region, is highly polymorphic. Several polymorphisms appear to be functional, with variable levels of TNF release in response to either infection in vivo or stimulation in vitro. Carriage of the A allele of TNF-308 SNP has been associated with an increased risk of septic shock, especially in surgical and trauma populations. The risk of septic shock appears to be less if the cause of infection is community-acquired pneumonia.[16,17] This discrepancy may relate to a differential effect in predominantly Gram-negative versus Gram-positive infections.

A SNP in the adjacent lymphotoxin alpha (LTA) gene has also been associated with increased TNF levels. Carriage of this LTA+250 AA genotype was associated with a substantially greater risk of septic shock and death from septic shock,[18] including in patients with community-acquired pneumonia.[16] Interestingly, respiratory failure in the absence of shock in community-acquired pneumonia strongly correlated with the opposite GG genotype (Fig. 45-4). This finding has important implications for the clinical definitions of severe sepsis and the systemic inflammatory response syndrome. Genetic predisposition to septic shock may be different from that to one manifestation of severe sepsis—hypoxemia. Similarly, the coagulation abnormalities of severe sepsis may be associated with polymorphisms in different genes, such as plasminogen activator inhibitor-1.[19]

The discrepancies in association studies of the TNF-308 SNP may be explained by significant linkage disequilibrium with the LTA SNP.[16] Linkage disequilibrium occurs when polymorphisms within the same or different genes are usually inherited together, resulting in a more frequent association than would be expected by chance of one allele in one gene with a specific allele in a nearby SNP. For example, the LTA+250 A allele is nearly always associated with a G allele at the TNF-308 site. Because the LTA+250 A allele is much more common than the TNF-308 A allele, provided that the degree of influence of each of these polymorphic sites is roughly equivalent, the LTA effect is much easier to observe when both sites are examined in the same population.

In addition to the very important HLA loci, the TNF and LTA genes are in close proximity to other immunologically important genes on chromosome 6, such as complement components and heat shock protein (HSP). The association between one HSP70 gene SNP and septic shock in a cohort of patients with community-acquired pneumonia was even stronger than that of the LTA+250 site mentioned earlier.[20] However, the two sites are in linkage disequilibrium, and haplotype analysis suggests that chromosomes containing an adenine at both the LTA+250 and the HSP70 loci are associated with the greatest risk of septic shock. These data suggest that

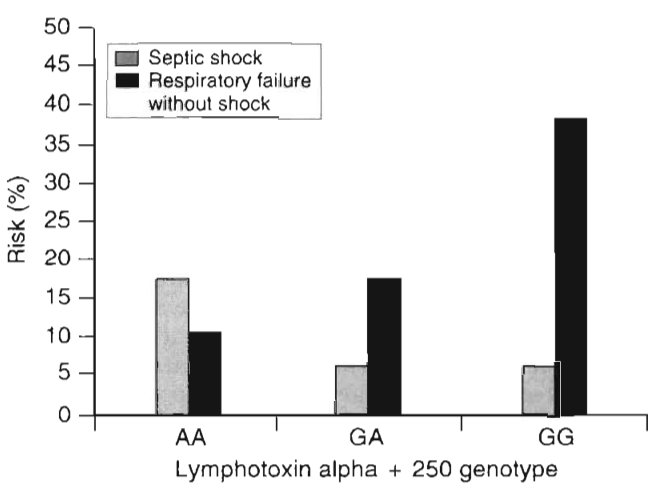

FIGURE 45–4. Relative risk of septic shock and hypoxemia without shock in different genotypes of the LTA+250 single-nucleotide polymorphism in a community-acquired pneumonia cohort. (From Waterer GW, Quasney MW, Cantor RM, et al: Septic shock and respiratory failure in community-acquired pneumonia have different TNF polymorphism associations. Am J Respir Crit Care Med 2001;163: 1599-1604.)

neither site is the true causative mutation; instead, they may be markers for some other important mutation in this area, which is rich in genes that are important in the inflammatory response.

Interleukin (IL)-6 levels are a marker of the severity and outcome of sepsis. Carriage of the low IL-6 secretor phenotype of the −174 SNP was associated with improved survival in those with severe sepsis. However, the in vitro IL-6 response is affected more by levels of TNF, IL-10, and IL-1 (and possibly gender) than it is by this polymorphism, casting doubt on the clinical importance of this SNP and emphasizing the importance of multivariate analysis in association studies.[17]

Anti-inflammatory Mediators

The ability to modulate the proinflammatory response is important for avoiding persistent inflammation and organ failure. An association study from a large cohort of meningitis patients illustrates the importance of this balance, as well as other issues involved in genetic association studies.[21] The IL-1 family includes the agonists IL-1α and IL-1ß and the IL-1 receptor antagonist IL-1RN, with genes located in a cluster on chromosome 2. IL-1β and IL-1RN SNPs were examined concurrently in 1106 patients with meningococcal meningitis. The investigators consciously chose SNPs that were not likely to be causative mutations but were known to be in tight linkage disequilibrium with functional genetic variants in the same gene. Mortality was independently related to age, serogroup of the infecting microorganism, and both genotypes. This study illustrates the ability of multivariate analysis in association studies to determine the effect of genotype independent of nongenetic host factors and the variable pathogenicity of the infecting microorganism.

The IL-1RN polymorphism considered most likely to be causative is a variable 86–base pair tandem repeat, which contains at least three sites for DNA-binding proteins. Alleles are designated A1, A2, A3, A4, and A5, based on their relative frequencies in healthy populations. Although the results regarding the risk of infection with the A2 allele have been inconsistent, an increased risk of death from infection (up to 6.47-fold higher) has been found for IL-1RN A2 carriers in several studies.[14,22] Similar to the findings in meningitis patients, the combination of proinflammatory gene polymorphisms (IL-1α, IL-1β, or LTA+250) and the IL-1RN A2 polymorphism was associated with an even greater risk of death.

Another major anti-inflammatory protein is IL-10. Like TNF, IL-10 is highly polymorphic. Family members of children who died from meningococcemia had significantly greater IL-10 production after lipopolysaccharide stimulation than did family members of children who survived.[5] A specific IL-10 SNP (−1082) was not randomly distributed in first-degree relatives of patients with meningococcal disease.[23] These family studies suggest that genetic differences in IL-10 production may be important in the outcome of severe sepsis, and they are supported by population-based association studies. Homozygotes for the G allele of the IL-10 −1082 SNP had an increased risk of septic shock (odds ratio, 6.1) among patients with pneumococcal bacteremia.[24] The −592 SNP A allele was associated with death in a cohort of critically ill patients. Interestingly, the excess deaths occurred both in patients who developed sepsis and in critically ill patients without sepsis. Generally, the IL-10 association studies suggest that polymorphisms may play a role in disease severity while not predisposing to infection.

ACQUIRED IMMUNE RESPONSE

Because the acquired immune response does not occur immediately, its role in critically ill patients is not as well studied as the innate response. Genetic variation may still play a role in illnesses requiring ICU care.

Infection

Attachment of immunoglobulin bound to specific bacterial antigens occurs via their receptors on the surface of leukocytes. Several polymorphisms in immunoglobulin receptors lead to reduced binding affinity. The most well studied is the CD32 (FcγRII) subclass polymorphism associated with decreased binding of the immunoglobulin G2 subclass, important for encapsulated microorganisms as well as C-reactive protein.

Homozygosity for the lower-affinity allele was more common in patients with bacteremic pneumococcal pneumonia than in either nonbacteremic or control populations, with all early deaths in homozygotes.[25] Complicating the association is the fact that the Fcγ receptor genes are located on chromosome 1, near other immunologically important genes, especially IL-10. Although not clearly in linkage disequilibrium with known IL-10 SNPs, the SNP combinations were not randomly distributed in first-degree relatives of patients with meningococcal disease.[23]

Autoimmune Disease

The acquired immune response can result in autoimmune disease if it is directed at antigens similar to host antigens. Autoimmune diseases such as systemic lupus erythematosus or Wegener's granulomatosis are common causes of ICU admission. The extremely variable responses and presentations of these diseases strongly suggest a genetic component, and associations with multiple polymorphisms have been suggested. The risk of complications, such as renal failure with lupus, may be increased in certain genotypes. In addition, many of the chronic inflammatory disorders, such as rheumatoid arthritis and inflammatory bowel disease, have been associated with the same inflammatory response polymorphisms studied in sepsis and other infections. Although the increased risk of infectious complications is usually ascribed to the use of immune-modulating agents, the genetic risk may also play a role.

Organ Transplant Immunology

Although the importance of matching donor and recipient for HLA and other tissue antigens is well known, evidence is accumulating that genetic variation in the inflammatory response may play a role in both acute and chronic graft rejection. For example, a hypersecretory polymorphism in the transforming growth factor-ß gene results in a significantly increased risk of bronchiolitis obliterans after lung transplantation.[26] This is a rapidly expanding area of research. Once again, the increased risk of infection in these patients may reflect a genetic predisposition, in addition to the effect of immunosuppressants.

Specific Organ Failure Modulators

With severe infection, a variety of organs can fail. Most of the attention has focused on the risk of septic shock. However, not every patient with septic shock experiences failure of the same organs. Differences in resuscitation are probably the major explanation, but genetic variability probably plays a role as well.

One of the worst complications is the development of ARDS. An insertion-deletion polymorphism in the angiotensin-converting enzyme gene has been associated with an increased risk for the development of ARDS, as well as increased mortality once ARDS had occurred.[27] This fact illustrates the importance of appropriate control groups. As seen in Figure 45-5, ICU patients without ARDS have a slightly lower incidence of the DD genotype than do normal controls or cardiac surgery patients. If the difference in incidence were smaller, a statistically significant difference might have been seen only if compared with a control group of non-ARDS ICU patients, whereas a nonsignificant difference would have been found if healthy controls or post–cardiac surgery patients were chosen as the control group. Use of three control groups adds to the reliability of the association found. A SNP in the surfactant protein B gene has also been associated with a 2.4-fold increase in the odds of developing ARDS, particularly ARDS due to pneumonia.

The coagulation abnormalities of sepsis are also likely to have a genetic component. The prototypical coagulation abnormality with sepsis is meningococcemia, and several cohorts have been studied. This disease is more common in children, facilitating family-based association studies. The relatively common factor V Leiden mutation has been associated with an increased risk of complications in heterozygotes.[28] The plasminogen activator inhibitor-1 insertion-deletion polymorphism is also associated with an increased risk of shock and other complications.[19] The availability of drotrecogin alfa for the treatment of sepsis will undoubtedly increase interest in the variability in coagulation pathways in sepsis and inflammation.

RISK OF COAGULATION OR THROMBOSIS

Genetic hypercoagulability syndromes play a role in many disorders leading to ICU admission. Chief among these are deep venous thrombosis, pulmonary emboli, myocardial infarction, cerebrovascular disease, and complications of pregnancy. Because of the frequency of these diseases, large-scale studies can be performed, allowing highly significant statistical associations to be found despite a very small attributable risk. These associations tend to be more apparent in younger patients, in whom the effect of comorbid illnesses and environmental factors cause less interference with the genetic risk signal.

Deficiencies in protein C, protein S, or antithrombin are the classic examples of genetic risk factors for deep venous thrombosis and pulmonary emboli.[29] However, the genetic basis of these deficiencies is the combination of more than 120 specific mutations for each factor. Screening based on genotyping is therefore impractical, and the diagnosis of these genetic diseases relies on the measurement of blood levels. With the discovery of the factor V Leiden and prothrombin G20210A polymorphisms, the percentage of patients (especially whites) with venous thromboemboli who can be documented to have a hypercoagulable state increased from less than 10% to approximately 30%. In patients with a family or personal history suggesting an increased risk, the proportion diagnosed may reach 70%. A functional assay, activated protein C resistance, screens for factor V Leiden and several less common polymorphisms. However, genotyping is routinely available.

Factor V Leiden in thromboembolic disease illustrates the goal for most gene association studies in common clinical illnesses. This SNP impacts clinical management in that homozygous patients or heterozygotes with other concomitant causes of thrombophilia warrant prolonged treatment with anticoagulants. Clinical suspicion can lead to a high frequency of confirmed diagnoses, and a screening test is readily available. A definite diagnosis has implications for the individual, as well as family members. The role of this polymorphism is unquestioned, despite interactions with other genes and environmental factors. In spite of large studies, the clinical utility of diagnosing genetic variations in patients with myocardial infarction or stroke is poor compared with that in the hypercoagulable model.

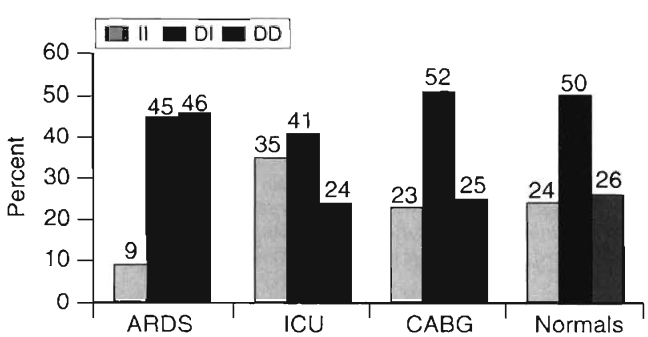

FIGURE 45–5. Comparison of angiotensin-converting enzyme (ACE) gene insertion-deletion polymorphism frequencies in acute respiratory distress syndrome (ARDS) patients versus other comparison populations. CABG, coronary artery bypass graft. (From Marshall RP, Webb S, Bellingan GJ, et al: Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome. Am J Respir Crit Care Med 2002;166:646-650.)

PHARMACOGENOMICS

Pharmacogenomics is the use of genetic information to individualize drug therapy. It has been heralded as one of the most likely immediate benefits of the Human Genome Project. This is clearly another area in which genetics will have an impact on critical care medicine. The genetic influence will be seen in two main areas—effects on drug metabolism and individualized therapy.

DRUG METABOLISM

Interindividual differences in drug metabolism are well known. These differences commonly are responsible for adverse drug reactions. It is logical to assume that functional genetic polymorphisms may be a major component of these interindividual differences and, by extension, the adverse drug reactions associated with them.[30] Polymorphisms most often result in poor drug metabolism, but occasionally they can cause ultrarapid metabolism.

One of the more extensively studied metabolic pathways is the cytochrome P_{450} (CYP) enzyme superfamily. More than 30 CYP enzymes are known, with functional polymorphisms described in most of the common ones. Table 45-1 lists such enzymes that alter the metabolism of drugs commonly used in the ICU. At least 55% of the drugs cited in studies of acute drug reactions are metabolized by enzymes with variant alleles. Interestingly, simply altering drug metabolism may not increase the number of acute drug

TABLE 45–1. COMMON ICU DRUGS METABOLIZED BY ENZYMES WITH VARIANT ALLELES

Enzyme	Drugs
CYP1A2	**Verapamil, isoniazid, acetaminophen, haloperidol,** theophylline, diltiazem, erythromycin, imipramine, phenytoin, rifampin, fluoxetine
CYP2C9	**Warfarin, rifampin, ibuprofen, imipramine,** phenytoin, tolbutamide, fluoxetine, naproxen, isoniazid, verapamil
CYP2C18	Fluoxetine, imipramine, rifampin
CYP2C19	**Isoniazid,** omeprazole, diazepam, cyclophosphamide, nortriptyline, S-mephenytoin, rifampin, warfarin, fluoxetine
CYP2D6	**Metoprolol, imipramine, nortriptyline, codeine, encainide, flecainide,** dextromethorphan, fluoxetine, theophylline, diltiazem
CYP2E1	Theophylline, isoniazid, verapamil, fluoxetine
NAT2	**Isoniazid**

CYP, cytochrome P_{450}; NAT, *N*-acetyltransferase.
Bold indicates a major metabolic pathway.

reactions directly. Although CYP1A2 is the metabolic pathway for only 5% of all prescribed drugs, it is at least partially involved in the metabolism of 75% of the drugs that are associated with adverse reactions and metabolized by enzymes with variant alleles.[30]

One of the better examples of the clinical application of genetically determined drug metabolism is in the dosing of warfarin (Coumadin). Warfarin is metabolized by the CYP2C9 enzyme, and variant alleles of this enzyme lead to poor metabolism. Patients who carry these alleles (6% to 9% of whites) require significantly lower doses of warfarin. However, the risk of adverse drug reactions has not been shown conclusively to be greater. The genetic effect is partially offset by the individualization of dose and is clearly affected by environmental factors (diet) and other medical conditions (liver disease, cor pulmonale). However, time to therapeutic dosing, an important cost issue, may be optimized if the genotype is known. Lack of a commercially available assay limits the clinical use of individualized dosing regimens based on genotyping.

In addition to drug metabolism, drug receptor polymorphisms may play a role in therapeutic response. Polymorphisms in genes coding for a variety of common drug receptors are known, such as the beta-adrenergic agonist or glucocorticoid receptors.

INDIVIDUALIZED THERAPY

Although the polymorphisms involved in drug metabolism may be able to determine the appropriate individual dose, one of the nebulous goals of pharmacogenomics is individualizing drug choice in a specific clinical scenario. In the ICU, these decisions are increasingly important because of the availability of expensive drugs with low therapeutic ratios, such as drotrecogin alfa.

One concern is that not accounting for genetic variability may have sidetracked the development of effective agents. For example, would use of anti-TNF strategies or therapeutic use of IL-10 be beneficial in septic patients with TNF hypersecretor genotypes? Many of the novel agents studied in sepsis trials had good theoretical, experimental, and animal study support for their efficacy. The failure to document any benefit in large human trials may reflect the inability to choose appropriate patient groups rather than the agents' ineffectiveness.

The ultimate goals of genetic studies in critically ill patients revolve around two issues: to better understand the pathogenesis of the disease (in order to design better treatment interventions) and to better define the patient group at increased risk (in order to choose the appropriate patients for treatment). In future editions of this textbook, discussions of genetics will no doubt be incorporated into individual chapters on the risks and treatment options of specific diseases.

ANNOTATED REFERENCES

Kiechl S, Lorenz E, Reindl M, et al: Toll-like receptor 4 polymorphisms and atherogenesis. N Engl J Med 2002;347:185-192.

This is one of the few long-term studies that provided data on the risk of infection based on genetic predisposition, although this was not a primary focus of the study.

Marshall RP, Webb S, Bellingan GJ, et al: Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome. Am J Respir Crit Care Med 2002;166:646-650.

This large study documented the association between the angiotensin-converting enzyme genotype and the risk and severity of ARDS. It also illustrated the potential risk of choosing different comparison populations.

Read RC, Cannings C, Naylor SC, et al: Variations within genes encoding interleukin-1 and the interleukin-1 receptor antagonist influence the severity of meningococcal disease. Ann Intern Med 2003;138:534-541.

This large study from a referral center demonstrated interactions among pathogen (serotype), host (age), two genetic factors, and outcome. A combination of excess inflammatory and anti-inflammatory polymorphisms was associated with the worst outcome.

Sorensen TI, Nielsen GG, Andersen PK, et al: Genetic and environmental influences on premature death in adult adoptees. N Engl J Med 1988;318:727-732.

This landmark study of adoptees demonstrated an increased risk of death from infection if one natural parent died of infection.

Stuber F, Petersen M, Bokelmann F, et al: A genomic polymorphism within the tumor necrosis factor locus influences plasma tumor necrosis factor-alpha concentrations and outcome of patients with severe sepsis. Crit Care Med 1996;24:381-384.

This seminal article outlines the genetic influence on sepsis and critical illness.

Waterer GW, Quasney MW, Cantor RM, et al: Septic shock and respiratory failure in community-acquired pneumonia have different TNF polymorphism associations. Am J Respir Crit Care Med 2001;163:1599-1604.

The authors document that different manifestations of severe community-acquired pneumonia are associated with different LTA genotypes.

Section III

CENTRAL NERVOUS SYSTEM

Chapter 46

BIOCHEMICAL, CELLULAR, AND MOLECULAR MECHANISMS OF NEURONAL DEATH AND SECONDARY BRAIN INJURY IN CRITICAL CARE

Robert S.B. Clark • Larry Jenkins • Yi-Chen Lai • Xiaopeng Zhang • Patrick M. Kochanek

KEY POINTS

1. Many of the biochemical, cellular, and molecular mechanisms that are important to the evolution of secondary damage after insults in neurointensive care, including cardiopulmonary arrest, stroke, traumatic brain injury, subarachnoid hemorrhage, status epilepticus, and hypoglycemia, share cerebral ischemia and/or energy failure as a critical initiator of damage.
2. Global cerebral ischemic insults, such as those that result from cardiopulmonary arrest, are generally brief in cases of patients who can be resuscitated successfully. The pathobiologic condition that results is characterized by delayed neuronal death in selectively vulnerable brain regions, and the biochemical and molecular cascades in these cases involve components of programmed cell death. However, classic apoptosis has not been observed.
3. Focal cerebral ischemic insults, such as those that result from stroke and subarachnoid hemorrhage, generally include an ischemic focus surrounded by peri-ischemic penumbral regions. The biochemical and molecular cascades involve necrosis and/or infarct expansion into the penumbra. Cell death in the penumbra can include phenotypes that span the continuum from necrosis to apoptosis.
4. In cases of traumatic brain injury, the biochemical and molecular mechanisms involved depend on the specific type of insult, ranging from focal contusion (in which local osmolar swelling and excitotoxicity predominate) to diffuse axonal injury (in which secondary axotomy from proteolysis predominates).
5. Excitotoxicity, resulting from increases in brain interstitial concentrations of a number of excitatory amino acids, is a common mediator of secondary injury across insults.
6. Programmed cell death, or apoptosis, involves several distinct pathways, including an extrinsic pathway triggered by external cell signals such as death receptor-ligand interaction; an intrinsic pathway triggered by signals from mitochondrial or endoplasmic reticulum; and a caspase-independent pathway involving mitochondrial dysfunction. However, delayed neuronal death in patients with critical central nervous system insults in the intensive care unit does not demonstrate classic apoptotic features but rather commonly exhibits a mixed phenotype.
7. Cerebral swelling can result from a variety of cellular mechanisms, including vasogenic edema, astrocyte swelling, increased tissue osmolar load, or vascular dysregulation with increased cerebral blood volume.
8. Inflammation appears to have a dichotomous role after cerebral ischemia or traumatic brain injury, including early exacerbation of damage by inflammatory mediators but secondary benefit through the link between inflammation and regeneration.

In this chapter, we provide a general discussion of the biochemical, cellular, and molecular mechanism of neuronal death and secondary brain injury that are germane to the central nervous system (CNS) insults that require neurointensive care, highlighting the important shared mechanisms in these conditions. In the chapter that follows, Dr. Kofke builds upon the biochemical and molecular mechanisms to address general pathophysiologic principles in neurointensive care, focusing on intracranial dynamics and the cerebral circulation. Finally, the chapters that follow address other important facets of neurointensive care, such as monitoring and coma, along with the specific pathophysiology and treatment of the key disease processes central to neurointensive care in both adults and children. This includes traumatic brain injury (TBI), cardiopulmonary arrest, stroke, subarachnoid hemorrhage (SAH), and seizures, among other insults.

A thumbnail sketch of the most important mechanisms of secondary injury involved in the brain after a traumatic or ischemic insult is provided in Figure 46-1. Central to all brain insults relevant to neurointensive care is the occurrence of cerebral ischemia and/or cerebral energy failure. Indeed, for cardiopulmonary arrest and stroke, global or focal brain

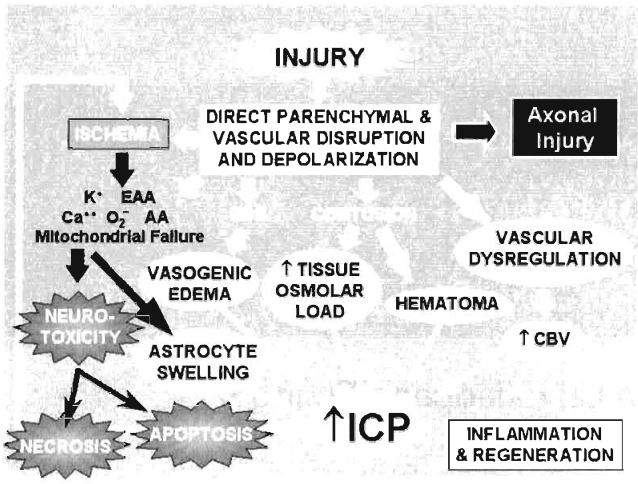

FIGURE 46–1. Categories of biochemical, cellular, and molecular mechanisms proposed to be involved in the evolution of secondary damage after ischemic or traumatic brain injury. Three major categories for these secondary mechanisms include (1) ischemia, excitotoxicity, energy failure, and cell death cascades; (2) cerebral swelling; and (3) axonal injury. A fourth category, inflammation and regeneration, contributes to each of these cascades.

ischemia, respectively, energy failure defines the insult. In cases of TBI, direct parenchymal or vascular disruption or vasospasm often leads to cerebral ischemia, although tissue deformation such as axonal and vascular stretching and shearing along with hemorrhage and dendritic injury also are involved. In cases of SAH, hemorrhage is often followed by delayed vasospasm, with subsequent secondary cerebral ischemia. Finally, seizures and hypoglycemia can lead to neuronal death and represent situations in which relative ischemia is produced, either from enhanced metabolic demands that are greater than supply or from reduced substrate delivery, respectively. Energy failure ensues, and if the insult is sufficient in duration, cellular injury or death can occur. Clearly, ischemia and energy failure are key culprits in producing the pathophysiology of neurointensive care insults.

The principal consequence of ischemic injury and/or energy failure is neuronal death. The two principal forms of ischemia in neurointensive care are global and focal, as seen in cases of cardiopulmonary arrest and stroke, respectively.

GLOBAL CEREBRAL ISCHEMIA

In patients with global cerebral ischemia, insults are dense and often square-wave in nature.[1] The classic example of a global cerebral ischemic insult in neurointensive care is ventricular fibrillation cardiopulmonary arrest (see Chapter 50). Using conventional approaches, patients can be successfully resuscitated from these insults only if they are brief in nature; that is, circulation must be restored in approximately 5 to 12 minutes, although the maximal duration compatible with intact neurologic outcome can depend on a variety of factors, such as temperature. In cases of complete global cerebral ischemia, adenosine triphosphate (ATP) and phosphocreatine levels in brain are depleted in less than 2 minutes.[1-3] Membrane failure ensues, with loss of ion homeostasis that includes cellular release of K^+ and uptake of Ca^{++}, Na^+, and Cl^-.[2,3] Upon reperfusion, a complex sequence of events is set into motion that depends on the duration of the insult. Disturbances in lipid metabolism such as free fatty acid release and DNA damage result, along with a series of deleterious cascades including oxidative and nitrosative stress, excitotoxicity, poly-ADP-ribose polymerase (PARP) activation, mitochondrial and endoplasmic reticulum (ER) dysfunction, and a host of cell-signaling abnormalities. A number of endogenous neuroprotectant responses are also initiated. The specific biochemical, cellular, and molecular events are discussed later. The aforementioned increases in intracellular calcium level are believed to play a critical role in initiating many of these events. In situations in which there is potential salvage of the patient, such as with threshold insults, reperfusion results in transient hyperemia (minutes) followed by delayed hypoperfusion (hours).[1,4,5] The pattern of neuronal damage that is seen after global cerebral ischemia is classically termed *selective vulnerability*. This is often delayed and primarily neuronal in nature, and it is believed to result from complex biologic cascades involving some features of programmed cell death (discussed later).

A number of brain regions are specifically vulnerable to ischemia, including the CA1 region of the hippocampus, cortical layers 3, 5, and 6, portions of the amygdaloid nucleus, and cerebellar Purkinje cells, among others.[2,3,5] Global ischemic insults from cardiopulmonary arrest from which there is some potential for recovery are generally believed to be devoid of important increases in intracranial pressure, since, based on studies in animal models, it has been shown that the threshold for producing poor outcome in patients with global ischemic insults is less than that needed to generate clinically significant intracranial hypertension.[6] Thus, brain edema and vascular injury are not believed to represent important therapeutic targets after global cerebral ischemia. Two relevant but atypical global insults in neurointensive care are asphyxial cardiopulmonary arrest (particularly important in children and discussed in Chapter 59), and near-hanging episodes. In the latter, obstruction of cerebral venous drainage during the asphyxial insult compounds the ischemic insult.

FOCAL CEREBRAL ISCHEMIA

Focal ischemic insults in neurointensive care are produced by thrombotic or embolic events and generally produce a dense ischemic focus that is surrounded by a peri-ischemic penumbral region with intermediate cerebral blood flow (CBF) values.[2] The ischemic focus is generally believed to be unsalvageable unless reperfused almost immediately. In contrast, the ischemic penumbra is a region with some collateral flow and represents a therapeutic target for reperfusion with thrombolytics and/or pharmacological therapy. In cases of focal cerebral ischemia, a hierarchy of CBF thresholds has been demonstrated in experimental studies, with inhibition of protein synthesis being the most sensitive to CBF reductions, followed by loss of electrical activity (evoked potentials and electroencephalogram), and eventually membrane failure.[7,8] Unlike the selective vulnerability seen in global ischemic insults, focal cerebral ischemia produces pan-necrosis of the vasculature and astrocytes, resulting in infarction. However, cell death in the penumbra can demonstrate necrotic, apoptotic, and mixed phenotypes. Again, however, classic apoptosis is not seen. Astrocyte swelling and blood-brain barrier injury, with focal cerebral edema, can play important roles. In the penumbra, spreading depression waves resulting in depolarization can enhance excitotoxic damage with expansion of the lesion core. Reperfusion can occur spontaneously or

with the administration of thrombolytics and can produce a microcosm of the aforementioned oxidative and nitrosative stress, mitochondrial and ER damage, and cell signaling abnormalities seen in global cerebral ischemia. In patients with focal cerebral ischemia, with large infarcts, brain swelling can be substantial enough that secondary ischemia can result from intracranial hypertension. Dr. Kofke discusses these concepts in greater detail in Chapter 47. Focal cerebral ischemia from delayed vasospasm is also the most common critical complication of SAH and is discussed in Chapter 52.

TRAUMATIC BRAIN INJURY

In cases of severe TBI, the biochemical and molecular mechanisms involved depend on the specific type of injury. In cases of focal contusion, direct disruption of parenchyma with local necrosis and hemorrhage results in superimposed vascular disruption, blood-brain barrier permeability, and local ischemia. This sets the stage for excitotoxicity and necrotizing cascades in the contusion penumbra, including oxidative and nitrosative stress, and calpain-mediated proteolysis, among other mechanisms.[9,10] Local axonal injury is also seen in patients with contusions. Focal contusions are commonly complicated by marked local swelling and often by intracranial hypertension with the potential for secondary focal or global ischemic insults or herniation syndromes. In contrast, in diffuse injury, a constellation of diffuse axonal and vascular disruption can be seen with characteristic findings of petechial hemorrhages in the white matter.[11] This insult can be devastating even in the absence of intracranial hypertension.[12] The biochemical and molecular events involved in axonal injury are discussed later. In cases of severe TBI, combined insults that include both multiple contusions and diffuse injury are also common. Finally, in addition to secondary ischemia from refractory intracranial hypertension, secondary extracerebral insults such as hypotension and hypoxemia can also negatively affect outcome and, importantly, complicate the biochemical and molecular response to severe TBI, markedly enhancing delayed neuronal death in brain regions that might otherwise have recovered.[13,14]

KEY BIOCHEMICAL AND MOLECULAR MECHANISMS OF NEURONAL SECONDARY DAMAGE

A number of pathologic cascades are shared by these important insults in neurointensive care, including excitotoxicity, programmed cell death, axonal injury, and inflammation, along with a spectrum of endogenous neuroprotectant responses.

EXCITOTOXICITY

Excitotoxicity describes the process by which glutamate and other excitatory amino acids cause neuronal damage. Lucas and Newhouse[15] first described the toxicity of glutamate. Olney[16] subsequently reported that intraperitoneal administration of glutamate produces brain injury in experimental animals. Although glutamate is the most abundant neurotransmitter in the brain, exposure to toxic levels produces neuronal death.[17] Glutamate exposure produces neuronal injury in two phases. Minutes after exposure, sodium-dependent neuronal swelling occurs.[18] This is followed by delayed, calcium-dependent degeneration. These effects are mediated through both ionophore-linked receptors, labeled according to specific agonists (*N*-methyl-D-aspartate [NMDA], kainite, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA]), and receptors linked to second messenger systems, called metabotropic receptors. Activation of these receptors leads to calcium influx through receptor-gated or voltage-gated channels, or through the release of intracellular calcium stores. Increased intracellular calcium concentration is the trigger for a number of processes that can lead to cellular injury or death (Fig. 46-2). One mechanism involves activation of neuronal nitric oxide (NO) synthase, leading to NO production, peroxynitrite formation, and resultant DNA damage. PARP is an enzyme operative in DNA repair, and in the face of DNA damage, PARP activation leads to ATP depletion, metabolic failure, and cell death.[19-21] This may be important, since PARP knockout mice exhibit improved outcome versus controls after experimental stroke or TBI.[20,22]

There is considerable evidence in experimental laboratory models supporting an important contribution of excitotoxicity to the evolution of secondary damage in cases of global and focal cerebral ischemia, severe TBI, SAH, and status epilepticus.[23-30] Evidence supporting an important role for excitotoxicity in humans has similarly been provided in cases of severe TBI, stroke, and SAH. Persson and Hillered[31] reported increases in brain interstitial levels of glutamate in a patient with SAH as early as 1992. Palmer and associates[32] first demonstrated increased concentrations of excitatory amino acids in ventricular cerebrospinal fluid (CSF) from adult patients with TBI. Glutamate concentrations were about fivefold greater than in control patients (up to 7 μM)—levels sufficient to cause neuronal death in cell culture.[33] Bullock and associates[34] characterized patterns of glutamate release by measuring excitatory amino acids by microdialysis in patients after TBI. Patients with a normal head computed tomography scan and no secondary ischemic events had interstitial concentrations of glutamate that were increased early in their course, then returned to normal. In contrast, patients with a progressively rising level of glutamate died. Similarly, in cases of human stroke, Bullock and associates[35] reported massive increases in the excitatory amino acids glutamate and aspartate in a patient who required decompressive craniectomy to prevent brainstem herniation.

Despite these and many other clinical reports, clinical trials with anti-excitotoxic therapies have been unsuccessful in patients with either stroke or TBI. This may be due to problems with patient selection, side effects of the anti-excitotoxic agents that were tested, and the likelihood that treatment was initiated too late.[36] Inhibition of plasticity by anti-excitotoxic therapies may also limit their efficacy, especially at the interface between the acute and subacute periods after injury.[37]

APOPTOSIS/PROGRAMMED CELL DEATH CASCADES

It is now increasingly clear from experimental models and human data that cells dying after global or focal cerebral ischemia or TBI can be categorized on a morphologic continuum ranging from necrosis to apoptosis.[38,39] Apoptosis is a morphologic description of cell death defined by cell shrinkage and nuclear condensation, internucleosomal DNA fragmentation, and the formation of apoptotic bodies.[40] In contrast, cells dying of necrosis display cellular and nuclear swelling with dissolution of membranes. Apoptosis requires

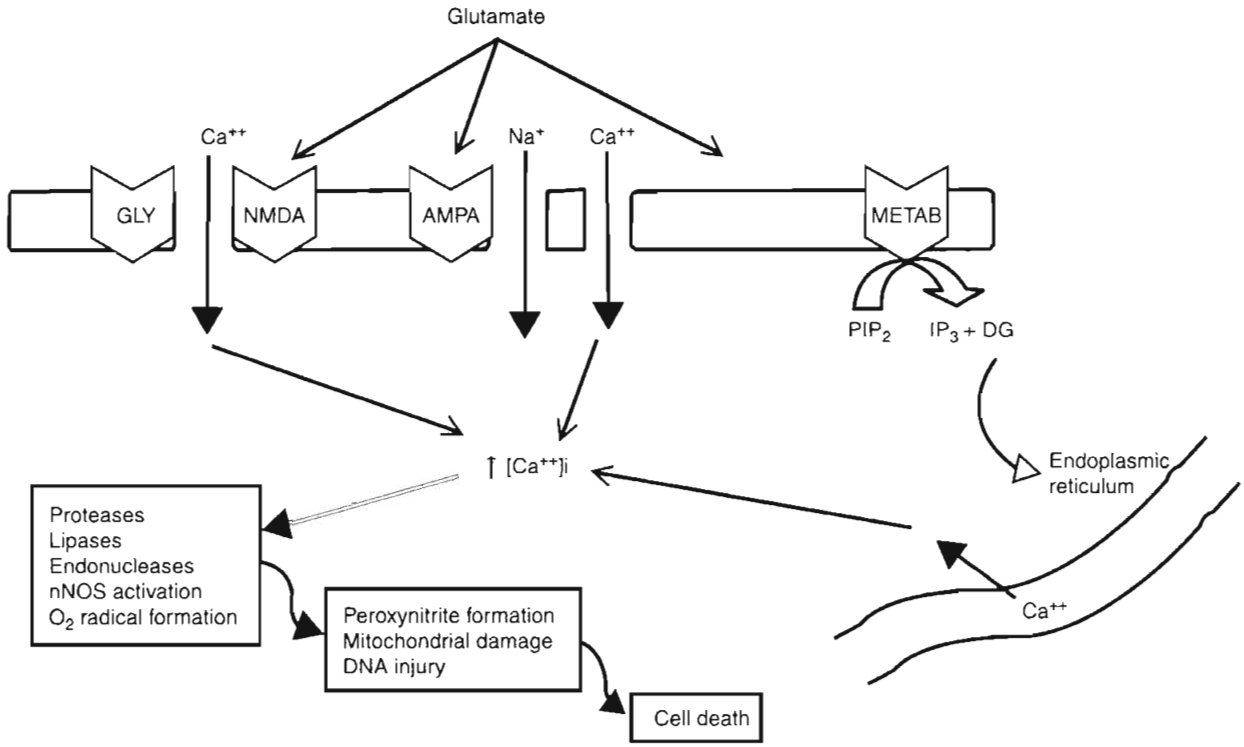

FIGURE 46–2. Mechanisms involved in excitotoxicity. Glutamate causes an increase in intracellular calcium concentration through stimulation of (1) the NMDA receptor with opening of the receptor-linked calcium ionophore, (2) the AMPA receptor with opening of the voltage-gated calcium channels, and (3) the metabotropic receptor, with the release of intracellular calcium stores via the second messengers inositol triphosphate and diacylglycerol. Increased intracellular calcium concentration leads to activation of proteases, lipases, and endonucleases, along with neuronal NOS (nNOS) stimulation and production of oxygen radicals. This results in peroxynitrite formation, mitochondrial damage, and DNA injury with subsequent cellular injury and death. AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; DG, diacylglycerol; GLY, glycine co-agonist site; IP_3, inositol triphosphate; METAB, glutamate metabotropic receptor; NMDA, *N*-methyl-D-aspartate receptor; PIP_2, phosphoinositide.

a cascade of intracellular events for completion of cell death; thus, *programmed cell death* is the currently accepted term for the process of cell death that leads to apoptosis.[41] In diseases with complex and multiple mechanisms, such as stroke and TBI, it is typically difficult to distinguish clinical apoptotic from necrotic cell death as classically defined.[42] Some cells may display DNA fragmentation and activation of proteases involved in programmed cell death, despite having nuclear and cellular swelling. Dying cells with mixed phenotypes are very common and may represent particularly difficult therapeutic targets.

Biochemical Pathways in Delayed Neuronal Death

Programmed cell death is an evolutionarily conserved process required for selective cell elimination during development, and it occurs in all tissues, including brain. Execution of programmed cell death requires novel gene expression and protein synthesis.[43-45] Programmed cell death is an intricate and critical mechanism for balancing cell proliferation, remodeling of tissues during development, and maintenance of tissues with a high rate of cell turnover. Programmed cell death can be thought of as "molecular débridement," delicately eliminating unwanted cells with minimal disturbance of neighboring cells. Programmed cell death is cybernetic and may occur via multiple pathways that can be independent (Fig. 46-3); however, cross-talk between these pathways also may occur.[46] At present, neuronal programmed cell death can be segregated into two pathways, one involving the activation of a family of cysteine proteases termed *caspases*, and one that is caspase independent.[47]

Caspase family proteases include 14 currently identified members that are synthesized as pro-enzymes,[48] which for the most part are proteolytically activated.[49] Initiator caspases, including caspase-8, -9, and -10, are activated by autocleavage and aggregation. Executioner caspases, including caspase-3, -6, and -7, are cleaved and activated by initiator caspases. The proteolytic cleavage of caspase substrates produces the phenotypic changes characteristic of programmed cell death, including cytoskeletal disintegration, DNA fragmentation, and disruption of cellular and DNA repair processes (Fig. 46-4). Cytoskeletal caspase targets include spectrin and nuclear lamin[50]; in addition, caspase-3 activates the enzyme gelsolin, which cleaves actin.[51] Active caspase-3 can also cleave the inhibitor of caspase-dependent deoxyribonuclease, permitting caspase-dependent deoxyribonuclease to digest DNA into small oligonucleosomal fragments.[52] These small DNA fragments (multiples of approximately 180 base pairs) can be seen on a DNA gel as a ladder and are a hallmark of caspase-dependent programmed cell death. Caspase-3 also inhibits DNA repair by proteolytically inactivating many DNA repair proteins, including PARP.[53-55] This combination of features—silencing of the genome and incapacitation of DNA repair processes, and destruction of key cytoskeletal components, all with surgical-like precision and ultimately leading to cell death—illustrates why programmed cell death has been referred to as "cell suicide."

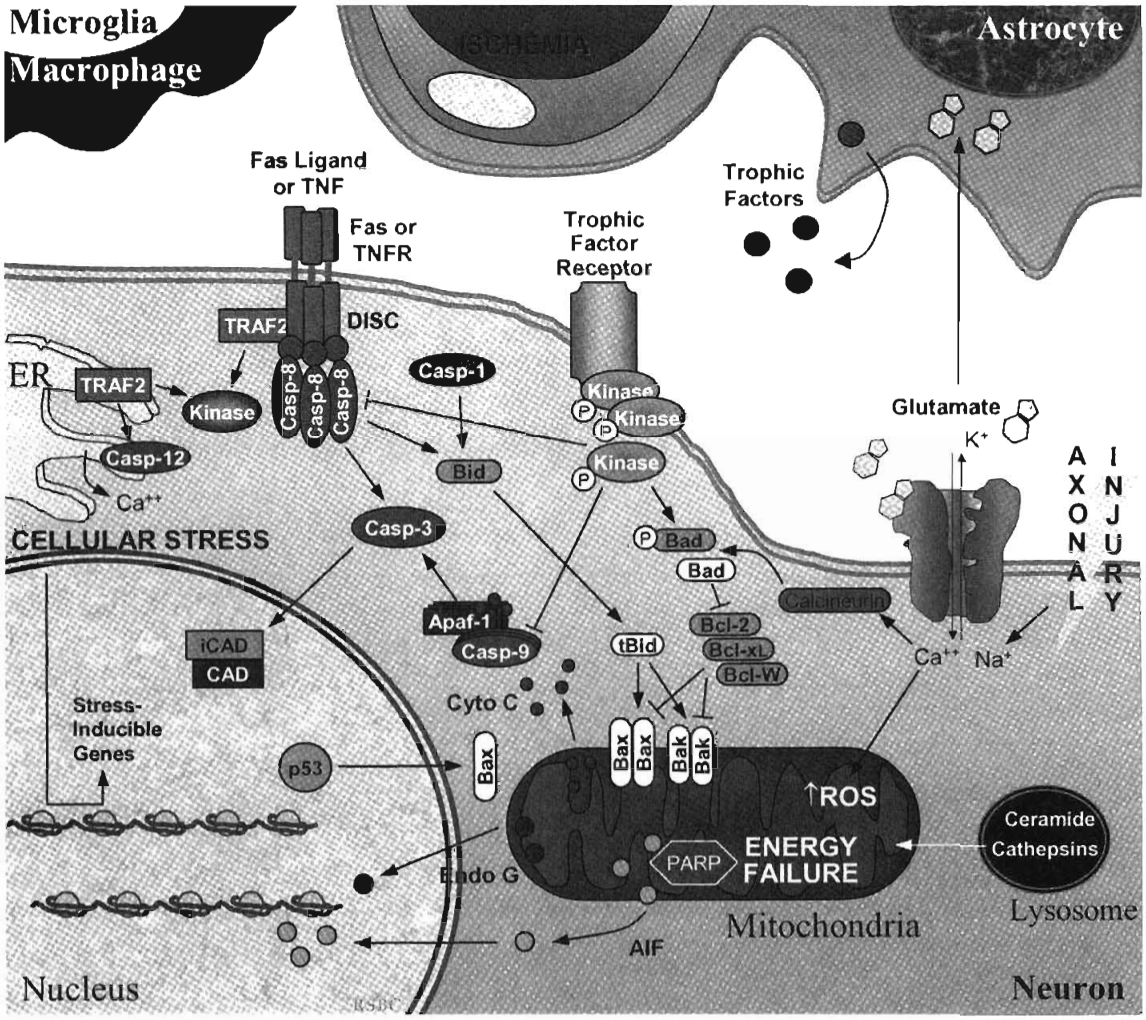

FIGURE 46–3. A simplified schematic representation of the initiation and regulation of neuronal programmed cell death after brain injury. Pathologic mechanisms triggering programmed cell death after brain injury include ischemia, oxidative stress, energy failure, excitotoxicity (primarily excess glutamate), axonal injury, trophic factor withdrawal, ER stress, and death receptor-ligand binding (e.g., TNF, Fas). Regulation of programmed cell death occurs via multiple pathways, including kinase-dependent intracellular signaling pathways and Bcl-2 family proteins. AIF, apoptosis inducing factor; Apaf-1, apoptotic protease activating factor-1; Bcl, B-cell lymphoma; CAD, caspase-activated deoxyribonuclease; casp, caspase; cyto c, cytochrome c; DISC, death-inducing signaling complex; Endo G, endonuclease G; ER, endoplasmic reticulum; iCAD, inhibitor of CAD; ROS, reactive oxygen species; tBid, truncated Bid; TNF, tumor necrosis factor; TNFR, TNF receptor; TRAF2, TNF receptor associated factor.

Extrinsic Pathways of Programmed Cell Death

Programmed cell death can be initiated by extrinsic or intrinsic signals. Extrinsic signals include cell surface death receptor-ligand interactions and cell signaling pathways. The most prominent cell death receptor family is the tumor necrosis factor (TNF) receptor superfamily, which includes TNF-α and Fas.[56] The coupling of cell surface TNF or Fas receptors with extracellular TNF-α or Fas ligand induces trimerization of the receptors that leads to the formation of submembrane complexes with intracellular death domain-signaling molecules. This death-inducing signaling complex then activates caspase-8[57] or -10.[58] Caspase-3 is then cleaved and activated, perpetuating the cascade. The extrinsic pathway can also be regulated by multiple intracellular signal transduction pathways that are initiated by G-protein coupled cell surface receptors, which can be either activated by neurotransmitters (e.g., cyclic nucleotides) or inactivated by interruption of trophic factors (e.g., nerve growth factor) after injury.[59] Perturbations in neurotransmitters and trophic factors controlling these pathways occur after ischemia and TBI. Multiple interrelated pro-death or pro-survival kinase pathways have been identified, including those involving mitogen-activated protein kinases, and protein kinase B and protein kinase C.[60,61]

Intrinsic Pathways of Programmed Cell Death

The intrinsic programmed cell death pathway is triggered by stress on cellular organelles, notably mitochondria and ER. Mitochondrial stress can lead to caspase-dependent programmed cell death via mitochondrial release of cytochrome C induced upon mitochondrial membrane depolarization. Egress of cytochrome C into the cytosol enables interaction with apoptotic protease activating factor-1 (Apaf-1), dATP, and pro-caspase-9 to form a complex termed an *apoptosome*. Apaf-1 activates caspase-9 and subsequently caspase-3.[62] Several mitochondrial proteins are capable of inducing programmed cell death without direct activation of the caspase cascade, thus exemplifying pathways that are caspase-independent. Apoptosis-inducing factor (AIF) within the mitochondria serves as an antioxidant[63]; however, upon

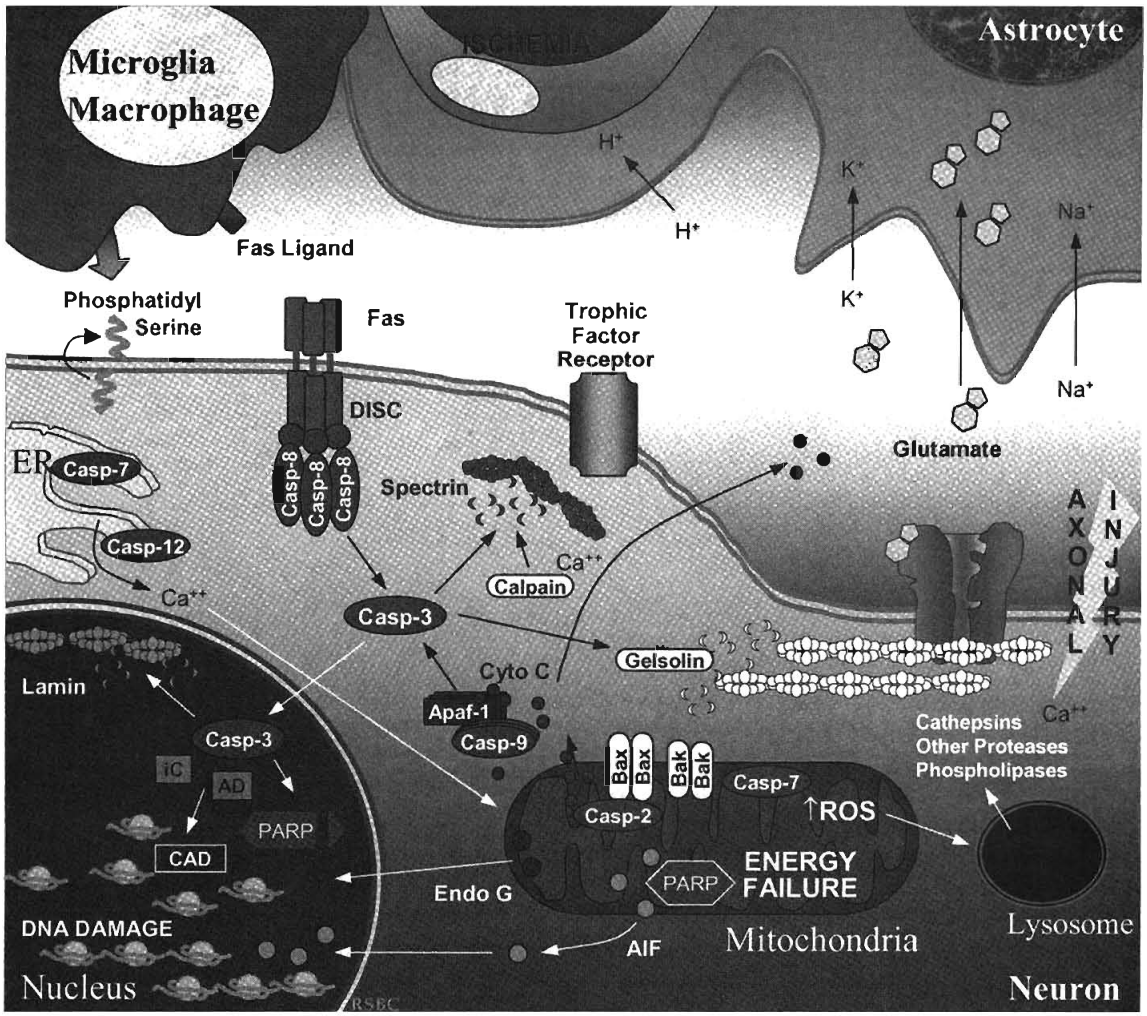

FIGURE 46–4. A simplified schematic representation of the execution of neuronal programmed cell death after brain injury. Execution of programmed cell death involves the caspase cascade and/or release of apoptogenic factors from organelles such as mitochondria. Ultimately, DNA fragmentation, cytoskeletal disintegration, and externalization of membrane phosphatidyl serine occur, signaling macrophages and microglia to engulf cellular debris. AIF, apoptosis inducing factor; Apaf-1, apoptotic protease activating factor-1; Bcl, B-cell lymphoma, CAD, caspase-activated deoxyribonuclease; casp, caspase; cyto c, cytochrome c; DISC, death-inducing signaling complex; Endo G, endonuclease G; ER, endoplasmic reticulum; ICAD, inhibitor of CAD; ROS, reactive oxygen species.

mitochondrial membrane depolarization, it can translocate from the mitochondria to the nucleus, where it is sufficient to induce programmed cell death.[64] Translocation of AIF into the nuclei induces the formation of large-scale DNA fragmentation (>50 kilobase pairs), in contrast to cytochrome C-mediated, caspase-dependent programmed cell death, which leads to oligonucleosomal DNA fragmentation (180-1200 base pairs). AIF-mediated programmed cell death occurs in neurons under conditions of experimental TBI[65] and cerebral ischemia.[66] Other mitochondrial proteins related to programmed cell death include endonuclease G,[67] Htr2A/Omi,[68] and Smac/Diablo[69]; however, their roles in neuronal death after brain injury remain unexplored. Disruption of ER calcium homeostasis and/or accumulation of excess proteins can lead to ER stress, which in turn can trigger programmed cell death via activation of ER-localized caspase-12, an upstream initiator caspase. ER stress–related activation of caspase-12 has been detected in experimental models of cerebral ischemia[70] and TBI.[71]

Regulation of Programmed Cell Death by the Bcl-2 Protein Family

Both caspase-dependent and caspase-independent programmed cell death are regulated by the B-cell lymphoma-2 (Bcl-2) family of proteins. The Bcl-2 family contains both pro-death and pro-survival members.[72] Bcl-2 family proteins regulate changes in permeability of the mitochondrial outer membrane independent of permeability transition pore formation. Bcl-2 family proteins contain highly conserved Bcl-2 homology domains (BH 1-4) essential for homo- and hetero-complex formation.[73] Complexes formed between proteins containing BH-3 domains such as Bax, truncated Bid, and Bad can facilitate mitochondrial cytochrome C release.[74,75] The anti-apoptotic members Bcl-2, Bcl-xL, and Mcl-1L prevent the release of mitochondrial proteins by inhibiting the pore formation.[76] Bax expression is associated with neuronal cell death after cardiac arrest in dogs.[77] Transgenic mice overexpressing Bcl-2 are partially protected from the neuropathologic sequelae of TBI versus wild-type

mice.[78] Overexpression of Bcl-xL also inhibits neuronal cell death after focal cerebral ischemia.[79]

Programmed Cell Death in Human Brain Injury

Phenotypic descriptions of programmed cell death occurring after brain injury in humans date back to the 1940s.[80,81] However, biochemical evidence of programmed cell death after brain injury in humans has been reported only within the last decade and has now been reported after TBI,[82-84] stroke,[85] and epilepsy.[86] Brain tissue samples from TBI patients requiring decompressive craniectomy for the treatment of life-threatening intracranial hypertension were found to have evidence of DNA fragmentation by terminal deoxynucleotidyl transferase-mediated nick-end labeling (TUNEL) and cleavage of caspase-1 and -3, suggesting activation of the programmed cell death cascade.[82] Recently, the up-regulation of caspase-8 in human brain after TBI at both transcriptional and translational levels has been reported.[84] Caspase-8 was found predominantly in neurons and was associated with relative levels of the death receptor Fas, providing evidence of the extrinsic programmed cell death pathway within neurons. Increases in Fas and Fas ligand have also been reported in cerebrospinal fluid from TBI patients, with Fas levels correlating with intracranial pressure.[87,88] Activation of the intrinsic pathway also occurs after TBI. Alteration of Bcl-2 family proteins has been reported in human brain from adults and in CSF from infants and children after TBI.[82,83,89] In pediatric patients, lower concentrations of Bcl-2 were detected in patients who died than in those who survived, supporting a pro-survival role for Bcl-2.[83] After TBI in adults, the presence of pro-death Bcl-2 family protein Bax in patients in whom Bcl-2 was also detectable represented a more favorable outcome as compared with patients in whom Bax but not Bcl-2 was detectable.[90] In contrast to TBI patients, patients after stroke demonstrate reductions in soluble Bcl-2 and soluble Fas within CSF,[85] suggesting dysregulation of programmed cell death after stroke. In adolescents and young adults with refractory seizures, increases in Bcl-2 and Bcl-xL, as well as increases in expression and proteolysis of caspase-1 and -3, occur in resected temporal lobe.[86] These patients have had medically refractory seizures for several years, implying protracted as well as acute programmed cell death within the brain. Protracted programmed cell death after TBI also occurs. Cells with apoptotic morphologies and DNA damage detected by TUNEL have been reported in autopsy specimens from patients dying up to 12 months after injury,[91] perhaps implying that a relatively wide therapeutic window exists for the administration of treatments aimed at reducing programmed cell death.

Several notes of caution are in order. First, it is unclear what the quantitative contribution of programmed cell death is in clinical cases of cerebral ischemia or TBI.[92] It is likely that dying cells demonstrate some biochemical and phenotypic features of programmed cell death, but that the actual deathblow to the cell is not dependent on an active process.[92,93] In addition, even if programmed cell death mechanism plays a key role, it is not clear whether inhibiting neuronal death after injury is entirely beneficial, since programmed cell death is a vital mechanism for biologic systems to eliminate abnormal or aging cells. In other words, quiet elimination, via "cell suicide" of damaged or dysfunctional cells may lead to overall benefit of the patient, in essence "molecular débridement." Only clinical trials of novel therapies targeting programmed cell death will be able to determine whether this mechanism represents an important target in neurointensive care. Recent studies of the efficacy of mild hypothermia after experimental and clinical cardiopulmonary, however, suggest that the success of this intervention may be derived from its effects on programmed cell death.[94-96]

AXONAL INJURY

White matter damage is important in infarction that results from stroke but probably plays only a limited role in the pathology of reversible global cerebral ischemia. In contrast, axonal injury is of paramount importance in patients with TBI. This has been demonstrated both clinically[97-100] and in experimental models.[101-103] The extent and distribution of traumatic axonal injury depends on injury severity and category (focal versus diffuse).[104] The classic view that traumatic axonal injury occurs because of immediate physical shearing is represented primarily in cases of severe injury in which frank axonal tears occur.[97,98,105,106] However, recent experimental studies suggest that axonal damage predominantly occurs by a delayed process termed *secondary axotomy.*[102,107,108] Two hypothetical sequences have attempted to explain secondary axotomy, one attributing axolemmal permeability and calcium influx as the initiating event (Fig. 46-5), and the other a direct cytoskeletal abnormality impairing axoplasmic flow.[102,108,109] It has been posited that both forms of reactive axonal swelling take place but in different proportions depending on the severity of injury. Superimposed on these theories is the finding that hypoxic/ischemic insults can also produce axonal swelling. As a result, differing as well as unifying theories for axonal injuries in patients with brain injury have been proposed.[102,108-111] Common mechanistic features include focal ion flux, calcium dysregulation, and mitochondrial and cytoskeletal dysfunction.

Traumatic axonal injury contributes to the morbidity after TBI.[102,104-106] Until recently, the contributions of axonal injury to morbidity have remained speculative, since traumatic axonal injury has remained refractory to treatment even in the laboratory. However, recent studies in experimental TBI models have shown that hypothermia or cyclosporin-A can both reduce white matter damage.[112,113] These therapeutic advances should help determine more definitively the contributions of traumatic axonal injury to secondary damage. Recent application of magnetic resonance imaging (MRI) to the study of traumatic axonal injury[114,115] and axonal connectivity[116,117] may improve our understanding of both this injury mechanism and axonal regeneration.

CEREBRAL SWELLING

In addition to cascades of neuronal death and axonal damage, brain swelling is a hallmark finding in cases of focal cerebral ischemia, severe TBI, and severe global cerebral ischemia from prolonged cardiopulmonary arrest. Brain swelling often results in the development of intracranial hypertension. Cerebral swelling and accompanying intracranial hypertension contribute to secondary damage in two ways. Intracranial hypertension can compromise cerebral perfusion, leading to secondary ischemia. It can also produce the devastating consequences of brain deformation and vascular compression through herniation syndromes. Intracranial hypertension results from increases in intracranial volume

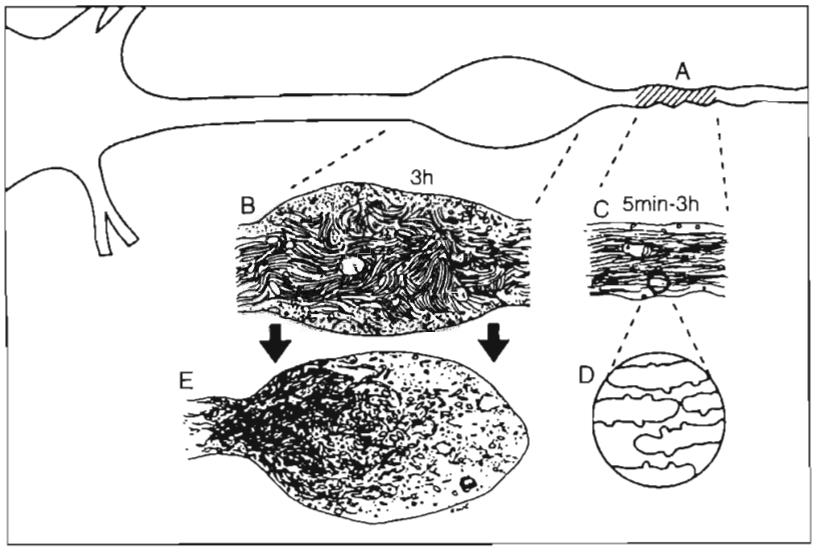

FIGURE 46–5. Reactive axonal swellings have been proposed to result from focal axolemmal disruption, ionic shifts, and neurofilamentous compaction at site *A* results in a reactive swelling at site *B* in an upstream region of the axon. At the site of ionic influx, neurofilamentous compaction and mitochondrial swelling is seen (*C*). Neurofilament compaction is associated with neurofilament sidearm loss (*D*). Obstructed axonal transport results in upstream axonal enlargement, neurofilament misalignment, organelle accumulation, and formation of the typical reactive axonal swelling (*E*).

from a variety of sources, which are outlined in Figure 46-1. In some cases of TBI or spontaneous intracranial hemorrhage, such as with epidural, subdural, or parenchymal hematoma formation, an extra-axial or parenchymal blood collection is the key culprit and can be addressed by surgical evacuation.[118] However, there are several important mechanisms that are more uniformly involved in the development of intracranial hypertension. These are related to either brain swelling from vasogenic edema, astrocyte swelling, and an increase in tissue osmolar load, or vascular dysregulation with swelling secondary to an increase in cerebral blood volume (CBV).

Most of the mechanistic work in this area has come from studies in the field of TBI. Recent data suggest that brain swelling after severe TBI results from edema rather than increased CBV. Marmarou and colleagues[119] measured both CBV and brain water in adults with TBI. Using a dye indicator technique (coupled to computed tomography) to measure CBV and MRI to quantify brain water, increases in brain water were commonly observed but were generally associated with reduced (not increased) CBV (see Fig. 46-6).

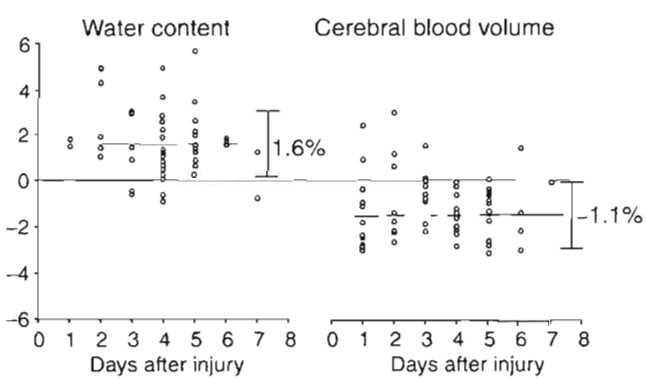

FIGURE 46–6. The percentage change in brain water content as assessed by magnetic resonance imaging and cerebral blood volume (CBV) as measured by computed tomography and indicatory dilution technique in 109 studies of adults with traumatic brain injury (TBI). Brain water is increased and CBV is reduced in adults with severe TBI. (From Marmarou A, Barzo P, Fatouros P, et al: Traumatic brain swelling in head injured patients: Brain edema or vascular engorgement? Acta Neurochir Suppl [Wien] 1997;70:68-70.)

Thus, edema rather than increased CBV appears to be the predominant contributor to cerebral swelling after TBI. Both cytotoxic and vasogenic edema may play important roles in cerebral swelling. However, the biochemical and molecular pathways involved in our traditional concept of cytotoxic and vasogenic edema are evolving. There appear to be four putative mechanisms for edema formation in the injured brain. First, vasogenic edema may form in the extracellular space as a result of disruption of the blood-brain barrier. Second, cellular swelling can be produced in two ways. Astrocyte swelling can occur as part of the homeostatic uptake of substances such as glutamate. Glutamate uptake is coupled to glucose utilization via a sodium/potassium ATPase, with sodium and water accumulation in astrocytes. Astrocyte swelling appears to be importantly linked to water movement through the aquaporin-4 channel found in the astrocyte foot processes near capillaries.[120-123] Recent studies have demonstrated reduced cerebral edema in mice genetically deficient in this channel.[124] Swelling of both neurons and other cells in the neuropil can also result from ischemia- or trauma-induced ionic pump failure. This can be important in the penumbral regions of focal cerebral ischemia and around cerebral contusions. Finally, osmolar swelling may also contribute to edema formation in the extracellular space, particularly in maturing cerebral contusions. Osmolar swelling, however, is actually dependent on an intact blood-brain barrier or an alternative solute barrier.

In both ischemic and traumatic brain injury, cellular swelling may be of greatest importance. Using a model of diffuse TBI in rats, Barzo and colleagues[125] applied diffusion-weighted MRI to localize the increase in brain water. A decrease in the apparent diffuse coefficient after injury suggested predominantly cellular swelling, rather than vasogenic edema, in the development of intracranial hypertension. Cellular swelling may be of even greater importance in the setting of TBI with a secondary hypoxemic-ischemic insult.[126] Katayama and colleagues[127] also suggested that the role of blood-brain barrier in the development of post-traumatic edema might have been overstated, even in the setting of cerebral contusion. One intriguing possibility is that as macromolecules are degraded within injured brain regions, the osmolar load in the contused tissue or infarcts increases. As the blood-brain barrier reconstitutes (or as other osmolar

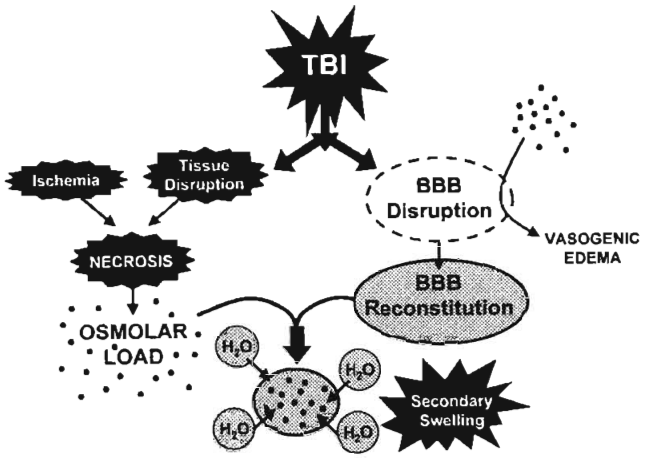

FIGURE 46–7. Schematic based on hypothesis of Katayama and colleagues[127] suggesting that as the osmolar load increases (breakdown of macromolecules in the region of contusion necrosis), a considerable driving force develops for the accumulation of water, resulting in the secondary swelling so often seen in and around cerebral contusions.

barriers are formed), a considerable osmolar driving force for the local accumulation of water develops, resulting in the marked swelling so often seen in and around cerebral contusions (Fig. 46-7). This has been supported by recent clinical studies of human cerebral contusion.[128]

In some cases, increases in CBV can be seen after TBI and contribute to intracranial hypertension. When an increase in CBV is seen, it may result from local increases in cerebral glycolysis, "hyperglycolysis" as described by Bergsneider and colleagues.[129] In regions with increases in glutamate levels, such as in contusions, increases in glycolysis are observed because astrocyte uptake of glutamate is coupled to glycolysis rather than oxidative metabolism. Recall that oxidative metabolism is generally depressed by approximately 50% in comatose victims of severe TBI in the intensive care unit.[130] Hyperglycolysis results in a marked local increase in cerebral glucose utilization with a coupled increase in CBF and CBV and resultant local brain swelling. A detailed discussion of this topic is beyond the scope of this chapter, but an expanded discussion of intracranial dynamics and vascular dysregulation in neurointensive care is provided in the next chapter.

As MRI and magnetic resonance-spectroscopic methods continue to develop and become applied to critically ill patients,[131] our knowledge of the mechanisms involved in cerebral swelling should greatly advance. It must be remembered that although neuronal and axonal injury are key downstream events in the evolution of damage after severe TBI, brain swelling and resultant intracranial hypertension is still the principal target for titration of therapy in the intensive care unit.

INFLAMMATION AND REGENERATION

There appear to be both acute detrimental and subacute/chronic beneficial aspects of inflammation in cerebral ischemia and TBI. Inflammatory mechanisms in the evolution of secondary injury and repair have the greatest support in stroke and TBI, although some support for a role of inflammation in the regulation of neuronal death has been suggested even in cases of transient global ischemic insults.[132-135] There is robust acute inflammation after stroke and TBI.[136,137] This has been shown in experimental models and in patients.[138-146] Nuclear factor-κB,[147] TNF-α,[85,148-151] interleukin (IL)-1β,[152,153] eicosanoids,[154] neutrophils,[139,155,156] and macrophages[157,158] contribute to both secondary damage and repair.

Markers of inflammation after TBI have been assessed in humans using two general strategies, (1) examination of inflammation in contused brain tissue or cerebral infarcts resected from patients with refractory intracranial hypertension, and (2) study of mediator levels in CSF. Consistent with a role for IL-1β in the evolution of tissue damage in cases of human TBI, Clark and associates[39] performed Western analysis of brain samples resected from adults with refractory intracranial hypertension secondary to severe contusion. Interleukin-1-converting enzyme (ICE) was activated, as evidenced by specific cleavage in patients with TBI. ICE activation is critical to the production of IL-1β. ICE activation was not detected in patients who died of non-CNS causes (Fig. 46-8). This supports the production of IL-1β, a pivotal proinflammatory mediator, in the traumatically injured brain in humans. Similar support for increases in a variety of inflammatory mediators exists in human stroke.[85,145,146,150,151,156]

Studies of CSF further support a role for inflammation in TBI. Marion and associates[142] demonstrated increases in IL-1β in CSF after severe TBI in adults. These increases were attenuated by the use of moderate therapeutic hypothermia. Similarly, there are increases of a number of cytokines in CSF after severe TBI and stroke, including IL-6 and IL-8.[85,144,150,151,159] Contusion and local tissue necrosis

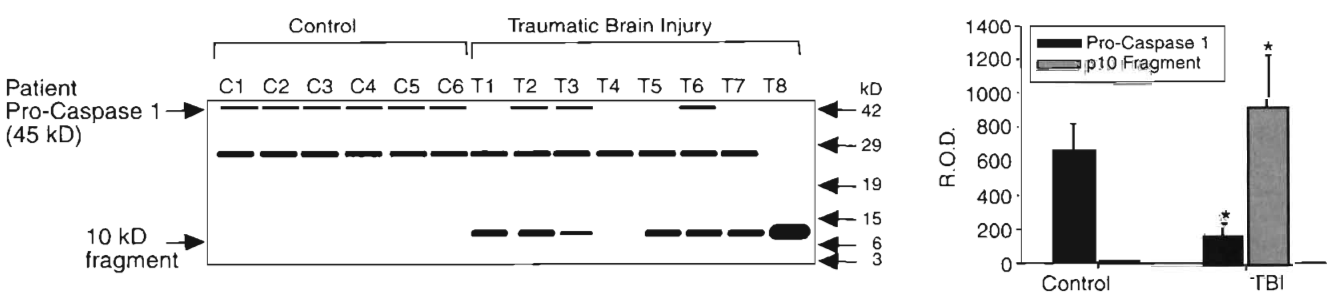

FIGURE 46–8. Evidence for activation of interleukin-1β converting enzyme (ICE) activation in cerebral contusions resected from adult patients with severe traumatic brain injury (TBI) and refractory intracranial hypertension. Western analysis demonstrating cleavage of the intact 45 kD pro-caspase-1 to the 10 kD fragment in each of eight victims of severe TBI but in none of six control brain samples from patients who died of non-central nervous system causes. (From Clark RS, Kochanek PM, Chen M, et al: Increases in Bcl-2 and cleavage of caspase-1 and caspase-3 in human brain after head injury. FASEB J 1999;13:813-821.)

appear to be important to trigger neutrophil influx with resultant secondary tissue damage.[139] Neutrophil influx is accompanied by increases in inducible nitric oxide synthase (iNOS) in brain[140,146] and is followed by macrophage infiltration, which peaks between 24 and 72 hours after injury.[160] Macrophage infiltration and the differentiation of endogenous microglia into resident macrophages may signal the link between inflammation and regeneration, with elaboration of a number of trophic factors (i.e., nerve growth factor [NGF], nitrosothiols, vascular endothelial growth factor).[153,159,161,162] Kossmann and associates[159] reported a link between IL-6 production and the production of neurotrophins, such as NGF in human head injury. Cultured astrocytes treated with either IL-6 or IL-8 in CSF from brain-injured adults produced NGF. Cytokine production after cerebral ischemia and TBI may be important to neuronal plasticity and repair, as discussed later.

Studies in models of TBI[149,163] suggest early detrimental effects of a number of inflammatory mediators but beneficial effects of inflammation on long-term outcome. Mice deficient in TNF-α exhibit improved functional outcome (versus wild-type) early after TBI. However, the long-term consequences of TNF-α deficiency on outcome are detrimental.[149] Similarly, despite a detrimental role for iNOS in the initial 72 hours after trauma,[165] iNOS-deficient mice demonstrated impaired long-term outcome versus controls.[164] iNOS is important in wound healing, and iNOS-derived nitrosylation of proteins may play a role.[162,165] Regeneration and plasticity play important roles in mediating beneficial long-term effects on recovery, and these responses are linked to inflammation. Analogs of these beneficial consequences of inflammation are anticipated in humans but remain to be demonstrated.

The contribution of the inflammatory response to cerebral ischemia and TBI remains to be determined. Although there are a few promising reports in models of the use of anti-inflammatory therapies in TBI and ischemia (targeting IL-1β, ICE, and TNF-α), it is unclear whether anti-inflammatory therapies will improve outcome after stroke or TBI in humans. Some of the initial trials have not been promising.[156] Finally, the consequences of anti-inflammatory therapies on the incidence of sepsis or secondary infectious complications must also be considered.[166] Similarly, the potential deleterious (or beneficial) CNS consequences of novel immunostimulatory therapies (such as GCSF or GMCSF) for the treatment of sepsis and multiple organ failure must also be carefully considered when these agents are used in patients with multisystem disease that includes CNS injury.[167]

ENDOGENOUS NEUROPROTECTANTS

Ischemia, excitotoxicity, or their combination, are a key facet of secondary injury. These mechanisms are linked to calcium overload, oxidative stress, and mitochondrial failure. There is, however, a coupled endogenous retaliatory response to these ischemic and excitotoxic insults. Two important components of this cascade are adenosine and heat shock protein 70 (HSP-70). Adenosine is an endogenous neuroprotectant produced in response to both ischemia and excitotoxicity. It antagonizes a number of events thought to mediate neuronal death.[168] Breakdown of ATP leads to formation of adenosine, a purine nucleoside that decreases neuronal metabolism and increases CBF, among other mechanisms. Adenosine binding to A1 receptors decreases metabolism by increasing K^+ and Cl^- and decreasing Ca^{++} conductances in the neuronal membrane. A1 receptors bind adenosine with high affinity and are located on neurons in brain regions that are susceptible to injury and are spatially associated with NMDA receptors.[169] Thus, locally released adenosine minimizes excitotoxicity. Binding of adenosine to lower affinity A2 receptors (on cerebrovascular smooth muscle) causes vasodilation, although binding to A2a receptors on neurons may be detrimental. Brain interstitial levels of adenosine are increased 50- to 100-fold early after experimental cerebral ischemia or TBI.[170-173]

In clinical studies, marked increases in brain interstitial levels of adenosine in adults with TBI were seen during episodes of jugular venous desaturation (secondary insults), supporting a role of adenosine as a "retaliatory" defense metabolite.[174] Surprisingly, increases in CSF levels of the commonly consumed adenosine receptor antagonist caffeine were associated with favorable outcome after severe TBI in humans, a finding that may be explained by up-regulation of A1 receptors by chronic caffeine exposure.[175,176] Another endogenous neuroprotectant that plays a role after cerebral ischemia, severe TBI, and SAH is HSP-70. HSP-70 optimizes protein folding as a molecular chaperone. It also inhibits proinflammatory signaling.[177] HSP-70 is induced as part of the preconditioning response in brain and has been shown to be increased in both CSF and brain tissue after severe TBI in humans.[178-180] Thus, the brain mounts an important endogenous defense response to TBI. Therapies designed to augment these pathways have not been examined adequately.

SUMMARY

Biochemical, cellular, and molecular mechanisms involved in the evolution of secondary brain injury after global and focal ischemia and TBI have been reviewed with particular attention to clinical studies relevant to neurointensive care. Our understanding of the biochemical, cellular, and molecular responses has progressed, particularly with the application of molecular biology methods to human materials. Future investigation should integrate these findings with bedside physiology and an improved assessment of outcome. Finally, novel imaging and diagnostic methods, particularly MRI, magnetic resonance spectroscopy, and positron emission tomography must be coupled with biochemical and molecular methods to clarify the mechanisms involved in secondary damage and the local effects of novel therapies, including the study of brain pharmacodynamics.

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Bullock R, Zauner A, Woodward JJ, et al: Factors affecting excitatory amino acid release following severe human head injury. J Neurosurg 1998;89:507-518.

A superb clinical report on excitotoxicity that used cerebral microdialysis to assess levels of glutamate in 80 consecutive severely head-injured patients. Four patterns of brain interstitial levels of excitatory amino acids were described, and increases in glutamate were as much as 50 times normal in 30% of the patients. This manuscript raises the important point that mechanisms such as excitotoxicity appear to vary greatly depending on the type of traumatic injury, time after injury, and presence of secondary insults such as hypoxemia or intracranial hypertension.

Clark RS, Kochanek PM, Chen M, et al: Increases in Bcl-2 and cleavage of caspase-1 and caspase-3 in human brain after head injury. FASEB J 1999; 13:813-821.

This is a bench-to-bedside study of a number of key molecular events in cases of secondary damage in human cerebral contusions including activation caspase-1 and caspase-3. These two processes are central to inflammation and programmed cell death. This was the first report of caspase activation in either ischemic or traumatic brain injury in humans.

Povlishock JT: Traumatically induced axonal injury: Pathogenesis and pathobiological implications. Brain Pathol 1992;2:1-12.

This is an outstanding review on the biochemical and molecular events that are involved in the evolution of axonal damage after severe traumatic brain injury. This article discusses the evidence supporting the now accepted concept of secondary axotomy and its consequences.

Siesjo BK: Cell damage in the brain: A speculative synthesis. J Cereb Blood Flow Metab 1981;1:155-185.

Highly quoted classic reference discussing a number of speculative biochemical mechanisms involved in the evolution of secondary damage after cerebral ischemia, epilepsy, and hypoglycemia. Despite being written before the molecular explosion, many of these hypotheses have shown merit as research in this area has progressed over the subsequent 25 years.

Siesjo BK, Katsura K, Zhao Q, et al: Mechanisms of secondary brain damage in global and focal ischemia: A speculative synthesis. J Neurotrauma 1995; 12:943-956.

This is an outstanding review article that contrasts the biochemical and molecular alterations seen in focal versus global cerebral ischemia. The discussion is based on studies done in experimental models but is germane to the clinical conditions of cardiopulmonary arrest and stroke.

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Experimental animal study that constituted the first description of the development of early postischemic hypoperfusion after complete global cerebral ischemia, a fundamental finding in cardiopulmonary arrest and resuscitation that has withstood the test of time.

Chapter 47
CRITICAL NEUROPATHOPHYSIOLOGY

W. Andrew Kofke

KEY POINTS

1. The contributors to intracranial hypertension are defined by the contents of the brain: brain tissue, cerebrospinal fluid, blood, and masses. Brain tissue becomes important in the presence of edema, cerebrospinal fluid in the presence of hydrocephalus, blood volume in the presence of vasodilating or vasoconstricting conditions, and masses when of an unacceptable size. In clinical practice, physiologic and pharmacologic manipulations have the most impact on blood volume.
2. There are two types of intracranial hypertension, categorized according to cerebral blood flow as hyperemic or oligemic. Abrupt noxious stimuli briefly increase intracranial pressure (ICP) in the setting of decreased intracranial compliance. Such situations are associated with hyperemia, strongly suggesting that brief hyperemic intracranial hypertension is not a dangerous situation. However, it is reasonable to be concerned about such hyperemia related to herniation risk. In contrast, oligemic intracranial hypertension is associated with compromised cerebral perfusion and is clearly deleterious.
3. One category of pressure waves has been identified as plateau waves, which are known to be associated with increased cerebral blood volume (CBV). CBV increases exponentially as perfusion pressure decreases to levels of 80 mm Hg and below. A small decrease in blood pressure produces exponential increases in CBV in a setting of abnormal intracranial compliance with the ICP at the elbow of the ICP-intracranial volume curve.
4. Positive end-expiratory pressure can increase ICP in two ways. The first is through impedance of venous return, increasing cerebral venous pressure and ICP. The second is through decreased blood pressure and reflex increase of CBV increasing ICP.
5. Intracranial pressure can also be influenced by antihypertensive drugs. In general, vasodilator drugs such as nitroprusside, nitroglycerin, and nifedipine can be expected to increase ICP. Conversely, nonvasodilator antihypertensive drugs, generally sympatholytic drugs such as trimethaphan or beta-adrenergic blocking drugs such as esmolol or labetalol, can be expected to have little or no effect on ICP.
6. Temperature management can be critical in neurointensive care. In animal models, hyperthermia has been shown to have deleterious effects on outcome after cerebral ischemia, head trauma, and seizure. Conversely, mild hypothermia (32-36°C) has been shown to be protective.
7. Cerebrovascular reserve is compromised in many intracranial pathologic processes. Normally, the brain compensates for decrements in supply of oxygen and substrates by vasodilating to maintain or increase flow. Clinical examples of attenuated cerebrovascular reserve include cerebral edema, hypoxemia, carotid artery stenosis, peri-infarct penumbra, and anemia. In each of these situations, although not easy to quantitate, it is clear that added situations of compromised O_2 supply to the brain will risk neuronal injury.
8. Hyperglycemia is clearly deleterious in the context of global cerebral ischemia. Clinical studies suggest a deleterious effect in head trauma and stroke. It seems most appropriate to maintain blood glucose levels as close to normal as possible and feasible.
9. Ample laboratory and clinical evidence supports the notion that endogenous and exogenously administered catecholamines can be deleterious with compromised cerebral perfusion.

Neural function is essential to human existence. Thus, loss of any neural element in the course of a critical illness represents a major loss to a given individual. Neurons or supporting elements can be lost in a small, virtually unnoticeable manner, or there can be widespread selective neuronal loss or tissue infarction. Based on the notion that neural function is the essence of acceptable survival from critical illness, it is crucial for critical care management to include considerations of neural viability and the impact and interactions of the primary diseases and therapeutics on the nervous system.

There are numerous clinical scenarios in which a critically ill patient may present with a primary neurologic illness. In a general sense, these scenarios often involve ischemia, trauma, or neuroexcitation. Each of these may include a period of decreased cerebral perfusion pressure (CPP), usually due to elevated intracranial pressure, eventually compromising cerebral blood flow (CBF) sufficiently to produce permanent neuronal loss, infarction, and possibly brain death. In this chapter, I review the physiologic factors and intracranial

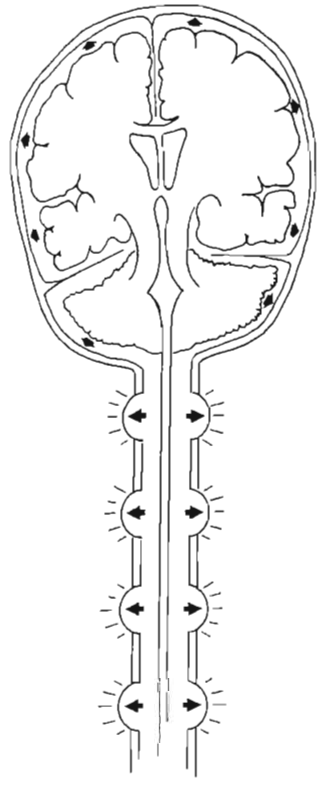


FIGURE 47–1. The brain, spinal cord, and blood are encased in the skull and vertebral canal, thus constituting a nearly incompressible system. System capacitance is thought to be provided via intervertebral spaces. (From Kofke W, et al: Neurologic intensive care. In Albin M [ed]: Textbook of Neuroanesthesia. New York, McGraw-Hill, 1997.)

pressure (ICP) considerations critical to contemporary neurointensive care.

ELEVATED INTRACRANIAL PRESSURE

PHYSIOLOGY

The brain, spinal cord, cerebrospinal fluid (CSF), and blood are encased in the protecting but noncompliant skull and vertebral canal, constituting a nearly incompressible system (Fig. 47-1). In a totally incompressible system, pressure would rise linearly with increased volume. However, there is capacitance in the system, thought to be provided by the intervertebral spaces. Once this capacitance is exhausted, the ICP increases dramatically with increased intracranial volume.

Based on the following relationship:

$$CBF = (MAP - ICP)/CVR,$$

the concern is raised mathematically that increasing ICP is associated with decrements in CBF. However, the effect of increasing ICP on CBF is not straightforward, as mean arterial pressure (MAP) may increase with ICP elevations,[1] and cerebral vascular resistance (CVR) adjusts with decreasing CPP (increasing cerebral vessel diameter) to maintain CBF until maximal vasodilatation occurs.[2,3] This results in an increase in cerebral blood volume (CBV). This is thought to occur at a CPP less than 50 mm Hg, although considerable individual heterogeneity in this value exists. Thus, increasing ICP initially is often associated with vasodilatation and/or increasing MAP to maintain CBF without a nutritive decrement.

Normal ICP is less than 10 mm Hg. ICP greater than 20 mm Hg is generally treated with ICP-reducing agents.[4] However, this is an epidemiologically derived action. Head trauma studies have indicated that patients with ICP greater than 20 mm Hg generally do poorly,[4] although simply elevating ICP to greater than 20 mm Hg (in experimental animals) is not necessarily associated with decrements in CBF or permanent sequelae, provided the above-noted compensatory mechanisms occur.[5]

Nonetheless, increasing ICP due to mass lesions or obstruction of CSF outflow can exhaust compensatory mechanisms with compromise of CBF. Initially, distal runoff of the cerebral circulation increases. As the process continues, the normally continuous (through systole and diastole) cerebral perfusion becomes discontinuous (systolic perfusion only) (Fig. 47-2).[6] Further compromise of CPP results in further oxygen extraction progressing to anaerobic metabolism, exacerbation of edema, and ultimately intracranial circulatory arrest.[6] Thus, when ICP increases, early recognition is important to determine whether a deleterious sequence of events is starting.

CONTRIBUTORS TO INTRACRANIAL HYPERTENSION

Brain. The brain normally occupies about 80% of the contents of the skull, but its volume can be increased by edema. There are two types of edema, cytotoxic and vasogenic, referring to swelling produced by cellular or vascular processes, respectively.[7] Any edema can increase ICP. It can be heterogeneously distributed such that pressure gradients occur, leading to a variety of herniation syndromes.

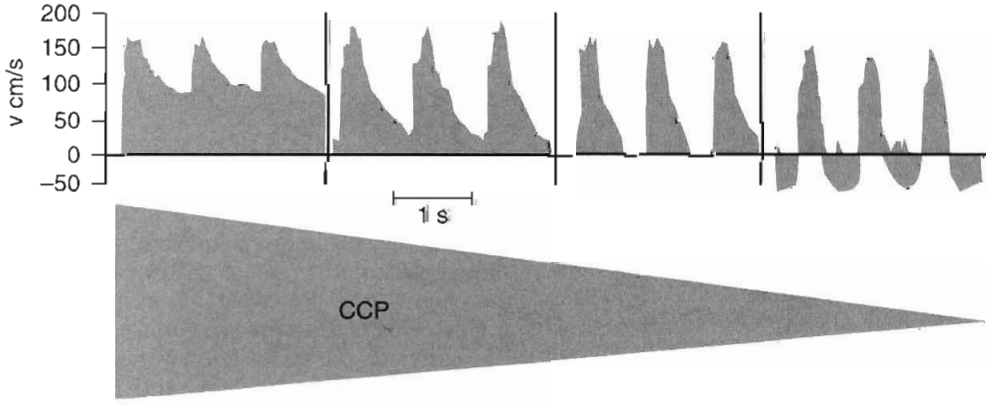


FIGURE 47–2. Progression of transcranial Doppler waveforms with decreasing cerebral perfusion pressure after head injury. Progression is apparent from a normal-appearing transcranial Doppler waveform to intracranial hypertension sufficient to induce intracerebral circulatory arrest. (From Hassler W, Steinmetz H, Gawlowski J: Transcranial Doppler ultrasonography in raised intracranial pressure and in intracranial circulatory arrest. J Neurosurg 1988;68:745.)

Cerebrospinal Fluid. CSF is generated in the choroid plexus and absorbed in the arachnoid villi. An equilibrium normally exists between production and absorption. Disruption of this equilibrium can lead to increased ICP with hydrocephalus, the condition wherein there is an excess of fluid in all or part of the CSF in the brain. Hydrocephalus is generally categorized as communicating or noncommunicating. In communicating hydrocephalus, the CSF circulation between the site of CSF production and absorption is intact. However, abnormally decreased absorption or increased production results in increased CSF accumulation. In noncommunicating hydrocephalus, the pathways are blocked such that CSF cannot circulate to the convexity of the brain to be absorbed. This results in accumulation of CSF in the ventricles, producing distension.[8]

Blood. CBV is an important contributor to variations in ICP, in part due to the wide variations in CBV that can occur with normal physiologic homeostasis and with the effects of drugs and disordered physiology. When CBV increases due to increased CBF, this can produce a dramatic increase in ICP, if intracranial compliance is abnormal. However, unlike ICP elevation due to increased CSF volume, edema, or a tumor, in which decreased CBF is expected, this variety of ICP increase is often produced by increased CBF, making the significance of the ICP elevation unclear. This is discussed later.

Another mechanism of increased CBV occurs with obstruction of venous outflow. This results in brain engorgement and CBV-mediated increased ICP, but without increased CBF.[9]

Masses. The fourth cause of increased ICP is pathologic masses. These can be in the form of hematoma or neoplastic tumors. In both cases, the faster the onset of the mass effect is, the more acute the rise in ICP. Evidently, there are compensatory mechanisms in intracranial compliance that can allow quite large slow-growing masses to arise in the brain without elevated ICP. On the other hand, similarly sized masses, arising acutely, are associated with symptomatic increases in ICP.

TYPES OF INTRACRANIAL HYPERTENSION

There are two types of intracranial hypertension, categorized according to CBF as hyperemic or oligemic (Fig. 47-3). In the normal state, increases in CBF are not associated with increased ICP, because capacitive mechanisms compensate for the CBV-mediated increased intracranial volume. However, in the situation of disturbed intracranial compliance, small increases in intracranial volume produce significant increases in ICP.[2,3]

This suggests an important issue: raised ICP has traditionally been considered to be a concern because it indicates that cerebral perfusion might be jeopardized. It is unclear whether it is appropriate to be concerned about the potential for ICP-induced intracranial oligemia when the cause of the high ICP is intracranial hyperemia with associated increased CBV. There have been no detailed examinations of this question, although there have been some studies that allow reasonable inferences about the significance of hyperemic intracranial hypertension.

For many years it has been known that abrupt noxious stimuli briefly increase ICP in the setting of decreased intracranial compliance. Recent studies have revealed that such situations are associated with hyperemia, strongly suggesting that brief hyperemic intracranial hypertension is not a dangerous situation.[10] However, it is reasonable to be concerned about such hyperemia for three reasons. First, elevated ICP due to hyperemia in one portion of the brain may increase ICP to compromise CBF in other areas of the brain in which CBF is marginal. Secondly, increased pressure in one area of the brain may produce gradients that might lead to a herniation syndrome. Thirdly, there is theoretical concern that inappropriate hyperemia predisposes the brain to worsened edema or hemorrhage as occurs with hyperperfusion syndromes. Thus, hyperemic intracranial hypertension has a theoretical potential to be deleterious, although this has yet to be demonstrated in a systematic fashion. For brief periods, as may occur during intubation or other limited exposure to noxious stimuli, it is suggested (but not proven) that it may not be problematic.[11] An example of this conundrum is illustrated in Figure 47-4.

In contrast, oligemic intracranial hypertension is associated with compromised cerebral perfusion and is clearly deleterious.[6] This is supported by the high mortality rate observed in head trauma patients in whom ICP rises due to brain edema with decrements in CBF.[6,12] Transcranial Doppler echography and CBF studies on these patients have demonstrated that CBF is low and perfusion is discontinuous

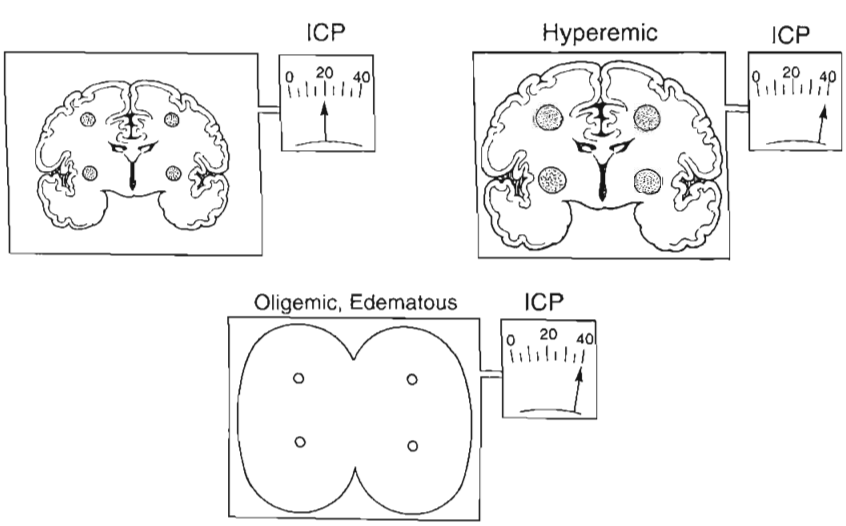


FIGURE 47–3. Two types of intracranial hypertension. From a baseline condition, ICP can increase in two ways. One is via an increase in cerebral blood volume associated with reflex vasodilation due to moderate blood pressure decreases. The second is via malignant brain edema or other expanding masses encroaching on the vascular bed to produce intracranial ischemia. The stippled circles in each coronal brain section represent the cerebral vasculature/blood volume. (From Kofke W, et al: Neurologic intensive care. In Albin M [ed]: Textbook of Neuroanesthesia. New York, McGraw-Hill, 1997.)

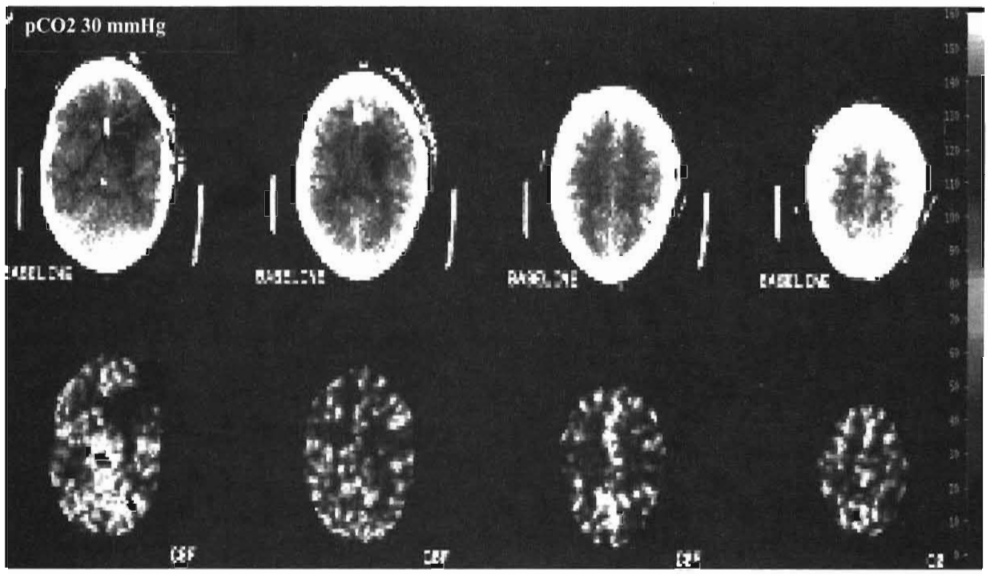


FIGURE 47–4. Computed tomography scans of a head-injury patient with an intracranial pressure (ICP) of 70 mm Hg and $Paco_2$ of 30 mm Hg but diffusely normal to hyperemic cerebral blood flows. (See color section in this text.) (Courtesy of Howard Yonas, University of Pittsburgh.)

during the cardiac cycle (see Fig. 47-2).[6,13] Moreover, jugular venous bulb data indicate that oxygen extraction is markedly increased, suggesting loss of reserve with occurrence of anaerobic metabolism.[13] In this setting, noxious stimuli can further increase the ICP, thus producing the situation of hyperemic, added to oligemic, intracranial hypertension. Presumably, in this setting, the hyperemic rise in ICP acts to further reduce regional CBF in compromised areas with brain edema and may contribute to vasogenic edema.

BLOOD PRESSURE EFFECTS ON INTRACRANIAL PRESSURE: PLATEAU WAVES

Lundberg, in a pioneering 1960 study,[13] monitored ICP in hundreds of patients, identifying characteristic pressure waves. One category of these waves has been identified as *plateau waves*, which are known to be associated with increased CBV (Fig. 47-5).[2] Such waves occur when the ICP abruptly increases to systemic blood pressure levels for about 15 to 30 minutes, occasionally accompanied by neurologic deterioration. Rosner[3] had synthesized the data and convincingly suggests that intracranial blood volume dysautoregulation is responsible for plateau waves. He induced mild head trauma in cats and subsequently intensively monitored the animals after the insult. With normal fluctuations in blood pressure, while in the normal range, he observed that mild blood pressure decrements to a mean of approximately 70 to 80 mm Hg preceded the development of plateau waves (Fig. 47-6). Cerebral blood volume in normally autoregulating brain tissue increases with decreasing blood pressure. However, the increase in CBV is nonlinear. There is an exponential increase in CBV as CPP decreases to levels of 80 mm Hg and below (Fig. 47-7).[3] A small decrease in blood pressure, although in the normotensive range, produces exponential increases in CBV in a setting of abnormal intracranial compliance with the ICP at the elbow of the ICP-intracranial volume curve. Thus, a small decrease in blood pressure introduces an exponential CBV change upon an exponential

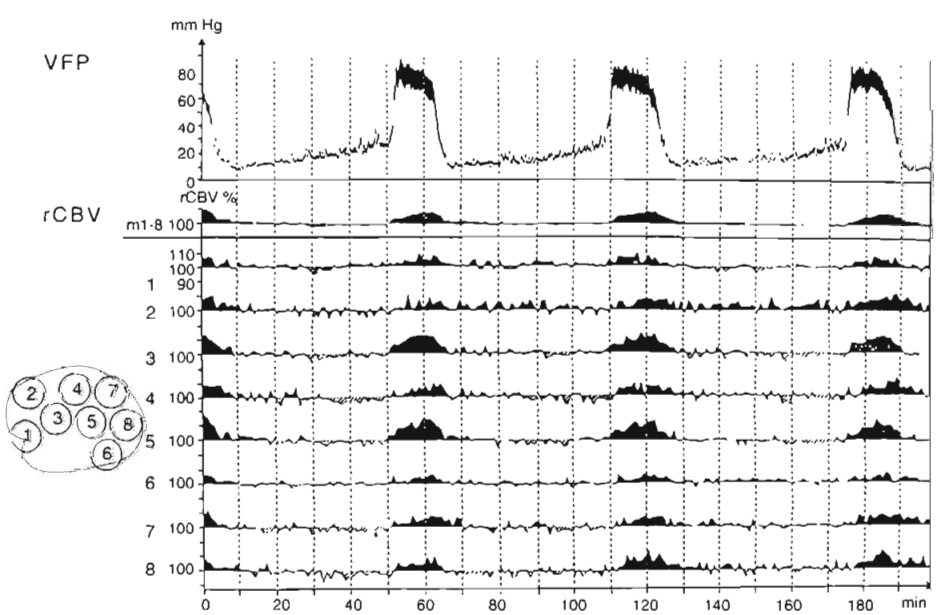


FIGURE 47–5. Plateau waves. Simultaneous recordings of regional cerebral blood volume (rCBV) and ventricular fluid pressure (VFP) during three consecutive plateau waves. The rCBV was measured in eight regions over the left hemisphere. The mean changes in the eight regions are shown in the uppermost curve of the rCBV diagram. Note that the rCBV and VFP curves show a very similar course during the three waves. (From Risberg J, Lundberg N, Ingvar DH: Regional cerebral blood volume during acute transient rises in the intracranial pressure (plateau waves). J Neurosurg 1969;31:303.)

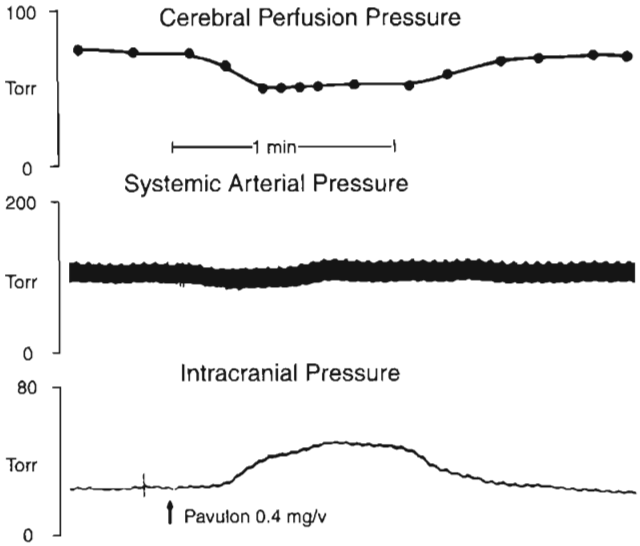


FIGURE 47–6. In an animal head trauma model, a trivial-appearing and transient decrease in systemic arterial blood pressure in the setting of borderline cerebral perfusion pressure precipitates sufficient cerebral vasodilatation to markedly increase the intracranial pressure. Restoration of cerebral perfusion pressure is associated with abolition of the plateau wave. (From Rosner MJ, Becker DP: Origin and evolution of plateau waves: Experimental observations and a theoretical model. J Neurosurg 1984;50:312.)

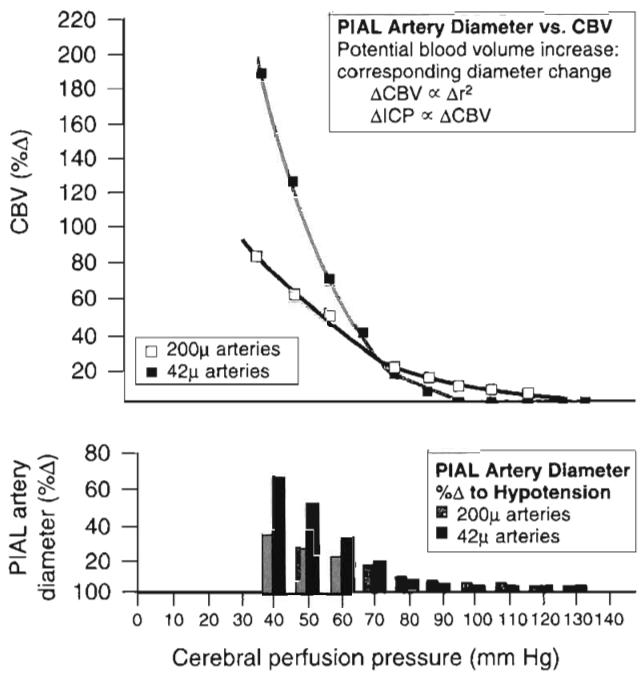


FIGURE 47–7. Cerebral vasodilatation occurs exponentially as cerebral perfusion pressure is reduced. (From Rosner MJ, Becker DP: The etiology of plateau waves: A theoretical model and experimental observations. In Ishii S, Nagai H, Brock M [eds]: Intracranial Pressure V. New York, Springer-Verlag, 1983, p 301.)

ICP relationship such that ICP will increase abruptly and to a significant extent.

Plateau waves spontaneously resolve with a hypertensive response or with hyperventilation that will act to oppose the increase in CBV. Clearly, to develop a plateau wave there must be a portion of the brain with normally reactive vasculature in the presence of other brain areas with a mass effect and raised ICP, a situation of *heterogeneous autoregulation.* In addition to preventing and treating plateau waves, data indicate that it is probably important to maintain MAP in the 80 to 100 mm Hg range in patients with high ICP.

Conversely, hypertension can also increase ICP, with animal models showing increased brain water with dopamine-induced increased blood pressure.[14] Typically, within the normal autoregulatory range, changes in blood pressure have no effect on ICP. However, with brain injury and associated vasoparalysis, blood pressure increases mechanically produce cerebral vasodilatation, increasing ICP (Fig. 47-8).[15]

It appears that both increasing and decreasing blood pressure can increase ICP, suggesting the presence of a CPP optimum for ICP, probably 80 to 100 mm Hg, although this has not been definitively determined experimentally (Figs. 47-9 and 47-10).

POSITIVE END-EXPIRATORY PRESSURE AND INTRACRANIAL HYPERTENSION

Positive end-expiratory pressure (PEEP) can increase ICP in two ways. The first is through impedance of venous return, increasing cerebral venous pressure and ICP. The second is through decreased blood pressure and reflex increase of CBV, increasing ICP (Fig. 47-11). The latter is likely the most

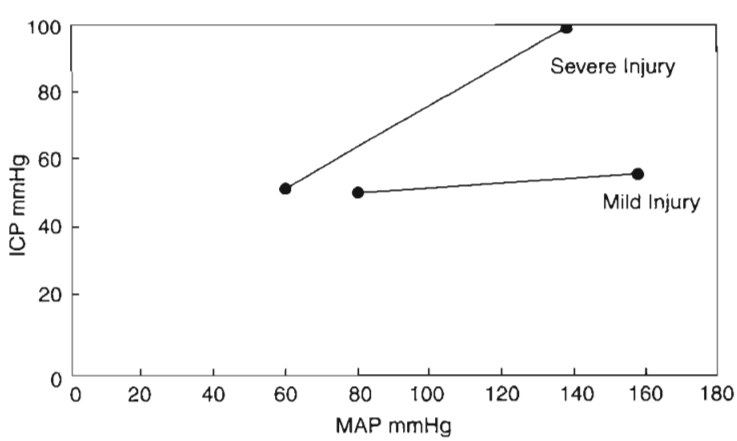


FIGURE 47–8. Blood pressure changes within the normal autoregulatory range have no effect on intracranial pressure (ICP). However, with brain injury, increases in mean arterial pressure (MAP) produce increases in ICP with this effect more pronounced with more severe injury. Presumably, this effect is due to distention of vasoparalyzed blood vessels with a consequent increase in cerebral blood volume. (From Kofke W, et al: Neurologic intensive care. In Albin M [ed]: Textbook of Neuroanesthesia. New York, McGraw-Hill, 1997.)

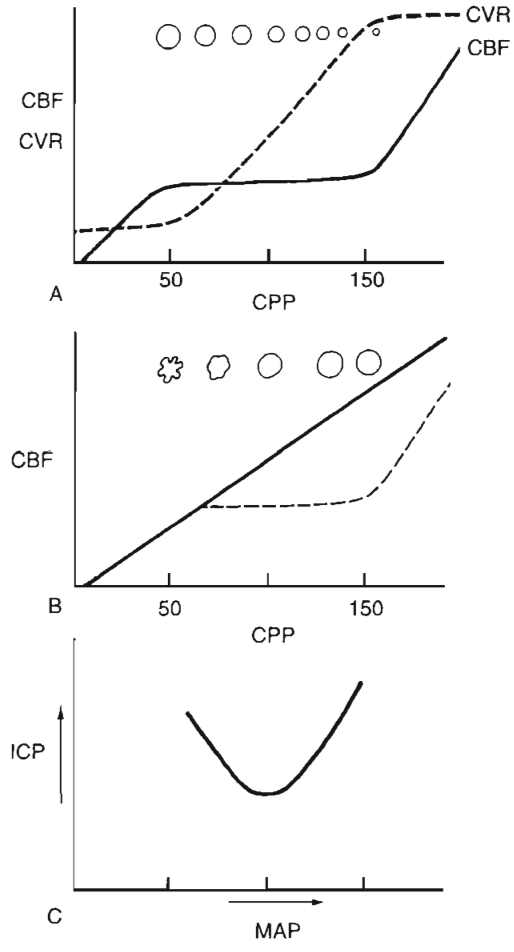


FIGURE 47–9. Cerebral perfusion pressure (CPP) versus cerebral blood flow (CBF) and cerebrovascular resistance (CVR). (**A**) Blood flow is normally maintained constant through changes in CVR, depicted as changes in vascular diameter (and therefore cerebral blood volume [CBV]) in the figure. CBV varies inversely with CPP. (**B**) With vasoparalysis due to injury, CVR does not change with CPP variations, such that CBF and CBV vary directly with CPP. (**C**) In the situation of decreased intracranial compliance, both of the factors illustrated in parts **A** and **B** may interact to increase ICP. Normally autoregulating tissue as in part **A** will predispose to CBV-mediated ICP elevation with decreasing blood pressure, whereas vasoparalyzed tissue (**B**) will predispose to CBV-mediated ICP elevations with increasing blood pressure, leading to the notion of an ICP optima (probably approximately 80 to 100 mm Hg) with varying CPP. (From Kofke W, et al: Neurologic Intensive Care. In Albin M [ed]: Textbook of Neuroanesthesia. New York, McGraw-Hill, 1997.)

common mechanism, as Huseby's data[16] suggest that cerebral venous effects only occur with very high PEEP.

Shapiro and colleagues[17] demonstrated increases in ICP in head-injured humans during intracranial hypertension with application of PEEP (Fig. 47-12). Examination of their data suggests that the most profound decreases in CPP occurred in patients with PEEP-induced decrements in MAP. This is consistent with the notion put forth by Rosner[3] that decreases in blood pressure increase CBV and ICP. Aidinis and colleagues,[18] in studies on cats, confirmed these observations in a more controlled setting. In addition, they assessed the role of pulmonary compliance, finding that decreased pulmonary compliance induced by oleic acid injections results in less effect of PEEP to increase ICP. In situations in which PEEP is likely to be needed, with decrements in pulmonary compliance, such observations indicate that any adverse effects on ICP are less likely to be manifest. This may be related to observations that hemodynamic effects of PEEP are less apparent with noncompliant lungs,[18,19] such that hypotensive-mediated increases in CBV do not occur.

The intuitive notion that PEEP increases cerebral venous pressure to increase ICP is not as straightforward as it initially may seem. For PEEP to increase cerebral venous pressure to levels that will increase ICP, the cerebral venous pressure must at least equal the ICP. Thus, the higher the ICP, the higher PEEP must be to have such a direct hydraulic effect on ICP. This concept was nicely proved by Huseby and colleagues[16] in dog studies in which PEEP was increased progressively with different starting levels of ICP (Fig. 47-13). It is important to note that they prevented PEEP-induced decrements in blood pressure, thus avoiding any reflex increases in cerebral blood volume. They suggested a hydraulic model to better conceptualize this (Fig. 47-14). For example, if all of a 10 cm H_2O PEEP application were transmitted to the cerebral vasculature, which is unlikely given the decreased pulmonary compliance associated with the need for such PEEP, ICP will only be affected if it is less than 10 cm H_2O (7.7 mm Hg), increasing to a level no higher than the applied PEEP. This presupposes no PEEP-induced arterial pressure decrement.

ANTIHYPERTENSIVE THERAPY EFFECTS ON INTRACRANIAL PRESSURE

Intracranial pressure can also be influenced by antihypertensive drugs. In general, vasodilator drugs such as nitroprusside,[20-22] nitroglycerin,[23] and nifedipine[24] can be expected to increase

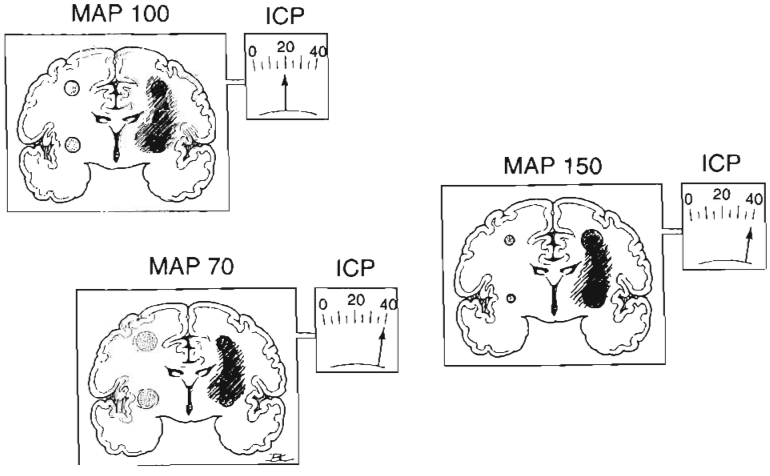


FIGURE 47–10. In the setting of heterogeneous autoregulation in the brain, conditions may predispose to cerebral blood volume (CBV)–mediated increases in intracranial pressure (ICP) with both increases or decreases in blood pressure. The stippled circles in each coronal brain section represent the cerebral vasculature/blood volume.

Low PEEP → ↓CO → ↓BP → ↑CBV → ↑ICP

High PEEP → ↑CVP → ↑P_{SS} > ICP → ↑ICP

FIGURE 47–11. Two mechanisms of positive end-expiratory pressure (PEEP)–mediated increases in intracranial pressure (ICP). The addition of PEEP decreases cardiac output (CO) and blood pressure (BP), leading to a reflex increase in cerebral blood volume (CBV). If cerebral perfusion pressure is marginal with heterogeneous autoregulation, this can lead to further increases in ICP. Conversely, to increase sagittal sinus pressure to an extent sufficient to further increase ICP, which is already elevated, PEEP levels at or greater than the ICP must be applied. Pss, sagittal sinus pressure.

ICP. Conversely, nonvasodilator antihypertensive drugs, generally sympatholytic drugs such as trimethaphan, or beta-adrenergic blocking drugs such as esmolol or labetalol,[25] can be expected to have little or no effect on ICP. These observations suggest that the rise in ICP due to vasodilators is caused by increased CBF with attendant increase in CBV. The increase in ICP thus does not threaten ischemia, although herniation and hyperperfusion syndromes may occur and might be problematic. There has been a report of neurologic deterioration with nitroprusside use despite no change in blood pressure.[22] Another consideration in the use of vasodilators is the propensity to reflexively increase plasma catecholamines.[26] Such increases in plasma catecholamines may be deleterious to the marginally perfused injured brain.[27-29]

HYPERPERFUSION SYNDROMES

In a variety of clinical situations, CBF may be inappropriately increased for a given blood pressure. In the extreme case of such situations, vasoparalysis is present and CBF becomes more or less a linear function of blood pressure. Such hyperperfusion syndromes may occur early in cases of severe hepatic encephalopathy,[30] 2 to 3 days after severe head injury,[13] after resection of large arteriovenous malformations (AVMs),[31-33] after carotid endarterectomy of severely stenotic lesions with poor collaterals,[34] probably after cerebral arterial thrombolysis,

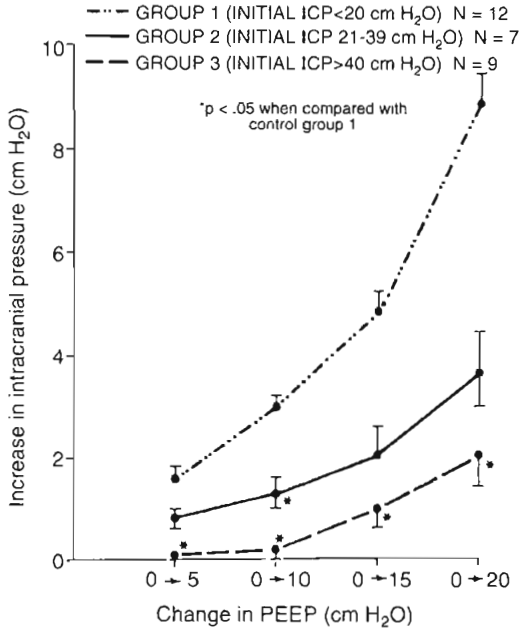


FIGURE 47–13. Increases in intracranial pressure (ICP) with positive end-expiratory pressure (PEEP) in dogs. Values are mean ± standard error of the mean. Group 1 included 12 animals with initial ICP less than 20 cm H_2O; group 2 included seven animals with initial ICP of 21 to 39 cm H_2O; group 3 included nine animals with initial ICP greater than 40 cm H_2O. Blood pressure was maintained constant in all animals. Note that with blood pressure maintained constant, the most significant increases in PEEP occur in the animals with the lowest starting PEEP level. (From Huseby JS, Luce JM, Cary JM, et al: Effects of positive end-expiratory pressure on intracranial pressure in dogs with intracranial hypertension. J Neurosurg 1981;55:704.)

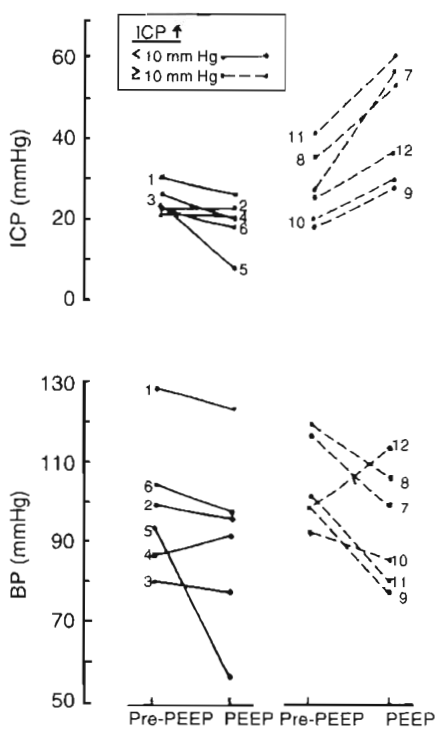


FIGURE 47–12. Intracranial pressure (ICP) and arterial blood pressure (BP) before and with the application of positive end-expiratory pressure (PEEP) (4-8 cm H_2O) in severely head-injured patients. The patients are arbitrarily divided into two groups: those with an ICP increase of 10 mm Hg or greater and those with ICP gains below 10 mm Hg. Note that PEEP-induced blood pressure decreases appear to be more marked in patients sustaining larger ICP increases. (From Shapiro HM, Marshall LF: Intracranial pressure responses to PEEP in head-injured patients. J Trauma 1978;18:254.)

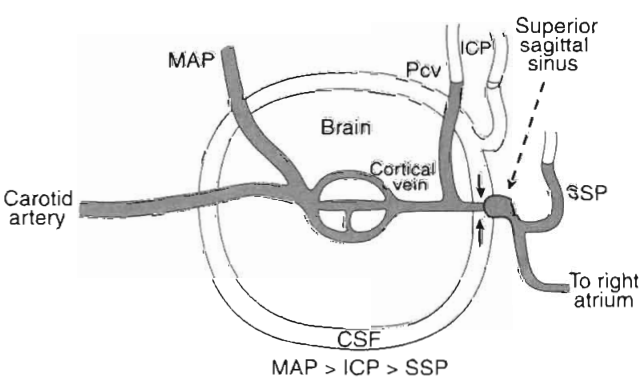


FIGURE 47–14. Schematic illustration of the intracranial space during raised intracranial pressure (ICP). The arrows indicate the position of the hypothesized Starling resistor. Here, the mean arterial pressure (MAP) is greater than ICP, which is greater than sagittal sinus pressure (SSP). Cortical vein pressure (Pcv) cannot fall below ICP, and thus flow is dependent on MAP minus ICP and independent of small changes in SSP. (From Huseby JS, Luce JM, Cary JM, et al: Effects of positive end-expiratory pressure on intracranial pressure in dogs with intracranial hypertension. J Neurosurg 1981;55:704.)

and possibly during administration of cerebral vasodilators at high systemic blood pressure.

Fulminant hepatic failure produces widespread physiologic changes, including altered cerebral physiology.[30] Aggarwal and coworkers[30] systematically examined cerebral hemodynamics and metabolism in severe hepatic encephalopathy and during recovery after hepatic transplantation. They have identified phases that are traversed in the course of going from normal cerebral physiology to brain death. Patients initially demonstrate elevated CBF at normotension. This is usually followed by hyperemic (high CBF and/or CBV) intracranial hypertension, then edema with oligemic intracranial hypertension, and finally intracranial circulatory arrest and brain death. The data clearly suggest that the hyperemia may be deleterious, possibly contributing to the development of subsequent cerebral edema. This is supported by observations that the cerebral edema seems to be prevented through the use of barbiturates and hyperventilation during the hyperemic phase.

Several investigators, in the course of examining cerebrovascular physiology after head trauma, have observed that patients with severe head injury initially have normal or low CBF. This is followed a few days later by increased CBF, which is associated with intracranial hypertension.[12] This may contribute to subsequent oligemic intracranial hypertension.

The concept of normal perfusion pressure breakthrough indicates hyperperfusion at normal blood pressure, such as after resection of a large AVM, when the remaining blood vessels lack the ability to constrict normally and regulate blood flow, resulting in abnormally high regional CBF. The pathogenesis is thought to be related to chronic arterial hypotension proximal to the AVM. The larger the AVM, the lower the intracranial blood pressure to which the patient is acclimated (i.e., the cerebral vasculature locally down-regulates the CBF-MAP autoregulatory relationship). Removing the AVM abruptly exposes the cerebral arterial vessels and arterioles to pressure never before experienced.[32] Thus, despite the blood pressure being within normal limits, the pressure-naive vasculature is unable to autoregulate and the physiology of malignant hypertension may ensue to cause cerebral edema and/or hemorrhage. This is an attractive hypothesis that makes physiologic sense. However, Young and coworkers[33] report that autoregulation of the vascular bed after AVM resection is generally intact, indicating that vasoparalysis due to chronic hypotension may not be the most important contributor to normal perfusion pressure breakthrough.

One cause of neurologic deterioration after carotid endarterectomy is cerebral edema and/or hemorrhage. This is rather unusual, but the presence postoperatively of a unilateral throbbing headache suggests that it may be present. Blood flow studies reveal such patients to have cerebral hyperemia associated with removal of a large proximal obstruction. While normotension is usually well tolerated, hypertension probably increases the risk of hemorrhage, especially if there was a preoperative cerebral infarction. Similar to the AVM situation, described earlier, vasculature that has acclimated to low proximal pressure now is presented with arterial pressure that is much higher, although within the epidemiologic norm.[34]

After thrombolysis of a cerebral artery, one important source of morbidity is edema or hemorrhage of the reperfused territory. With reperfusion of the ischemic tissue, hyperemia occurs for a period of time. If sustained, this suggests that irreversible endothelial damage has occurred and that the patient is at risk for secondary edema or hemorrhage, particularly if the depth of ischemia is sufficient to produce early changes on a computed tomography scan.[35]

Vasodilators such as nitroprusside are frequently used in patients with severe arterial hypertension. When CBF is measured, it is noted that nitroprusside has minimal CBF effect with induced hypotension.[36] However, data are not available on its CBF-CBV effects with treatment of hypertension. Such vasodilators are known to cause an increase in ICP,[22,37] suggesting an element of cerebral hyperemia. This is supported by reports of cerebral dysautoregulation induced by nitroprusside.[38] This ICP elevation and hyperemia[36,39] appear to decrease as blood pressure is lowered. This notion is supported by observations during neurosurgery with cerebral swelling present when nitroprusside is administered.[40] With its use for induced hypotension during neurosurgery, the brain is noted to be flaccid with no hyperemia evident. Thus, cerebral vasodilators can produce a cerebral dysautoregulation/hyperperfusion syndrome, the extent of which is likely dependent on blood pressure. Their use has not yet been reported to be associated with exacerbation of cerebral edema/hemorrhage.

All of the above syndromes describe a clinical course in humans consisting of inappropriate hyperemia for a given blood pressure followed by cerebral edema or hemorrhage. This suggests that the failure to autoregulate at normal pressure results in exposure of arterioles and capillaries to unacceptably high pressure. This then results in disruption of the blood-brain barrier with consequent transudation of fluid or frank bleeding.

HYPERTHERMIA

Temperature management can be critical in neurointensive care. In animal models, hyperthermia has been shown to have deleterious effects on outcome after cerebral ischemia,[41] head trauma,[41] and seizure.[42] Conversely, mild hypothermia has been shown to be protective.[43] It is of interest that the extent of hypothermia required to produce protection is modest (32-36°C). The extent of protection is not adequately explained by reduction in cerebral metabolic rate,[44] suggesting that hypothermia has additional beneficial effects, such as decreased free radical production or reduction in neurotransmitter neurotoxicity.[45]

Preliminary reports from a multicenter trial of head trauma indicate that moderate hypothermia confers cerebral protection when applied within 6 hours of insult and maintained for 24 to 48 hours.[43] This observation was not confirmed in a subsequent multi-institutional trial, although head-injured patients who presented with hypothermia had a better outcome.[46] In addition, two recent reports of hypothermia after cardiac arrest provide strong support for the notion that mild hypothermia is protective after cerebral ischemia.[47,48] Based on these reports, the American Heart Association has adopted hypothermia as a recommended therapy after resuscitation from cardiopulmonary arrest.[49]

Further complicating the role of hypothermia, however, are the recent results of the IHAST2 trial showing no protection from mild hypothermia during cerebral aneurysm surgery.

GAS EXCHANGE

Cerebrovascular reserve is compromised in many intracranial pathologic processes. Normally, the brain compensates for

decrements in supply of oxygen and substrates by vasodilating to maintain or increase flow.[50] Animal experiments indicate that it is possible to produce a condition in which cerebrovascular reserve is compromised with increased tendency to cerebral infarction. For example, occlusion of one carotid artery or inducing moderate hypoxemia does not produce symptoms as cerebral vasodilatation occurs to compensate. Indeed, some investigators contend that arterial hypoxemia occurring with normal cerebral vascular compensatory mechanisms does not cause brain damage. Of course, one contributing factor to this notion is that hypoxic myocardial dysfunction produces circulatory collapse and death such that isolated post-hypoxic (without ischemia) neuronal injury cannot occur. However, if hypoxemia is added to carotid occlusion, or vice versa, a stroke can occur because compensatory mechanisms, already fully utilized, cannot accommodate the further decrease in oxygen supply.[51,52] Examples of variants of this situation abound clinically.[53] Such examples of attenuated cerebrovascular reserve include cerebral edema, hypoxemia, carotid artery stenosis, peri-infarct penumbra, and anemia. In each of these situations, although not easy to quantitate, it is clear that added situations of compromised oxygen supply to the brain will risk neuronal injury.

Changes in $Paco_2$ have a profound impact on CBF. Normally, CBF varies linearly with $Paco_2$ between 20 and 60 mm Hg.[53] $Paco_2$-mediated changes in CBF occur with corresponding changes in CBV. Thus, in situations of abnormal intracranial compliance in which small changes in intracranial volume have large ICP effects, decreasing $Paco_2$ reduces ICP and increasing $Paco_2$ raises ICP.

The primary concern with raised ICP is that it may be associated with cerebral oligemia. Thus, these effects of $Paco_2$ on ICP are paradoxical. That is, decreasing $Paco_2$ reduces ICP, but at the expense of CBF (Fig. 47-15).[54] Minhas and colleagues[55] report that mild hyperventilation in brain-injured patients produces dangerous perilesional CBF decrements. However, Gupta and colleagues,[56] using tissue measures of brain-injured humans, reported sequential increases in $Ptio_2$ with decreasing $Paco_2$ with an optimum at 26 to 30 mm Hg. Nonetheless, data from head trauma studies indicate that routine use of hyperventilation can worsen outcome.[57] Conversely, allowing hypercapnia to occur, although leading to increased ICP, is associated with increased CBF. These observations pertain to normally autoregulating tissue. The CBF effects in injured brain tissue can be unpredictable. For example, allowing $Paco_2$ to increase CBF in autoregulating brain areas, by increasing ICP, may compromise flow in other injured, already fully vasodilated regions.

Related to these concerns is the growing practice of permissive hypercapnia in some types of respiratory failure, performed to reduce the risk of ventilator-mediated lung injury. Reports are somewhat conflicting regarding its safety in the brain-injured patient. In a non-trauma porcine model, van Huls and colleagues[58] found that hypercapnia to 90 mm Hg increased tissue po_2 while increasing ICP from 20 to 30 mm Hg. Their data and those of others suggest no harmful effects in the noninjured brain, but, theoretically, it seems this hyperemic elevation still might introduce a risk of hyperemia-mediated herniation. A recent report by Tasker and Peters,[59] however, suggests that the negative hyperemic effects associated with hypercapnia resolve over a day or so such that the pulmonary benefits of the hypercapnia can be gained as the adverse neurologic effects subside. This does raise the possibility of an unacceptable respiratory alkalosis on cessation of the permissive hypercapnia. Moreover, in neonates, hypercapnia increases CBF[60] that may lead to cerebral edema, increased ICP, and intraventricular hemorrhage.[61-64] Concerns are also raised by a pediatric case report of nonaneurysmal subarachnoid hemorrhage associated with and seemingly caused by permissive hypercapnia.[65]

The possibility of a neuroprotective effect of respiratory acidosis has also been reported.[66] Brain homogenates develop far fewer free radicals and less lipid peroxidation when pH is lowered by carbon dioxide than when it is lowered by hydrochloric acid,[67] and greater inhibition of tissue lactate production occurs when lowered pH is due to carbon dioxide than when it is due to hydrochloric acid.[68] Vanucci and collegues[69] report a protective effect of modest hypercapnia in an in vivo model of neuronal hypoxia. In trauma patients with multiple organ dysfunction, Gentiello and colleagues[70] found permissive hypercapnia to increase ICP but adjusted the level of hypercapnia if ICP rises occurred. Similar problematic ICP

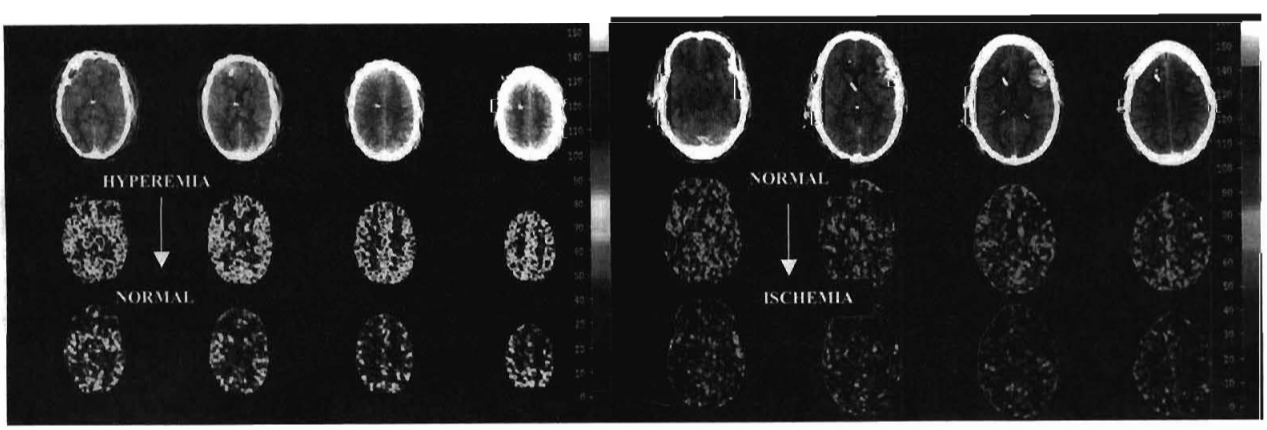


FIGURE 47–15. Effects of $Paco_2$ changes on cerebral blood flow (CBF). Two examples of disparate effects of hyperventilation on CBF. Both figures are stable xenon CBF scans in head trauma patients with and without hyperventilation. CBF scale is indicated on the right in mL/100 g/min and Pco_2 is indicated above each study. Computed tomography images are indicated in the upper figures and CBF maps in the lower figures. In the left figure, $Paco_2$ was decreased from 40 to 30 mm Hg. The baseline scan shows hyperemia and the hyperventilated scan shows CBFs of approximately 60 to 70 mL/100 g/min, probably acceptable flows. In the right figure, $Paco_2$ was decreased from 38 to 30 mm Hg. The baseline CBFs were acceptable. The effect of this modest extent of hyperventilation was to produce widespread areas of CBF less than 20 mL/100 g/min, probably unacceptable flows. (See color section in this text.) (Courtesy of Howard Yonas, University of Pittsburgh.)

increases were also observed in two head-injured patients by Levy and colleagues,[71] which they managed through the use of tracheal gas insufflation, which may be a compromise solution in this conundrum of conflicting physiology and no outcome data. In summary, the data are not conclusive regarding the safety of permissive hypercapnia in the presence of brain injury. It seems that the optimal approach would be to cautiously apply it and adjust according to the ICP response. If unacceptable ICP elevations arise, then the options would include abandoning permissive hypercapnia, treating the ICP to allow normalization of the CBF response to the CO_2 elevation over a few days, and possibly adding tracheal insufflation to the ventilator strategy.

HYPERGLYCEMIA

Hyperglycemia has been associated with exacerbation of brain damage with both head trauma and cerebral ischemia,[72-74] but it is not a straightforward issue. Clearly, neuronal damage after global cerebral ischemia is exacerbated by hyperglycemia.[75] Some studies have suggested that a blood glucose level over 120 mg% is deleterious in stroke patients.[72] However, subsequent studies with subhuman primates subjected to global ischemia have suggested a threshold of around 180 mg%.[58] Clearly, a blood glucose concentration greater than 400 mg% causes striking worsening of neurologic outcome with global ischemia.[73,76]

With focal cerebral ischemia, the situation is less clear. There have been animal and human studies showing that brain damage is worsened, not affected, or lessened with hyperglycemia.[77-81] One report by Prado and colleagues[81] in rats suggested that the discriminating factor regarding worsened brain damage with hyperglycemia is whether there is collateral flow. Areas of the brain with minimal or absent collateral vessels were not affected or were improved with hyperglycemia. Brain areas with a continued trickle of flow sustained worse damage. Presumably, the continued substrate supply in oligemic (not ischemic) areas allowed greater accumulation of organic acids in the cells, leading to worsening brain damage.[77,82] Unfortunately, these observations are difficult to apply clinically to individual patients with focal ischemia.

Hyperglycemia has not been shown to have either deleterious or protective effects in two animal models of status epilepticus.[83,84] The model used in Swan's report[84] produced limbic system damage, whereas Kofke and colleagues[83] used a model producing substantia nigra damage. Seizure-induced nigral damage in rats is associated with hypermetabolic lactic acidosis,[85] which was not exacerbated with hyperglycemia. The fact that nigral damage was not exacerbated with hyperglycemia suggests that metabolic acidosis may not be the sole factor in the development of brain damage after seizure.

SEPSIS

Sepsis is known, in animal models, to decrease CBF while increasing cerebral metabolic rate and disrupting the blood-brain barrier.[86] In addition, it can decrease blood pressure in a manner that may not be well tolerated by the brain with abnormal cerebrovascular reserve. Sepsis-induced decreases in blood pressure can turn an area of cerebral oligemia into an area of ischemic cerebral infarction; however, specific study of this is limited.

SODIUM

Hypernatremia. Hypernatremia can occur in neurologic intensive care unit patients because of nonketotic diabetic coma, dehydration from lack of fluid intake or diuretic use, hypertonic fluid administration, diabetes insipidus, or panhypopituitarism.[87] It can be associated with thirst, irritability, seizures, intracranial hemorrhage, or coma, although the rate of increase in sodium concentration is thought to be an important factor in the clinical presentation. For example, a sodium level of 170 mEq/L can be associated with little neurologic symptomatology if the rise occurs over a prolonged period. Indeed, hypertonic saline is occasionally used as a primary therapy for raised ICP,[88,89] in which case the elevation in sodium should be considered desirable, with desirable ICP, vasoregulatory, and neurochemical effects. Moreover, treating it could precipitate a rebound increase in ICP.

Diabetes insipidus can occur when disease processes affect the pituitary gland or its vascular supply. It should be suspected when urine output is inappropriately increased. Typically, urine output can increase abruptly to greater than 1 L per hour and be associated with severe hypernatremia and hypovolemic hypotension. Diagnosis of diabetes insipidus is based on continued output of dilute urine in the context of hypertonic serum. The specific gravity of urine will be close to 1.001 with osmolarity less than 200 mOsm/L despite serum osmolarity that may be greater than 320 mOsm/L.[90]

Hyponatremia. Hyponatremia can occur because of the syndrome of inappropriate secretion of antidiuretic hormone, so-called cerebral salt wasting, or excessive free water administration. Syndrome of inappropriate secretion of antidiuretic hormone is generally associated with hypervolemia and cerebral salt wasting with hypovolemia. Both syndromes can be associated with elevated urinary sodium concentrations, making differentiation between the two syndromes difficult in routine clinical practice.[91] Rapidly increasing the sodium concentration can produce permanent neurologic damage due to central pontine myelinolysis.[92] When the sodium level achieved with such overcorrection is extreme (i.e., 168 to 195 mMol/L), then extrapontine myelinolysis has also been reported.[93]

CATECHOLAMINES

Subarachnoid hemorrhage (SAH) is an entity particularly notable for catecholamine effects, some of which are described elsewhere in this book. However, catecholamine effects also occur with increased ICP, stroke, head trauma, or any situation of compromised midbrain-hindbrain oxygen delivery.

Serum catecholamine levels increase dramatically after SAH, notably peaking at the same time as the peak incidence of post-SAH vasospasm with symptom development corresponding to serum catecholamine levels.[94-98] This leads to the notion that hypothalamic injury with excess catecholamine release may be an important factor in the genesis of post-SAH spasm and stroke.[95] Several lines of evidence further support this hypothesis:

1. The cerebral vasculature is invested somewhat with adrenergic nerves. With SAH, the adrenergic receptors in the cerebral vessels decrease in quantity.[98,99] This suggests that denervation hypersensitivity may be occurring such that the increase in humoral catecholamines with SAH produces spasm in hyperreacting vessels.

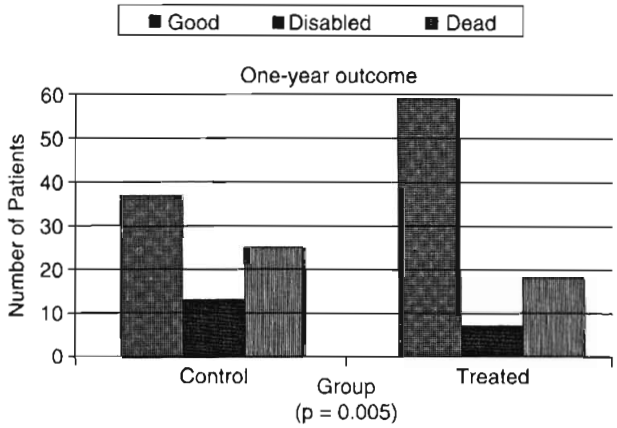


FIGURE 47–16. Subarachnoid hemorrhage patients were randomly treated with propranolol or placebo. Neurologic outcome was better in patients undergoing beta-blockade. (Data from Neil-Dwyer G, Walter P, Cruickshank JM: Beta-blockade benefits patients following a subarachnoid hemorrhage. Eur J Clin Pharmacol 1985;28[suppl]:25.)

2. Catecholamine release after SAH is sufficient to produce electrocardiographic changes[94,96,100,101] with ventricular wall motion abnormalities[102] and myocardial injury.[103,104]
3. Treatment of humans with SAH with beta- and alpha-adrenergic antagonists is associated with an improvement in neurologic outcome (Fig. 47-16)[28] and electrocardiographic abnormalities.[101]
4. In animal models, selective destruction of hindbrain adrenergic nuclei with cephalad projections prevents the development of vasospasm.[104] Moreover, laboratory studies indicate an important role for vasopressin in cases of vasospasm, because vasospasm cannot be produced in vasopressin-deficient rats.[105]
5. Studies in cerebral ischemia models provide strong support for the notion that catecholamines can exacerbate ischemic injury. Compared with hemorrhage-induced hypotension, ischemic damage was decreased with hypotension induced through the use of ganglionic blockade with hexamethonium,[27] central adrenergic blockade with alpha-2 agonists,[29] and angiotensin converting enzyme inhibition.[106] Hemorrhaged control rats were noted to sustain an increase in exogenous catecholamine concentrations. To test the hypothesis that these catecholamines contributed to brain damage, some of the animals treated with hexamethonium also received intravenous catecholamine infusions. Reversal of the hexamethonium brain protective effect was observed in these animals (Fig. 47-17).[27]
6. Brain protection has been observed in laboratory studies with preischemic[107] and preseizure[108] treatment using reserpine, a drug that depletes presynaptic catecholamine stores.
7. Application of catecholamines directly to nonischemic cortical tissue has also been observed to have neurotoxic potential.[109] In addition, intravenous administration can exacerbate brain swelling after head trauma, although this is most likely a direct effect of blood pressure on a dysautoregulating brain (see Fig. 47-8) rather than a manifestation of biochemical neurotoxicity.[14]

SUMMARY

Brain damage can arise from a variety of seemingly disparate neurologic disease states. Such conditions, discussed in subsequent chapters, include ischemia, seizures, trauma, or other adverse processes. Raised ICP typically occurs as these types of conditions progress. When episodes of intracranial hypertension occur, it is important to distinguish hyperemic (with high CBV) from oligemic causes. Any brain injury is significantly impaired by the extracranial environment. Such extracranial factors include temperature, gas exchange, glucose, sepsis, sodium, and catecholamines. Optimal physiology-guided therapy is essential to optimize outcomes in neurointensive care.

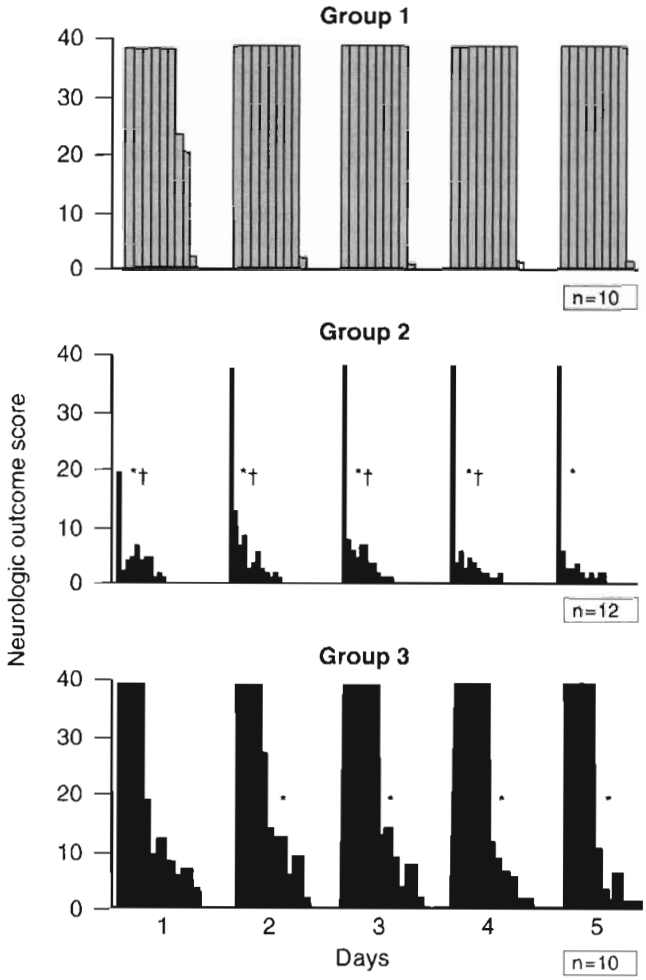


FIGURE 47–17. Neurologic deficit scores after incomplete focal cerebral ischemia in rats over a 5-day examination period. Each bar represents the neurologic score for each rat (*$P < .05$ vs. group 1; †$P < .05$ vs. group 3). The rats are ranked according to total outcome score in descending order (0 = normal). Cerebral ischemia was induced with occlusion of one carotid artery with hemorrhagic hypotension. Group 1 rats received no vasoactive drugs; group 2 rats received preischemic hexamethonium; and group 3 rats received hexamethonium plus intravenous epinephrine and norepinephrine. Protection was conferred by hexamethonium in a catecholamine-reversible manner. (From Werner C, Hoffman WE, Thomas C, et al: Ganglionic blockade improves neurologic outcome from incomplete ischemia in rats: Partial reversal by exogenous catecholamines. Anesthesiology 1990;73:923.)

ANNOTATED REFERENCES

Huseby JS, Luce JM, Cary JM, et al: Effects of positive end-expiratory pressure on intracranial pressure in dogs with intracranial hypertension. J Neurosurg 1981;55:704.

This study in dogs identified the role of hydraulic issues in the genesis of PEEP-induced increases, or lack of increases, in the presence of varying

levels of ICP. The authors nicely showed, while maintaining MAP constant, that the higher the ICP was, the less likely it was for PEEP to increase sagittal sinus pressure to an extent sufficient to increase ICP.

Levine S: Anoxic-ischemic encephalopathy in rats. Am J Pathol 1960;36:1.
This article demonstrated the importance of cerebrovascular reserve. Rodents exposed to either hypoxia or carotid ligation sustained no deficits. However, induction of both insults reproducibly caused a stroke.

Lundberg N: Continuous recording and control of ventricular fluid pressure in neurosurgical practice. Acta Psychiatr Neurol Scand 1960;36(suppl 149):1.
This is the original paper, now a classic, describing plateau waves in a large number of patients. Lundberg placed ICP monitors in patients with nontraumatic intracranial hypertension and recorded his observations, identifying three types of plateau waves.

Neil-Dwyer G, Walter P, Cruickshank JM: Beta-blockade benefits patients following a subarachnoid hemorrhage. Eur J Clin Pharmacol 1985; 28(suppl):25.
This paper in humans with SAH showed an improvement in neurologic outcome when sympatholytic drugs were employed.

Rosner MJ, Becker DP: Origin and evolution of plateau waves: Experimental observations and a theoretical model. J Neurosurg 1984;50:312.
This important paper identified the relationship between blood pressure variations and plateau waves, then synthesized it with work of others to suggest an important role for changes in cerebral blood volume in still autoregulating brain to produce plateau waves.

Werner C, Hoffman WE, Thomas C, et al: Ganglionic blockade improves neurologic outcome from incomplete ischemia in rats: Partial reversal by exogenous catecholamines. Anesthesiology 1990;73:923.
This paper (and that of Hoffman et al[29]) on rodents provides excellent support for the notion that catecholamines can worsen the results of brain ischemia.

Chapter 48
ADVANCED BEDSIDE NEUROMONITORING

Roman Hlatky • Claudia Robertson

KEY POINTS

1. Evaluation of **neurologic** and mental **status** should be included in the monitoring protocol whenever possible.
2. **Intracranial pressure (ICP)** cannot be reliably estimated from any clinical feature in critically ill patients. On computed tomography (CT) scans, signs of brain swelling, such as midline shift and compressed basal cisterns, are predictive of raised ICP, but intracranial hypertension can occur without these findings.
3. Patients with traumatic brain injury who are at particular **risk for developing elevated ICP** include those with Glasgow coma scale (GCS) scores of 8 or less after resuscitation and abnormal CT scans, as well as those with GCS scores of 8 or less, normal CT scans, but adverse features such as age older than 40 years, systolic blood pressure of 90 mm Hg or less, and motor deficit.
4. The **ventriculostomy catheter** remains the preferred device for monitoring ICP and is the standard against which all new monitors are compared.
5. The two major **complications of ICP monitoring** are ventriculitis (1% to 10% of cases) and intracranial hemorrhage (1% to 2%).
6. **Normal** resting **ICP** is less than 10 mm Hg. Transient elevations of ICP occur normally with straining, coughing, or the Trendelenburg position. A sustained ICP greater than 20 mm Hg is clearly abnormal. An ICP greater than 40 mm Hg represents severe, usually life-threatening, **intracranial hypertension.**
7. The simplest measure of cerebral perfusion is **cerebral perfusion pressure** (CPP). For equivalent levels of CPP, cerebral perfusion is impaired more by reductions in blood pressure than by increases in ICP.
8. In head-injured patients, the average **jugular venous oxygen saturation ($Sjvo_2$)** is higher than normal (55% to 71%), and the range for $Sjvo_2$ is considerably wider than it is in normal subjects. If the strategy is to use $Sjvo_2$ as a monitor of global oxygenation, cannulating the **dominant jugular vein** is logical, because it is the most representative of the whole brain.
9. Transcranial **Doppler ultrasonography** is a noninvasive monitor that provides indirect information about cerebral blood flow in one of the major arteries at the base of the brain. In the absence of vessel stenosis or vasospasm or changes in arterial blood pressure or blood rheology, the **pulsatility** reflects the distal cerebrovascular resistance.
10. The **Lindegaard (hemispheric) index** is a ratio of flow velocity in the middle cerebral artery and internal cerebral artery. The mean hemispheric index in normal individuals is 1.76 ± 0.1, and pathologic values suggestive of vasospasm are generally above 3.
11. The major limitation of $Sjvo_2$ as a monitor of the adequacy of cerebral blood flow is that regional ischemia is not identified. In situations in which regional differences in cerebral blood flow may occur, such as brain trauma, **brain tissue oxygen partial pressure ($Pbto_2$)** as a monitor of cerebral oxygenation may have an important advantage.
12. **Normal values for $Pbto_2$** are 20 to 40 mm Hg, and critical reductions are 8 to 10 mm Hg.
13. **Microdialysis** is a technique for sampling the extracellular space of a tissue. It is based on the diffusion of water-soluble substances through a semipermeable membrane and allows continuous and on-line monitoring of changes in brain tissue chemistry.
14. The use of **electroencephalograms (EEGs)** in the ICU to detect early subclinical seizures may help reduce mortality and morbidity in status epilepticus. Continuous EEG monitoring is also useful in detecting ischemic cerebral events, including vasospasm following subarachnoid hemorrhage and intracranial hypertension after head injury.

Currently, little can be done to reverse the primary brain damage caused by an insult; however, one of the major factors influencing outcome in patients with acute brain injury is the additional brain damage that occurs from secondary injury processes. Intracranial hypertension and cerebral ischemia are the most significant secondary injury processes that can be monitored and treated in the ICU. In addition, secondary ischemic insults of extracerebral origin (e.g., arterial hypotension, hypocapnia) can be prevented or treated before they become severe enough to injure the brain. The purpose of continuous monitoring of the brain in the ICU is to detect

these secondary insults, allowing for a more informed, individualized approach to treatment.

MONITORING OF NEUROLOGIC STATUS

Evaluation of neurologic and mental status should be included in the monitoring protocol whenever possible. Glasgow coma scale (GCS) score, motor function, status of cranial nerves, and any trend in neurologic status changes should be easily obtainable from the records. A 24-hour record of the patient's neurologic evaluation should be available on one sheet, together with information about vital signs and laboratory values. Computerized information systems are becoming more widespread in ICUs and can markedly reduce the burden of such record keeping. In critically ill patients, however, the neurologic examination is often obscured by the need to use sedation or neuromuscular blocking agents in the treatment of intracranial hypertension or other associated injuries or disorders.

One relatively new addition to the neurologic examination, which may reduce observer variability, is the hand-held pupillometer. A recent technical note reported good reliability in measuring pupillary diameter using the pupillometer; in addition, this device provides a quantitative measure of the velocity of the pupillary response to light.[1] Studies are needed to determine whether changes in the velocity of the pupillary response might be a sensitive measure of worsening neurologic status.

MONITORING OF INTRACRANIAL PRESSURE

Intracranial pressure (ICP) cannot be reliably estimated from any clinical feature in critically ill patients. Clinical symptoms of raised ICP, such as headache, nausea, and vomiting, are impossible to elicit in comatose patients. Papilledema is not a reliable sign of raised ICP in acute disorders. In one study of 426 patients with traumatic brain injury, only 3.5% had papilledema on funduscopic examination, although 54% of patients had increased ICP.[2] Other neurologic signs, including pupillary dilatation and decerebrate posturing, can occur in the absence of intracranial hypertension. On computed tomography (CT) scans, signs of brain swelling, such as midline shift and compressed basal cisterns, are predictive of raised ICP, but intracranial hypertension can occur without these findings.[3]

Because intracranial hypertension cannot be reliably determined clinically, the direct monitoring of ICP plays an important role in guiding therapy and assessing prognosis in patients with acute neurologic disorders. The ideal ICP monitor would be noninvasive; would provide an accurate, stable measure of pressure; and would provide continuously updated information. A number of noninvasive technologies have been explored as possible replacements or even adjuncts for the ICP monitor. These techniques include tissue resonance,[4] measurements of skull movement associated with ICP pulsations,[5] measurement of venous outflow pressure by ophthalmodynamometry,[6] measurement of tympanic membrane displacement,[7] and monitoring of visual evoked responses.[8] None of these tests is sufficiently reliable to replace the ventriculostomy catheter in the management of critically ill patients.

INDICATIONS

Monitoring of ICP can result in serious complications and is therefore indicated only in patients at significant risk of developing intracranial hypertension. In patients with traumatic brain injury, ICP has been systemically studied by many investigators, and there is a general consensus on the indications for invasive monitoring. Patients with traumatic brain injury who are at particular risk for developing raised ICP include those with GCS scores of 8 or less after resuscitation and abnormal CT scans, as well as those with GCS scores of 8 or less, normal CT scans, but adverse features such as age older than 40 years, systolic blood pressure of 90 mm Hg or less, and motor deficit.[9] More recent studies have shown that comatose patients without these adverse features may also have transiently elevated ICP, suggesting that all patients with GCS scores of 8 or less should have ICP monitoring.[10] Patients with GCS scores greater than 8 might be considered for ICP monitoring if they require treatment that would not allow serial neurologic examinations.[11] A severe coagulopathy is the only major contraindication to ICP monitoring. For critically ill patients with other, nontraumatic neurologic disorders, the indications for ICP monitoring are less clear, but the same general guidelines are often used.

TECHNIQUES

Although several new types of monitors have recently been marketed, the ventriculostomy catheter remains the preferred device for monitoring ICP and is the standard against which all new monitors are compared (Table 48-1).

TABLE 48-1. MONITORING OF INTRACRANIAL PRESSURE AND CEREBRAL PERFUSION

Monitoring Domain	Attributes of Ideal Monitor	Current Strategy of Choice		Current Alternatives
Intracranial pressure	Accurate, noninvasive	Ventriculostomy: most accurate, highest rate of complications		Parenchymal devices: cannot rezero, lower rate of complications Spiegelberg catheter: accurate pressure, also monitors intracranial compliance
Cerebral perfusion	Continuous or frequent serial bedside imaging of regional CBF	Early CBF imaging (xenon CT or perfusion CT) to determine nature of neurologic disorder		Plain CT imaging could substitute for CBF imaging by suggesting the likely nature of the disorder
		If diffuse: $Pbto_2$ or $Sjvo_2$ to monitor for secondary insults	If focal: $Pbto_2$ in area of hypoperfusion and $Sjvo_2$ as global monitor	Local CBF probes (laser Doppler or thermal diffusion) could substitute for $Pbto_2$ Global measures (CPP, flow volume) could substitute for $Sjvo_2$

CBF, cerebral blood flow; CPP, cerebral perfusion pressure; CT, computed tomography; $Pbto_2$, brain tissue oxygen partial pressure; $Sjvo_2$, jugular venous oxygen saturation.

The ventriculostomy catheter is positioned with its tip in the frontal horn of the lateral ventricle and is coupled by fluid-filled tubing to an external pressure transducer that can be reset to zero and recalibrated against an external standard. The ventriculostomy ICP monitor allows intracranial hypertension to be treated by the intermittent drainage of cerebrospinal fluid. However, the risk of ventriculitis and of intracranial hemorrhage is high with ventriculostomy,[9] and proper placement of the catheter tip in the lateral ventricle can be difficult in patients with small, compressed ventricles.

When the ventricle cannot be cannulated, alternative devices can be used. The microsensor transducer[12] and the fiberoptic transducer[13] are the most widely available. These miniature transducer-tipped catheters can be inserted in the subdural space or directly into brain tissue. The main advantage of these monitors is their ease of insertion, especially in patients with compressed ventricles; however, the transducers cannot be reset to zero after they are inserted into the skull, and they exhibit drift over time.[14] Another ventricular catheter, employing an air pouch balloon catheter technology, allows automated monitoring of the intraventricular volume-pressure relationship, in addition to the intraventricular pressure.[15] Investigations are needed to determine whether intracranial compliance can provide an earlier indication of a developing mass lesion or worsening brain swelling than does the simple measurement of ICP.

COMPLICATIONS

The two major complications of ICP monitoring are ventriculitis and intracranial hemorrhage. Infection may be confined to the skin wound, but in 1% to 10% of cases, ventriculitis occurs. Most studies have found a higher rate of infection in ventriculostomy-monitored patients than in those monitored with subarachnoid bolts or subdural catheters.[9,16] An analysis of data from the Traumatic Coma Data Bank study also suggests that there is no benefit in changing ventriculostomy catheters at 5-day intervals.[17] The best strategy for reducing the risk of ventriculitis associated with ICP monitoring is to minimize the duration of monitoring. No controlled studies have demonstrated that prophylactic antibiotics can reduce the incidence of ventriculostomy-related infections. A randomized trial of ventriculostomy catheters impregnated with minocycline and rifampin demonstrated that the impregnated catheters were half as likely to become colonized as the control catheters were (17.9% and 36.7%, respectively, $P < .0012$).[18] Positive cerebrospinal fluid cultures were seven times less frequent in patients with antibiotic-impregnated catheters compared with those in the control group (1.3% and 9.4%, respectively, $P = .002$).

The second major complication of ICP monitoring is intracerebral hemorrhage. Although the risk of hemorrhage is low (1% to 2%), it is an important complication to recognize and treat.[9] Patients with coagulopathies have a greater risk of developing this complication.

NORMAL VALUES

Normally, resting ICP is less than 10 mm Hg. Transient increases in ICP occur normally with straining, coughing, or the Trendelenburg position. A sustained ICP greater than 20 mm Hg is clearly abnormal; an ICP between 20 and 40 mm Hg is considered moderate intracranial hypertension; and an ICP greater than 40 mm Hg represents severe, usually life-threatening, intracranial hypertension.[19] These guidelines for determining the severity of intracranial hypertension assume a normal blood pressure. When a temporal mass lesion is present, however, herniation can occur at ICP values less than 20 mm Hg.[20] Both the American and European head injury guidelines recommend treatment of ICP that is greater than 20 to 25 mm Hg.[21,22]

MONITORING OF CEREBRAL PERFUSION AND OXYGENATION

The ideal neuromonitor for ischemia would provide continuously updated information about regional cerebral blood flow (CBF) and metabolism throughout the brain (see Table 48-1). Continuously updated information is needed because acute neurologic disorders evolve over time, and early intervention provides the best chance for a successful outcome. Regional information is required because neurologic disorders tend to develop regionally in the brain, especially early in the course.

An ideal monitor for ischemia does not currently exist. High-resolution maps of regional CBF are available with current imaging techniques; however, this type of study generally required that patients be taken out of the ICU to the radiology department. High-quality CT imaging, including of CBF, can now be obtained in the ICU. Reports suggest that this arrangement is safer for critically ill patients and is cost-effective.[23] It is likely that in the future, such imaging will be used in the ICU similar to a bedside monitor. The best monitoring strategy at present is the use of a monitor of global cerebral perfusion and a monitor of local cerebral perfusion placed strategically in the area of the brain considered most vulnerable to the development of ischemia.

There are several choices for measuring global and local cerebral perfusion. These monitors fall into two categories: those that measure CBF directly, and those that provide indirect information about CBF by measuring oxygen extraction. Measures of cerebral oxygenation, such as jugular venous oxygen saturation ($Sjvo_2$) or brain tissue oxygen partial pressure ($Pbto_2$), are widely used in place of quantitative CBF measurements in critically ill patients because they indicate the adequacy of CBF relative to cerebral metabolic requirements. Because cerebral metabolic requirements may be reduced after traumatic brain injury, normal CBF values may not be optimal. For instance, when CBF is low (25 to 30 mL/100 g per minute), it can be difficult to decide whether this is an appropriate response to lower cerebral metabolic requirements or whether the brain is hypoperfused. A measure of cerebral oxygenation can be helpful in making this distinction. If the brain is hypoperfused, oxygen extraction will be increased, and $Sjvo_2$ will be reduced. If CBF is appropriate for the brain's metabolic requirement, $Sjvo_2$ will be normal. This information is often more clinically useful than are absolute CBF values.

GLOBAL MONITORS

Cerebral Perfusion Pressure

The simplest measure of cerebral perfusion is cerebral perfusion pressure (CPP), which is calculated by subtracting the ICP from the mean arterial blood pressure. The normal lower limit of autoregulation for CPP is 50 mm Hg. In severely head-injured patients, the ability to autoregulate

TABLE 48–2. NORMAL VALUES FOR NEUROPHYSIOLOGIC PARAMETERS

Parameter	Normal Values	Critical Values
Cerebral blood flow		
Global	52±12 mL/100 g/min[67]	18-20 mL/100 g/min
Cortical	80 mL/100 g/min[68]	
Flow volume	268±60 mL/min[69]	
Cerebral oxygenation		
$Pjvo_2$	40 mm Hg[68]	20-30 mm Hg
$Sjvo_2$	55-71%[39]	50%[39]
$Pbto_2$	20-40 mm Hg[70]	8.5-10 mm Hg[70]
$AVDo_2$	4.5-8.5 mL/100 mL[67]	
Cerebral metabolism		
$CMRO_2$	3.4 mL/100 g/min[32]	0.6 µmol/g/min
CMRG	0.325 µmol/g/min[32]	
CMRL	−0.02 µmol/g/min[32]	
MD-glucose	1.7±0.9 µmol/L[71]	
MD-lactate	2.9±0.9 mmol/L[71]	
MD-pyruvate	166±47 mmol/L[71]	
MD-glutamate	16±16 µmol/L[71]	

$AVDo_2$, arteriovenous oxygen difference; CMRG, cerebral metabolic rate of glucose; CMRL, cerebral metabolic rate of lactate; $CMRO_2$, cerebral metabolic rate of oxygen; MD, microdialysate; $Pbto_2$, brain tissue oxygen partial pressure; $Pjvo_2$, jugular venous oxygen partial pressure; $Sjvo_2$, jugular venous oxygen saturation.

may be impaired, and CBF may be inadequate even with CPP values greater than 50 mm Hg. CPP can be reduced through either decreases in blood pressure or increases in ICP. For equivalent levels of CPP, cerebral perfusion is impaired more by reductions in blood pressure than by increases in ICP.[24] As a monitor for cerebral perfusion, CPP is widely available and convenient; its limitation is that only ischemia caused by increased ICP or decreased blood pressure is assessed. A normal CPP does not confirm that CBF is adequate.

Kety-Schmidt Technique

Measurement of global CBF by the classic Kety-Schmidt technique (based on the Fick principle) uses nitrous oxide as the diffusible indicator. It can be performed at the bedside with a minimum of expense and equipment. Instruments for measuring regional CBF using the stable xenon-enhanced CT technique are also commercially available.[25-27] However, both these measurements of CBF are intermittent and require the patient to be hemodynamically stable during the time required for the measurements. Therefore, transient CBF reductions or CBF reductions in an acutely unstable patient are difficult to document with these technologies.

Jugular Venous Oxygen Saturation

Placement of an internal jugular vein catheter, similar to the type used for central venous pressure monitoring but directed cephalad into the jugular bulb, allows repetitive sampling of $Sjvo_2$ without repeated needle punctures.[28-32] More recently, the development of in vivo reflectance oximetry using fiberoptic catheters has allowed continuous monitoring of $Sjvo_2$ without the need to sample blood, except for calibration purposes.[33-35]

Side of Catheterization. Studies comparing bilateral measurements of $Sjvo_2$ or comparing $Sjvo_2$ to oxygen saturation in the confluence of the cerebral sinuses clearly indicate that when there are focal lesions after traumatic brain injury, there may be significant differences in oxygen saturation measured in the left and right jugular bulbs.[36,37] If the strategy is to use $Sjvo_2$ as a monitor of global oxygenation, cannulating the dominant jugular vein is logical, because it is most representative of the whole brain. However, if the strategy is to identify the most abnormal oxygen saturation, the recommendations of Metz and colleagues should be followed.[37]

Normal $Sjvo_2$. Gibbs and coworkers studied 50 normal young males and observed that their $Sjvo_2$ ranged from 55% to 71% (mean, 61.8%; Table 48-2).[38] In head-injured patients, the average $Sjvo_2$ is higher than normal, and the range for $Sjvo_2$ is considerably wider than it is in normal subjects. In a series of 116 patients with continuous measurement of $Sjvo_2$ for the first 5 to 10 days after severe head injury,[39] $Sjvo_2$ averaged 68.1 ± 9.7% (range, 32% to 96%) in 1329 measurements. $Pjvo_2$ averaged 37 ± 7 mm Hg (range, 22 to 85 mm Hg).

Experimental studies have extensively examined the ischemic thresholds for CBF. Only a few studies have examined the $Sjvo_2$ threshold associated with the depletion of energy stores in animals and with loss of consciousness or electroencephalogram (EEG) changes during anoxia in normal humans.[40-42] From these studies, it appears that normal brain metabolism can be altered at $Sjvo_2$ values less than 50%, but that values less than 20% are required for irreversible ischemic injury.

LOCAL OR REGIONAL MONITORS

Transcranial Doppler Flow Velocity and Flow Volume

Transcranial Doppler ultrasonography is a noninvasive monitor that provides indirect information about CBF in one of the major arteries at the base of the brain. A 2-MHz pulsed ultrasound signal is transmitted through the skull (usually through the temporal bone) and, using the Doppler shift principle, measures red cell flow velocity. Flow volume is directly proportional to flow velocity and can be calculated by multiplying the velocity by the cross-sectional area of the vessel insonated.

Several studies have assessed the relationship between peak flow velocity and changes in CBF, suggesting that changes in middle cerebral artery flow velocity can be used as an indicator of relative changes in blood flow. Kofke and associates, investigating the relationship between middle cerebral artery flow velocity and CBF assessed by stable xenon CT during balloon test occlusion of the carotid artery in 31 patients, found a significant correlation in the alteration of

flow detected by the two methods.[43] More recently, changes in middle cerebral artery flow velocity and changes in CBF assessed by stable xenon CT in patients with various intracranial pathologies, including eight with closed-head injuries, showed a close correlation.[44]

In the absence of vessel stenosis or vasospasm or changes in arterial blood pressure or blood rheology, pulsatility reflects the distal cerebrovascular resistance. This resistance is usually quantified by the pulsatility (or Gosling) index, which is calculated as follows: (systolic flow velocity – diastolic flow velocity)/mean flow velocity. The pulsatility index (normal, 0.6 to 1.1) has been shown to correlate better with CPP than with ICP.

During arterial spasm, flow velocity increases through the narrowed segment proportional to the reduction in the vessel's diameter. Severe vasospasm, with a greater than 50% reduction in vessel diameter, is associated with a flow velocity greater than 200 cm/sec.[45] However, an increase in flow velocity may also reflect hyperemia, which often occurs as a post-traumatic event. To differentiate between these two hemodynamic phenomena in the absence of direct CBF measurements, the middle cerebral artery–extracranial internal carotid artery flow velocity ratio, also known as the Lindegaard or hemispheric index, can be measured. In the presence of hyperemia, a raised flow velocity in both extracranial and intracranial vessels does not alter the ratio; however, in vasospasm, flow velocity is high only in the intracranial vessels, resulting in a high hemispheric index. The mean hemispheric index in normal individuals is 1.76 ± 0.1, and pathologic values suggestive of vasospasm are generally above 3.[46]

Doppler devices that are capable of measuring the diameter of the vessel being insonated may be a better way to differentiate between these two hemodynamic causes of increased flow velocity by calculating flow volume. Flow volume of the internal carotid artery has a close correlation to hemispheric CBF measured by the ^{133}xenon clearance technique[47] and may be useful as a bedside estimation of hemispheric CBF.

Thermal Diffusion and Laser Doppler Methods

Two methods for continuously measuring local CBF are now commercially available: thermal diffusion and laser Doppler. Both methods are invasive, requiring that the probe be placed on the surface of the brain or in the brain parenchyma. Both methods measure CBF in only a small volume of brain, which may or may not be representative of the whole brain. However, the continuous nature of the measurements provides a dynamic picture of brain perfusion. Although there is extensive documentation of the reliability of these methods in the laboratory, there is limited experience in the ICU.[48-50] Especially for patients undergoing craniotomy, these may become practical methods for monitoring CBF postoperatively.

Thermal diffusion flowmetry uses heat transfer as a tracer in the measurement of blood flow. The sensor consists of two gold disks embedded in a 3-mm Silastic leaf. One disk is heated to slightly greater than brain temperature (to a maximum of 44° C), and the other is neutral. The probe is laid on the surface of the brain. The temperature difference between the two disks is monitored and converted to blood flow in milliliters/100 g per minute by the monitor, using a digital display. Carter and Atkinson[51] modified a thermal sensor described by Brawley[52] and were able to quantify the flow measured by the thermal sensor. They derived a mathematical formula by comparing thermal diffusion CBF with ^{133}xenon CBF[53] and confirmed the reliability through a comparison with hydrogen clearance.[54]

Gopinath and colleagues compared thermal diffusion CBF with global CBF values measured using the nitrous oxide saturation technique in a group of 35 patients with severe head injury.[55] As expected, the thermal diffusion CBF, which measures cortical flow, was significantly higher than the global CBF, which is a mixture of gray and white matter flow. However, there was a close temporal correlation between the two measures of CBF, and changes in thermal diffusion CBF reliably predicted a change in global CBF. These studies suggest that thermal diffusion CBF provides an accurate measure of local CBF under the probe and is a reasonable estimate of trend changes in global CBF.

Laser Doppler flowmetry is a technique whereby CBF is measured indirectly, based on the magnitude of frequency shift of monochromatic light by a moving column of blood. The laser light is directed at the region of interest through a small probe that illuminates about 1 mm^3 of tissue. With this high spatial resolution, it is designed primarily for measuring flow in capillaries.[56]

Brain Tissue Oxygen Partial Pressure

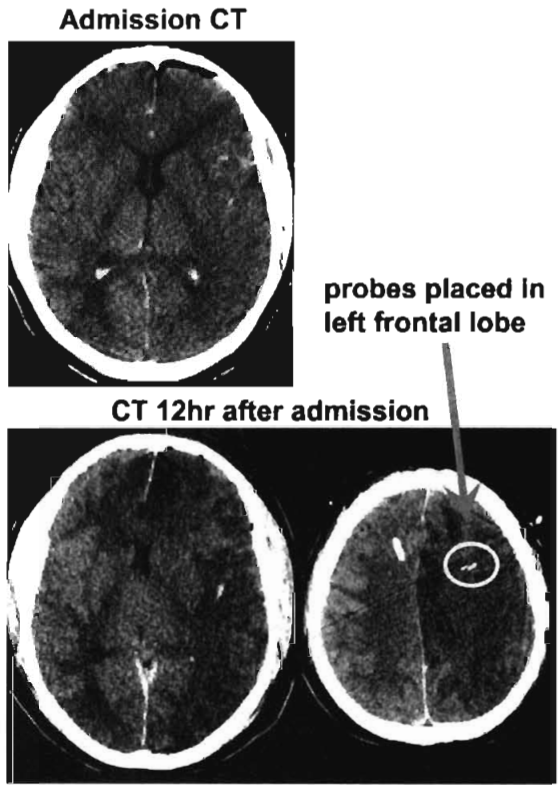
The major limitation of $Sjvo_2$ as a monitor of CBF adequacy is that regional ischemia is not identified. In cases of brain trauma, regional differences in CBF may occur, giving $Pbto_2$ an important advantage as a monitor of cerebral oxygenation.[57,58] Figure 48-1 illustrates the changes in $Pbto_2$ in a focal area of evolving ischemia. $Sjvo_2$ remains well preserved until the brain swelling from the infarction causes severe intracranial hypertension.

With recent technologic advances, two commercially available sensors have been produced. One sensor measures only brain tissue oxygen tension using a polarographic Clarke-type electrode; the other multiparameter sensor measures brain tissue oxygen, carbon dioxide, and pH using fiberoptic technology. Both these methods have the ability to measure brain temperature using a thermocouple. Both sensors are approximately 0.5 mm in diameter and can be inserted through a craniotomy intraoperatively or through a specially designed bolt that allows insertion and fixation to the skull in the ICU.

Normal values for $Pbto_2$ are 20 to 40 mm Hg, and critical levels are 8 to 10 mm Hg (see Table 48-2). Hoffman and coworkers, using single photon emission computed tomography, found that $Pbto_2$ in patients with ischemia averaged 10 ± 5 mm Hg, compared with 37 ± 12 mm Hg in normal brain.[59] Valadka and associates found that the likelihood of death following a severe head injury increased the longer the $Pbto_2$ remained at less than 15 mm Hg, and with any occurrence of $Pbto_2$ less than 6 mm Hg.[60] Kiening and colleagues correlated serial measurements of both $Sjvo_2$ and $Pbto_2$ and found that an $Sjvo_2$ of 50% generally correlates with a $Pbto_2$ of 8.5 mm Hg.[61]

Near-Infrared Spectroscopy

The principle of near-infrared spectroscopy is based on the fact that light in the near-infrared range (700 to 1000 nm) can pass through skin, bone, and other tissues relatively easily. Oxygenated hemoglobin, deoxygenated hemoglobin, and cytochrome aa_3 have different absorption spectra, depending on their oxygenation status. Changes in the concentration of



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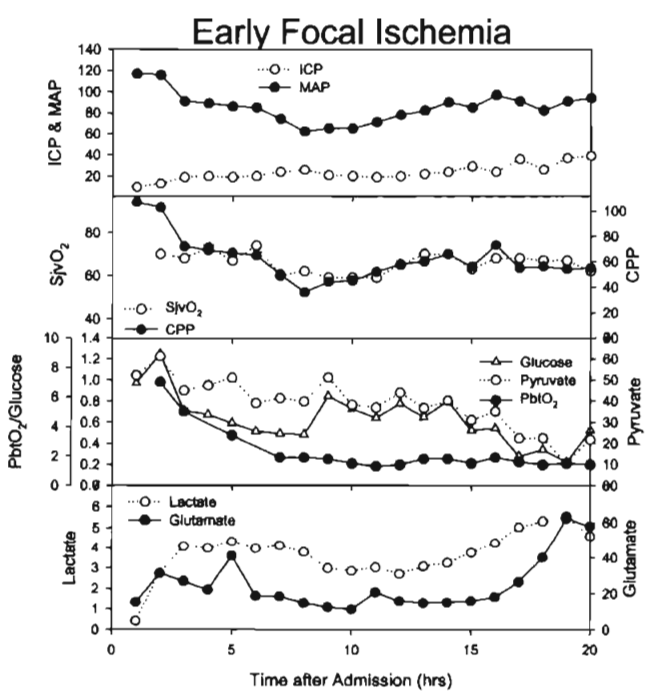

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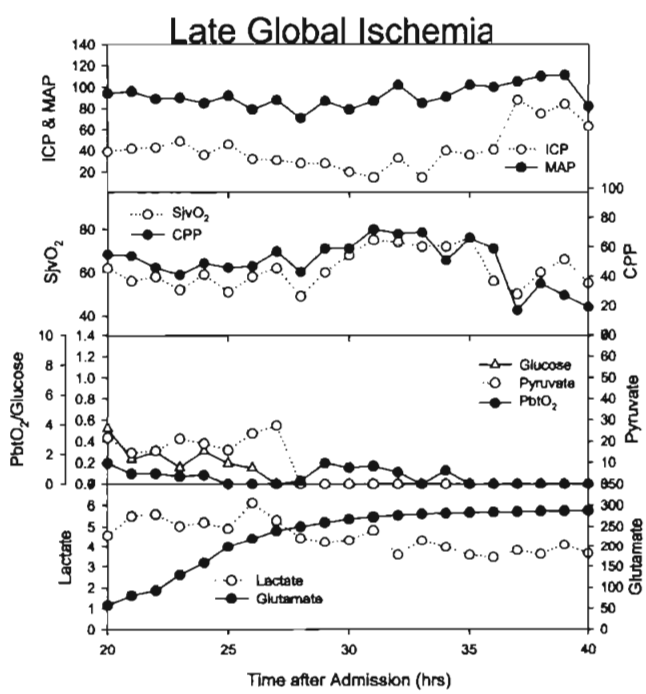

C

FIGURE 48–1. Monitoring in a patient with severe traumatic brain injury. Brain tissue oxygen partial pressure ($Pbto_2$) and microdialysis probes were placed in the left frontal lobe, where subarachnoid hemorrhage was present on the admission computed tomography (CT) scan. The $Pbto_2$ decreased, followed shortly by the microdialysate glucose and pyruvate. A follow-up CT scan showed a stroke developing in the brain surrounding the local probes. Cerebral perfusion pressure (CPP) and jugular venous oxygen saturation ($Sjvo_2$) provide measures of global cerebral perfusion, which is fairly well preserved until intracranial hypertension becomes severe and refractory to treatment. ICP, intracranial pressure; MAP, mean arterial pressure.

near-infrared light as it passes through these compounds can be quantified using a modified Beer-Lambert law, which describes optical attenuation. The main advantage of near-infrared spectroscopy is that it is a noninvasive method of estimating regional changes in cerebral oxygenation. However, its clinical use is limited by an inability to differentiate between intracranial and extracranial changes in blood flow and oxygenation, which adversely affects the reliability of the readings.[62]

MONITORING OF BRAIN METABOLISM

GLOBAL CEREBRAL METABOLIC RATE OF SUBSTRATES

The cerebral metabolic rate (CMR) of a substrate can be calculated by multiplying the arterial-jugular venous difference of the substrate by the global CBF. Measuring the CMR of oxygen, glucose, and lactate gives a comprehensive picture of

the brain's overall metabolism. However, the measurements are not continuous, and regional abnormalities may not be reflected.

Glucose is the major energy substrate for the brain. The average CMR of glucose in adults is 0.325 μmol/g per minute, and the gray matter has higher metabolic requirements than the white matter does. More than 90% of the normal brain's metabolic demands are met by aerobic metabolism of glucose through the glycolytic pathway, citric acid cycle, and respiratory chain, providing 38 moles of adenosine triphosphate per mole of glucose.

In the resting state, anaerobic glycolysis represents less than 10% of the total glucose usage, yielding only 2 moles of adenosine triphosphate and lactate per mole of glucose metabolized. Neuronal stimulation results in an increase in glucose metabolism compared with oxygen consumption, signifying the importance of glycolytic metabolism in electrical activation. Normally, there is a small production of lactate by the brain, and the mean CMR of lactate is –0.02 μmol/g per minute.

The normal CMR of oxygen in the healthy adult brain averages 3.4 mL/100 g per minute (1.5 μmol/g per minute) but may range from 1.8 to 3.9 mL/100 g per minute without neurologic sequelae. The CMR of oxygen increases minimally during changes in mental activity, with the increased energy expenditure being provided by the anaerobic metabolism of glucose. In acute neurologic disorders resulting in coma, the CMR of oxygen is typically reduced by about 50%. A CMR of oxygen less than 0.6 μmol/g per minute is insufficient to maintain normal cellular function.

MICRODIALYSIS

Microdialysis is a technique of sampling the extracellular space of a tissue. It is based on the diffusion of water-soluble substances through a semipermeable membrane. Small molecules (<20,000 Da) from the extracellular fluid can diffuse across the membrane and enter the perfusate. Conversely, substances that have been added to the perfusate can diffuse across the membrane to gain entry to the tissue. The degree of permeability of the membrane determines the molecular weight of the substances that cross it.

The concentration of substances in the dialysate depends on the flow rate and chemical composition of the perfusate, the length of the dialysis membrane, the type of dialysis membrane, and the diffusion coefficient or "tortuosity" of the tissue. The recovery of a particular substance is defined as the concentration in the dialysate divided by the concentration in the interstitial fluid. If the membrane is long enough and the flow slow enough, the concentration in the perfusate will be the same as that in the interstitial fluid (i.e., 100%). The parameters that are commonly used in clinical studies (i.e., 10-mm membrane, perfusion with Ringer's solution, and flow rate of 0.3 μL/min) provide an in vivo recovery rate (extrapolation to zero flow method) of approximately 70%.[63]

The technique of cerebral microdialysis allows continuous and on-line monitoring of changes in brain tissue chemistry. In common with brain tissue oxygenation monitoring, microdialysis involves inserting a fine catheter (diameter 0.62 mm) into the brain. The catheter has a polyamide dialysis membrane at the tip and is perfused with a physiologic solution (e.g., Ringer's) at ultra-low-flow rates (0.1 to 2.0 μL/min) using a precision pump. This allows measurement of the concentration of chemicals in the extracellular space of the brain. Molecules below the cutoff size of the semipermeable membrane (approximately 20,000 Da) diffuse from the extracellular space into the perfusion fluid, which is collected in vials that are changed every 10 to 60 minutes. The collected dialysate is then analyzed by sensitive assays.

In theory, any substance small enough to diffuse through the dialysis membrane can be measured,[63] but the key substances can be categorized as follows:

1. Energy-related metabolites (glucose, lactate, pyruvate, adenosine, xanthine)
2. Neurotransmitters (glutamate, aspartate)
3. Markers of tissue damage and inflammation (glycerol)
4. Exogenous substances (administered drugs)

Continuous on-line measurements of glucose, lactate, pyruvate, glutamate, and glycerol can be achieved using a bedside CMA600 microdialysis analyzer (CMA Microdialysis, Stockholm, Sweden). Cerebral microdialysis has been applied to patients in many different clinical situations, including those with head injury, subarachnoid hemorrhage, epilepsy, ischemic stroke, and tumor, as well as during neurosurgery.[64] Figure 48-1 illustrates the changes in these parameters that can be seen with evolving ischemia. Although the role of microdialysis as a reliable clinical tool in the ICU is not yet established, its usefulness as a research tool is undeniable.

MONITORING OF ELECTROENCEPHALOGRAPHIC ACTIVITY

An EEG represents spontaneous electrical activity of the cerebral cortex and is generated mainly by the summation of excitatory and inhibitory postsynaptic potentials of cortical neurons. It does not reflect activity in subcortical levels, cranial nerves, or the spinal cord. The electrical signal is amplified, filtered, and then displayed as either 8 or 16 channels (8 channels per hemisphere) to give an accurate representation of electrical activity throughout the cortex. EEG activity is usually interpreted in terms of frequency, amplitude, and location (focal or generalized activity).

To facilitate continuous EEG monitoring, several automated EEG processing systems have been developed. Power spectral analysis allows fast Fourier transformation of small intervals of an EEG to provide a graphic representation of the relative power content of the various frequency bands in each segment of the EEG. These spectral diagrams are then stacked to show how the frequency of the EEG alters with time to produce a compressed spectral array. This spectral analysis can also provide a single number (either the mean frequency or the frequency below which 95% of the signal lies) that can be tracked over time.

Cerebral function monitoring provides a single trace of total power that varies with both the amplitude and the frequency of raw EEG data. The cerebral function analyzing monitor is a similar method that produces displays of both amplitude and frequency and avoids the loss of information when these are processed together.

Use of EEGs in the ICU to detect early subclinical seizures may help reduce mortality and morbidity in status epilepticus.[65] Continuous EEG monitoring is also useful in detecting ischemic cerebral events, including vasospasm following subarachnoid hemorrhage and intracranial hypertension after head injury.[66] In sedated patients, EEGs may help detect

focal neurologic disease, especially in those who cannot be fully examined and in those who are too unstable to undergo neuroradiographic imaging. Metabolic suppression using intravenous anesthetic agents can be monitored using cerebral function monitoring, where burst suppression or isoelectricity is a useful endpoint to titrate suppression of cortical electrical activity.

CONCLUSION

Many tools are currently available for monitoring cerebral physiology. Some of these methods, such as ICP monitoring, have established roles in the management of critically ill patients. For other methods, such as microdialysis, their roles have yet to be determined. Clearly, the use of these advanced monitoring tools must be based on an understanding of the nature of the patient's neurologic disorder and a knowledge of the type of secondary injury processes that are likely to complicate the patient's course.

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Chapter 49
COMA

Joerg-Patrick Stübgen • Fred Plum

KEY POINTS

1. **Altered arousal** is due to an acute or subacute brain insult and reflects either diffuse and bilateral cerebral dysfunction, failure of the brainstemthalamic ascending reticular activating system, or both.
2. **Coma is not a permanent state.** Patients who survive evolve through and into altered behavioral states that reflect various degrees of recovery.
3. **Urgent steps are required to minimize additional brain damage** often before the cause of coma is definitely established.
4. The initial assessment must focus on vital signs to determine the appropriate resuscitation measures **(airway/breathing/circulation).**
5. When the patient's condition is stable, **clues to the cause of coma** must be sought from informative sources.
6. A **systematic, detailed examination** is necessary of the comatose patient, who is in no condition to describe past or current medical history.
7. The correct interpretation is required of neurologic signs that reflect the **integrity or impairment of brain functional levels** to determine the cause and evolution of coma.
8. The **categorization of coma** (supratentorial or infratentorial structural lesions, metabolic-toxic encephalopathy, or psychogenic unresponsiveness) is important in deciding the sequence of diagnostic and therapeutic steps that ensure the best possible patient outcome.
9. **CT is the most expedient imaging technique** to give rapid information about a brain structural lesion and its consequences.
10. Although the outcome of a comatose patient cannot be absolutely predicted, **a highly probable poor prognosis should be made within 24 hours after admission** to ration ICU services and protect families from false hope.
11. As a rule, patients in coma due to exogenous agents carry a favorable prognosis and patients in post-traumatic coma fare better than those in a medical coma.

Altered states of consciousness are a common reason for visits to the emergency department and admission to ICUs. Few problems are more difficult to manage than the unconscious patient because there are many potential causes of an altered mental status and the time for diagnosis and effective intervention is short. *Consciousness* is defined as the state of awareness of the self and the environment. The phenomenon of consciousness requires two intact and interdependent physiologic and anatomic components: (1) arousal (or wakefulness) and its underlying neural substrate, the ascending reticular activating system (ARAS) and diencephalon, and (2) awareness, which requires the functioning cerebral cortex of both hemispheres. Most disorders that acutely disturb consciousness are, in fact, impairments of arousal that create circumstances under which the brain's capacity for consciousness cannot be accurately assessed; in other words, failure of arousal renders it impossible to test awareness.

Alterations of arousal may be transient, lasting only several seconds or minutes (after seizures, syncope, and cardiac dysrhythmia), or sustained, lasting hours or longer. Four terms describe disturbed arousal of a patient. *Alert* refers to a normal state of arousal. *Stupor* describes a state of unarousability in which strong external stimuli can transiently restore wakefulness. Stupor implies at least a limited degree of cognitive activity accompanies the arousal, even if transient. *Coma* is characterized by an uninterrupted loss of the capacity for arousal. The eyes are closed, sleep-wake cycles disappear, and even vigorous stimulation elicits at best only reflex responses. *Lethargy* describes a range of behavior between arousal and stupor. Only the terms *alert* and *coma* have enough precision to be used without further qualification; possibly *coma* has gradations in depth, but this cannot be accurately assessed once the patient no longer responds to external stimuli. *Stupor* and *coma* imply an acute or subacute brain insult. The cerebral reserve capacity is large; therefore, altered consciousness reflects either diffuse and bilateral cerebral dysfunction, failure of the brainstem/thalamic ARAS, or both. All alterations in arousal should be regarded as acute and potentially life-threatening emergencies.

The evaluation of a comatose patient demands a systematic approach with appropriate, directed diagnostic and therapeutic endeavors; time should not be wasted on irrelevant considerations. Urgent steps are required to prevent or minimize permanent brain damage from reversible causes. Patient evaluation and treatment must necessarily occur simultaneously. Such a systematic approach demands an understanding of the pathophysiology of consciousness and mechanisms by which it may be deranged.

ANATOMY, PATHOLOGY, PATHOPHYSIOLOGY

Consciousness depends on an intact ARAS in the brainstem and adjacent thalamus that acts as the alerting or awakening element of consciousness together with a functioning cerebral cortex of both hemispheres that determines the content of that consciousness.[1,2] The ARAS lies within a more or less isodendritic core that extends from the medulla through the tegmentum of the pons to the midbrain and paramedian thalamus. The system is continuous caudally with the reticular intermediate gray matter of the spinal cord and rostrally with the subthalamus, the hypothalamus, the anterior thalamus, and the basal forebrain.[3] The ARAS itself arises within the rostral pontine tegmentum and extends across the mesencephalic tegmentum and its adjacent intrathalamic nuclei. ARAS functions and interconnections are considerable and likely contribute more than only a cortical arousal system. The specific role of the various links from the reticular formation to the thalamus has yet to be fully identified.[4] Furthermore, the cortex feeds back on the thalamic nuclei to contribute an important loop that amplifies arousal mechanisms.[5,6]

The ascending arousal system contains cholinergic, monoaminergic, and γ-aminobutyric acid (GABA) systems, none of which has been identified as the arousal neurotransmitter.[2,7,8] Acute structural damage to, or metabolic-chemical disturbance of, either the ascending brainstem/thalamic activating system or the thalamocorticothalamic loop can alter the aroused, attentive state. Consciousness depends on the continuous interaction between the mechanisms that provide arousal and awareness. The brainstem and thalamus provide the activating mechanism, and the cerebrum provides full cognition and self-excitation. Content of consciousness is best regarded as the amalgam and integration of all cognitive function that resides in the thalamocortical circuits of both hemispheres. Altered awareness is due to disruption of this cortical activity by diffuse pathology. Focal lesions of the cerebrum can produce profound deficits, such as aphasia, alexia, amnesia, and hemianopsia, but only diffuse bilateral damage, sparing the ARAS and diencephalon, can lead to wakeful unawareness. Thus, there are two kinds of altered consciousness: (1) altered arousal due to dysfunction of the ARAS-diencephalon and (2) altered awareness due to bilateral diffuse cerebral hemisphere dysfunction.

Four major pathologic processes can cause such severe, global, acute reductions of consciousness.[1,9] In the presence of diffuse or extensive multifocal bilateral dysfunction of the cerebral cortex, the cortical gray matter is diffusely and acutely depressed or destroyed. Concurrently, cortical-subcortical physiologic feedback excitatory loops are impaired, with the result that brainstem autonomic mechanisms become temporarily, profoundly inhibited, producing the equivalent of acute "reticular shock" below the level of the lesion.[2] Direct damage to a paramedian upper brainstem and posteroinferior diencephalic ascending arousal system blocks normal cortical activation.[3] Widespread disconnection between the cortex and subcortical activating mechanisms acts to produce effects similar to both these conditions.[4] Diffuse disorders, usually metabolic in origin, concurrently affect both the cortical and subcortical arousal mechanisms, although to a different degree according to the cause.

STRUCTURAL LESIONS CAUSING COMA

Intracranial mass lesions that cause coma may be located in the supratentorial or infratentorial compartments. From either location, impaired arousal or coma is caused by compression of the brainstem/hypothalamic activating mechanisms secondary to swelling and displacement of deep lying intracranial contents; the ultimate event occurs either by halting axoplasmic flow or by sustained neuronal depolarization because of ischemia or hemorrhage. Factors important to the degree of loss of arousal are the rate of development, the location, and the ultimate size of the lesion. Cerebral mass lesions distort the intracranial anatomy and thereby alter the cerebrospinal fluid (CSF) circulation and brain blood supply. These changes result in increased bulk of the injured tissue and a reduction in intracranial compliance.

Intercompartmental pressure gradients result in herniation syndromes that are not necessarily associated with large increases in intracranial pressure (ICP). Recently sustained or evolving mass lesions can disturb cerebrovascular autoregulation that results in abrupt, briefly lasting vasodilatation. This, in turn, causes recurrent increases in ICP (pressure waves), with additional compromise of cerebral blood supply to injured regions.

Two herniation syndromes demonstrate the mechanism by which *supratentorial lesions* produce coma. The rate of evolution of a mass dictates whether the anatomic distortion precedes (in slowly evolving lesions) or parallels the patient's deterioration of wakefulness. Transtentorial herniation can be central or predominantly unilateral. *Central herniation* results from caudal displacement by deep midline supratentorial masses, large space-occupying hemisphere lesions, or large unilateral or bilateral compressive extra-axial lesions, with compression of the ARAS. The progressive rostrocaudal clinical and pathologic stages of this herniation syndrome have been outlined.[1] Pathologically, bilateral symmetrical displacement of the supratentorial contents occurs through the tentorial notch into the posterior fossa. Alertness is impaired early, pupils become small (to 3 mm) and reactive, and bilateral upper motor neuron signs develop. Cheyne-Stokes breathing, grasp reflexes, roving eye movements, or depressed escape of oculocephalic reflexes are the clinical manifestations. In the absence of effective therapy at this diencephalic stage, herniation progresses caudally to compress the midbrain, leading to a deep coma and fixed, midposition (3 to 5 mm) pupils, signifying both sympathetic and parasympathetic interruption. Spontaneous eye movements cease and oculovestibular and oculocephalic reflexes become difficult to elicit. Spontaneous extensor posturing may occur. Once this stage is reached, full recovery becomes unlikely. As the caudal compression-ischemia process advances, pontine and medullary function becomes destroyed, with variable breathing patterns and absent reflex eye movements. Finally, autonomic cardiovascular and respiratory functions cease as medullary centers fail.

Uncus herniation results from laterally placed hemisphere lesions, particularly of the temporal lobes, which cause side-to-side cerebral displacement as well as transtentorial herniation. Focal hemisphere dysfunction (hemiparesis, aphasia, seizures) precedes unilateral (usually ipsilateral) compression paralysis of the third cranial nerve. An early sign of uncus herniation is an ipsilateral (rarely contralateral) enlarged pupil that responds sluggishly to light followed by a fixed,

dilated pupil and an oculomotor palsy (eye turned downward and outward).[1] The ipsilateral posterior cerebral artery can become compressed as it crosses the tentorium and causes ipsilateral occipital lobe ischemia. Progressively, the temporal lobe compresses the midbrain, with loss of arousal and bilateral or contralateral extensor posturing. Ipsilateral to the intracranial lesion, a hemiparesis may develop if the opposite cerebral peduncle becomes compressed against the contralateral tentorial edge (Kernohan's notch). Abnormal brainstem signs become symmetrical, and herniation proceeds in the same pattern seen with central herniation, as rostrocaudal brainstem displacement progresses.

Infratentorial lesions cause coma by displacement, compression, or direct destruction of the pontomesencephalic tegmental activating system. Displacement of the medulla downward sufficient to push the brainstem and cerebellar tonsils into the foramen magnum causes cardiorespiratory collapse. Acute intrinsic lesions of the brainstem, usually hemorrhagic or ischemic, cause abrupt onset of coma and are associated with abnormal neuro-ophthalmologic findings. Pupils are pinpoint, owing to disruption of pontine sympathetic pathways, or they are dilated, owing to destruction of the third cranial nerve nuclei or intra-axial exiting fibers. Dysconjugate eye movements and nystagmus occur, whereas vertical eye movements are relatively spared. Ocular bobbing signifies pontine damage. Upper motor neuron signs develop and patients can become quadriplegic; flaccidity in the upper extremities and flexor withdrawal responses in the lower extremities often accompany midbrain-pontine damage. Pathologically, *basilar artery occlusion* leads to asymmetric ischemia of the brainstem, with involvement of the ARAS, the neighboring densely packed neuropil, as well as the descending and ascending motor and sensory tracts. Thrombosis of the rostral basilar artery leads to infarction of the midline thalamic nuclei and brief coma without other obvious brainstem signs. Hemorrhage into the ventral pons sometimes spares consciousness but produces neuro-ophthalmologic signs and motor dysfunction. Extension of the hemorrhage into the rostral pontine tegmentum results in stupor, coma, or death. *Basilar artery migraine* can produce altered consciousness possibly by interfering with arterial blood flow in the basilar artery system. Rapidly developing, extensive central pontine myelinolysis may cause coma by extension into the pontine tegmentum. Other intrinsic brainstem lesions (e.g., tumor, abscess, granuloma, demyelination) tend to progress slowly and usually spare arousal mechanisms; however, they may reduce attention and other cognitive functions, leading to severe psychomotor retardation.

Extra-axial posterior fossa lesions cause coma by direct compression of the ARAS in the brainstem and in the diencephalon by upward transtentorial herniation. Compression of the pons may be difficult to distinguish from intrinsic lesions but is often accompanied by headache, vomiting, and hypertension due to a Cushing reflex. Upward herniation at the midbrain level is initially characterized by coma, reactive miotic pupils, asymmetric or absent caloric eye responses, and decerebrate posturing; caudal-rostral brainstem dysfunction then occurs, with midbrain failure and midposition, fixed pupils.[10] Causes of brainstem compression include cerebellar hemorrhage, infarction, and abscess; rapidly expanding cerebellar or fourth ventricle tumors; or, less commonly, infratentorial epidural or subdural hematomas. Drainage of the lateral ventricles to relieve obstructive hydrocephalus due to posterior fossa masses can potentially precipitate acute upward transtentorial herniation.[11,12]

Downward herniation of the cerebellar tonsils through the foramen magnum causes acute medullary dysfunction and abrupt respiratory and circulatory collapse. Less severe impaction of the tonsils in the foramen magnum can lead to obstructive hydrocephalus and consequent bihemispheric dysfunction with altered arousal. Clinical manifestations include headache, nausea, vomiting, lower cranial nerve signs, vertical nystagmus, ataxia, and irregular breathing. Lumbar puncture in this setting carries a risk of catastrophic consequences.[11]

NONSTRUCTURAL CAUSES OF COMA

Nonstructural disorders, such as metabolic or toxic disturbances, produce coma by diffusely depressing the function of the brainstem and cerebral arousal mechanisms. The anatomic locus of metabolic brain diseases has not been clearly defined. The onset of coma can be abrupt, as with toxic drug ingestion, general anesthesia, or cardiac arrest, or it may evolve slowly after a period of confusion and inattention. The chief manifestations of metabolic encephalopathy are disturbances in arousal and cognitive function. Other findings include abnormalities of the sleep-wake cycle, autonomic disturbances, and abnormal breathing variations.

A helpful distinguishing clinical feature of a diffuse encephalopathy is the preservation of the pupillary light response; the only exceptions are overdose of anticholinergic agents, near-fatal anoxia, or malingering. Usually, lack of pupillary reactivity requires a search for an underlying structural lesion. The neurologic examination shows a decreased level of arousal and a widespread cognitive decline. Deeply comatose patients without brainstem or hemisphere function and no known cause for coma must be assumed to have suffered accidental or intentional poisoning. Metabolic disturbances of arousal and cognition particularly affect elderly patients who suffer serious systemic illnesses or who have undergone complicated surgery.

Metabolic encephalopathy is clinically characterized by multilevel CNS dysfunction. At onset, abnormalities in cognition are at least as severe as the disturbance of arousal. Misperception, disorientation, hallucinations, concentration, and memory deficits, and, occasionally, hypervigilance, may progress to profound stupor and coma. The patient's level of arousal and consciousness often fluctuates between examinations. Motor abnormalities, if present, usually are symmetrical and bilateral. Patients often suffer tremor, asterixis, and multifocal myoclonus. Spontaneous motor activity may range from hypoactivity (in cases of sedating drug or endogenous metabolic disturbances) to hyperactivity (after drug withdrawal or overdose of stimulants, such as cocaine and phencyclidine). Seizures occasionally occur, particularly after alcohol or drug withdrawal, and in patients with established cortical pathology. Focal seizures may occur even without structural disease during hypoglycemia, hepatic encephalopathy, uremia, abnormal calcium levels, or toxin ingestion. Autonomic dysfunction can manifest as hypothermia due to hypoglycemia, myxedema, or sedative drug overdose. Hyperthermia can occur in withdrawal states, particularly delirium tremens, anticholinergic drug overdose, infection, neuroleptic malignant syndrome, or malignant hyperthermia.

The metabolic needs of the brain depend largely on the oxidation of glucose to carbon dioxide and water. Certain fatty

acids and ketone bodies can supply part of the metabolic needs in emergency circumstances, but these alternate fuels never provide an entirely sufficient substrate to meet all energy requirements. Normal cerebral blood flow (CBF) is around 55 mL/100 g tissue/min. With a CBF of less than 20 mL/100 g/min oxygen delivery becomes insufficient for normal levels of oxidative metabolism and cerebral glycolytic rate increases. Patients lose consciousness and the electroencephalogram (EEG) is suppressed owing to synaptic failure at CBF levels between 16 and 20 mL/100 g/min. The cortical evoked response is abolished below about 15 mL/100 g/min. At CBF around 8 mL/100 g/min the energy-dependent membrane pump fails and the membrane potential collapses. Unless CBF is restored promptly, irreversible neuronal injury will ensue. However, the threshold for ischemic neuronal injury is time dependent. Complete cessation of CBF leads to loss of consciousness in 8 seconds, and EEG suppression occurs at 10 to 12 seconds. Adenosine triphosphate exhaustion and ionic pump failure occurs in 120 seconds. Selective neuronal damage starts after periods as brief as 5 minutes, and severe neuronal damage occurs after 20 to 30 minutes. Brain necrosis or infarction starts in 1 to 2 hours.

Under physiologic conditions, glucose is the brain's only substrate and crosses the blood-brain barrier by facilitated transport. The normal brain uses about 55 mg glucose/100 g/min. If there is *hypoglycemia*, defined in adults as blood glucose concentration less than 40 mg/dL, signs and symptoms of encephalopathy result from dysfunction of the cerebral cortex before the brainstem. Neurologic presentation of hypoglycemia can vary from focal motor or sensory deficits to coma. Acute symptoms of hypoglycemia are better correlated with the rate at which blood glucose levels decrease than with the degree of hypoglycemia. The blood glucose level at which cerebral metabolism fails and symptoms develop varies among individuals, but, in general, confusion occurs at levels less than 30 mg/dL and coma at less than 10 mg/dL. The brain stores about 2 g of glucose and glycogen. Thus, a patient in hypoglycemic coma may survive 90 minutes without suffering irreversible brain damage. The pathophysiology of coma from hypoglycemia is not well understood. The disorder cannot solely be attributed to glucose starvation of neurons. Rather than such an internal catabolic death, evidence suggests than neurons are killed from without. Around the time the EEG becomes isoelectric, endogenous neurotoxins are produced and released by the brain into tissue and CSF. The distribution of necrotic neurons is unlike that of ischemia and is related to white matter and CSF pathways. The toxins act by first disrupting dendritic trees, sparing the intermediate axons, an indication of excitotoxic neuronal injury. The exact mechanism of excitotoxic neuronal necrosis is now becoming clear and involves hyperexcitation culminating in cell membrane rupture. Also, during hypoglycemia, the synthesis is suppressed of amino acids such as GABA, glutamate, glutamine, and alanine, as well as acetylcholine. Whether reduction of these molecules or alteration in nerve synaptic transmission significantly contributes to the onset of coma associated with severe hypoglycemia is not established.

The pathophysiology of other metabolic encephalopathies is less well established and is extensively discussed elsewhere.[1] *Hepatic encephalopathy* is caused not merely by ammonia intoxication but likely also involves accumulation of neurotoxins such as short- and medium-chain fatty acids, mercaptans, and phenols. Altered neurotransmission may play a role with accumulation of benzodiazepine-like substances, imbalance of serotonergic and glutaminergic neurotransmission, and the accumulation of false neurotransmitters. The identity of the neurotoxin in *uremic encephalopathy* is uncertain and includes urea itself, guanidine and related compounds, phenols, aromatic hydroxy acids, amines, various peptide "middle-molecules," myoinositol, parathormone, and amino acid imbalance. The cause of the dysequilibrium syndrome may entail more than osmotic water shifts from plasma into brain cells, and reduction is reported in cortical potassium, with intracellular acidosis due to increased production of organic acids in the brain. The pathogenesis of *pancreatic encephalopathy* may involve patchy demyelination of brain white matter owing to liberated enzymes from a damaged pancreas, disseminated intravascular coagulation, or fat embolism.

The mechanism of action of exogenous toxins or drugs depends partly on the structure and partly on the dose. As well as can be determined, none of the sedatives taken acutely produces permanent damage to the nervous system, making prompt diagnosis and effective treatment particularly important.

DIFFERENTIAL DIAGNOSIS

Several different behavioral states appear similar to, and can be confused with, coma. Differentiation of such states from true coma has important diagnostic, therapeutic, and prognostic implications. Moreover, coma is not a permanent state; patients who survive initial coma may evolve through and into these altered behavioral states. All patients who survive beyond the stage of acute, systemic complications reawaken and either proceed to recovery (with no or varying degrees of disability) or remain in a vegetative state.

The vegetative state can be defined as wakefulness without awareness and is the consequence of various diffuse brain insults.[1,13] It may be a transient phase through which patients in coma pass as the cerebral cortex recovers more slowly than the brainstem. Clinically, vegetative patients appear to be awake and to have cyclical sleep patterns; however, such individuals do not show evidence of cognitive function or learned behavioral responses to external stimuli. Vegetative patients may feature spontaneous eye opening and eye movements and stereotypic facial and limb movements; however, they are unable to speak or comprehend and they lack purposeful activity. Vegetative patients generate normal body temperature, usually have normally functioning cardiovascular, respiratory, and digestive systems, but are doubly incontinent. The vegetative state should be termed persistent at 1 month after injury and permanent at 3 months after nontraumatic injury or 12 months after a traumatic injury.[14,15] Extended observation of the patient is required to assess behavioral responses to external stimulation and to demonstrate cognitive unawareness. The EEG is never isoelectric but shows various patterns of rhythm and amplitude, inconsistent from one patient to the next. Normal EEG sleep-wake patterns are absent.

In *the locked-in syndrome*, patients retain or regain arousability and self-awareness but because of extensive bilateral paralysis (i.e., de-efferentation) can no longer communicate except in severely limited ways. Such patients suffer bilateral ventral pontine lesions with quadriplegia, horizontal gaze palsies, and lower cranial nerve palsies. Voluntarily, they are capable only of vertical eye movements and/or blinking.[1]

Sleep may be abnormal with marked reduction in non-rapid-eye-movement and rapid-eye-movement sleep phases. The most common cause is pontine infarction due to basilar artery thrombosis, but other causes are pontine hemorrhage, central pontine myelinolysis, and brainstem mass lesions. Neuromuscular causes of locked-in syndrome include severe, acute inflammatory demyelinating polyradiculoneuropathies, myasthenia gravis, botulism, and neuromuscular blocking agents. In these peripheral disorders, upward gaze is not selectively spared.

Akinetic mutism describes a rare subacute or chronic state of altered behavior in which an alert-appearing patient is both silent and immobile but not paralyzed.[16] External evidence of mental activity is unobtainable. The patient usually lies with eyes opened and retains cycles of self-sustained arousal, giving the appearance of vigilance. Skeletal muscle tone can be normal or hypertonic but usually not spastic. Movements are rudimentary even in response to unpleasant stimuli. Affected patients are usually doubly incontinent. Lesions that cause akinetic mutism may vary widely. One pattern consists of bilateral damage to frontal lobe or limbic-cortical integration with relative sparing of motor pathways. Vulnerable areas involve both basal medial frontal areas. Somewhat similar behavior also can follow incomplete lesions of the deep gray matter (paramedian reticular formation of the posterior diencephalon and adjacent midbrain), but such patients usually suffer double hemiplegia and act slowly yet are not completely akinetic or noncommunicative.

Catatonia is a symptom complex associated most often with psychiatric disease. This behavioral disturbance is characterized by stupor or excitement and variable mutism, posturing, rigidity, grimacing, and catalepsy. Catatonia can be caused by a variety of illnesses, both psychiatric (affective more than psychotic) disorders and structural or metabolic diseases (toxic- and drug-induced psychosis, encephalitis, and alcoholic degeneration). Psychiatric catatonia may be difficult to distinguish from organic disease because patients often appear lethargic or stuporous rather than totally unresponsive. Such patients also may have a variety of endocrine or autonomic abnormalities. Patients in catatonic stupor do not move spontaneously and appear unresponsive to the environment despite what appears to be a normal level of arousal and consciousness. This impression is supported by a normal neurologic examination and a subsequent recall of most events that took place during the unresponsive period. Patients usually lie with eyes opened and may not blink to visual threat, but one can usually elicit optokinetic responses. The pupils are semi-dilated and reactive to light, oculocephalic reflexes are absent, and vestibulo-ocular testing evokes normal nystagmus. Patients may hypersalivate and be doubly incontinent. Passive movement of the limbs meets with waxy flexibility, and catalepsy is seen in 30% of patients. Choreiform jerks of the extremities and facial grimaces are common. The EEG, both of catatonic excitement and stupor, most often shows a reactive, low-voltage, fast-normal record rather than the slow record of a comatose patient.

APPROACH TO COMA

The initial approach to stupor and coma is based on the principle that all alterations in arousal are acute, life-threatening emergencies. Urgent steps are required to prevent or minimize permanent brain damage from reversible causes often before the cause of coma is definitely established. Patient evaluation and treatment must necessarily occur simultaneously. Serial examinations are needed with accurate documentation to determine a change in state of the patient. Accordingly, management decisions (therapeutic and diagnostic) must be made. The clinical approach to an unconscious patient logically entails the following steps: (1) emergency treatment; (2) history (from relatives, friends, and emergency medical personnel); (3) general physical examination; (4) neurologic profile, the key to categorizing the nature of coma; and (5) specific management.

EMERGENCY MANAGEMENT

The initial assessment must focus on the vital signs to determine the appropriate resuscitation measures; the diagnostic process begins later. Urgent, and sometimes empirical, therapy must be given to avoid additional brain insult.

Oxygenation must be ensured by the establishment of an airway and ventilation of the lungs. The threshold for intubation should be low in the comatose patient, even if respiratory function is sufficient for proper ventilation and oxygenation: the level of consciousness may deteriorate and breathing may decompensate suddenly and unexpectedly. An open airway must be ensured and protected from aspiration of vomitus and blood. While preparing for intubation, maximal oxygenation can be ensured by suction of the upper airway, gentle extension of the neck, elevation of the jaw, and manual ventilation with oxygen using a mask and bag. Bag-valve mask ventilation with 100% oxygen and 1 mg of atropine given intravenously helps prevent cardiac dysrhythmias. If a severe neck injury is a possibility, or has not been excluded, intubation should be performed by the most skilled practitioner with cervical spine precautions. A brief neurologic examination is mandatory before sedation required for intubation.

The key points of the "rapid neurologic examination" are hand drop from over the head (to assess for malingering or hysterical loss of consciousness); pupillary size and response to light; abnormal eye movements (active dysconjugate, unilaterally paralytic, passively induced, or absent); grimacing and withdrawal from noxious stimulation; and abnormal plantar response (unilateral or bilateral Babinski's sign).[17] Assisted ventilation should continue during the examination if necessary. Neuromuscular blockade required for patient management and care should be deferred, if possible, until the neurologic examination is completed (3 to 5 minutes). Signs of arousal or inadequate sedation include dilated, reactive pupils, copious tears, diaphoresis, tachycardia, systemic hypertension, and increased pulmonary artery pressure. Thereafter, monitoring patients neurologically may require head CT more frequently.

Evaluate *respiratory excursions:* arterial blood gas measurement is the only certain method to determine adequate ventilation and oxygenation. Pulse oximetry is useful, however, because it provides immediate, continuous information regarding arterial oxygen saturation. The comatose patient ideally should maintain a PaO_2 greater than 100 mm Hg and a $PaCO_2$ between 34 and 37 mm Hg. Hyperventilation ($PaCO_2 < 35$ mm Hg) should be avoided unless herniation is suspected. Positive end-expiratory pressure (PEEP) should be avoided if increased ICP is suspected, unless hypoxemia is not responsive to supplemental oxygen. Place a nasogastric tube to facilitate gastric lavage and prevent regurgitation.

Maintain *circulation* to ensure adequate cerebral perfusion. Appropriate resuscitation fluid is lactated Ringer's solution;

normal saline is also used when intracranial hypertension is suspected. A mean arterial pressure at about 100 mm Hg is adequate and safe for most patients. While obtaining venous access, collect blood samples for anticipated tests (Table 49-1). Treat hypotension by replacing any blood volume loss, and use vasoactive agents (preferably dopamine). Judiciously manage systemic hypertension with hypotensive agents that do not substantially raise ICP by their vasodilating effect (labetalol, hydralazine, or a titrated nitroprusside infusion are the favored agents for managing uncontrollable hypertension). For most situations systolic blood pressure should not be treated unless it is greater than 160 mm Hg. Maintain urine output at at least 0.5 mL/kg/h; accurate measurement requires bladder catheterization.

Glucose (and *thiamine*) levels need to be determined. Hypoglycemia is a frequent cause of altered consciousness; administer glucose (25 g as a 50% solution i.v.) immediately after drawing blood for baseline values. Empirical glucose treatment will prevent hypoglycemic brain damage and outweighs the theoretical risks of additional harm to the brain in hyperglycemic, hyperosmolar, or anoxic coma. Thiamine (100 mg) must be given with the glucose infusion to prevent precipitation of Wernicke's encephalopathy in malnourished, thiamine-depleted patients. Rarely, an established thiamine deficiency can cause coma.

Repeated generalized *seizures* damage the brain and must be stopped. Initial treatment should include intravenous benzodiazepines, lorazepam (2 to 4 mg), or diazepam (5 to 10 mg). Seizure control can be maintained with phenytoin (18 mg/kg i.v. at a rate of 25 mg/min). Seizure breakthrough requires additional benzodiazepines.

Careful and mild *sedation* should be given to the agitated, hyperactive patient to prevent self-injury. Sedation facilitates ventilator support and diagnostic procedures. Small doses of intravenous benzodiazepines, intramuscular haloperidol (1 mg as often as hourly until desired effect), or morphine (2 to 4 mg, i.v.) are appropriate.

Consider specific *antidotes.* Drug overdose is the largest single cause (30%) of coma in the emergency department. Most drug overdoses can be treated by supportive measures alone. However, certain antagonists specifically reverse the effects of coma-producing drugs. Naloxone (0.4 to 2 mg i.v.) is the antidote for opiate coma. The reversal of narcotic effect, however, may precipitate acute withdrawal in an opiate addict. In suspected opiate coma the minimal amount of naloxone should be administered to establish the diagnosis by pupillary dilatation and to reverse respiratory depression and coma. Do not attempt to reverse completely all drug effects with the first dose. Intravenous flumazenil reverses all benzodiazepine-induced coma. Coma unresponsive to 5 mg of flumazenil in divided doses given over 5 minutes is not due to benzodiazepine overdose. Recurrent sedation can be prevented with flumazenil (1 mg i.v.) every 20 minutes.[18] The sedative effects of drugs with anticholinergic properties, particularly tricyclic antidepressants, can be reversed with physostigmine (1 to 2 mg i.v.). Pretreatment with 0.5 mg of atropine will prevent bradycardia. Only full awakening is characteristic of an anticholinergic drug overdose, because physostigmine has nonspecific arousal properties. Physostigmine has a short duration of action (45 to 60 minutes), and doses may have to be repeated.

Adjust *body temperature.* Hyperthermia is dangerous because it increases brain metabolic demand and, at extreme levels, denatures brain proteins.[19] Hyperthermia greater than 40° C requires nonspecific cooling measures, even before the underlying etiology is determined and treated. Hyperthermia most often indicates infection, but it may be due to intracranial hemorrhage, anticholinergic drug intoxication, or heat exposure. A body temperature of less than 34° C should be slowly increased to greater than 35° C to prevent cardiac dysrhythmia. Hypothermia accompanies profound sepsis, sedative-hypnotic drug overdose, near-drowning, hypoglycemia, or Wernicke's encephalopathy.

TABLE 49–1. EMERGENCY LABORATORY TESTS OF METABOLIC COMA

Immediate Tests

Venous Blood
Glucose
Electrolytes (Na^+, K^+, Cl^-) and CO_2, PO_4
Urea and creatinine
Osmolality

Arterial Blood (check color)
pH
Po_2
Pco_2
HCO_3^-
HbCO (if available)

Cerebrospinal Fluid
Gram stain
Cell count
Glucose

Electrocardiogram

Deferred Tests (initial sample, process later)

Venous Blood
Sedative and toxic drugs
Liver function tests
Coagulation studies
Thyroid and adrenal function
Blood cultures
Viral titers

Urine
Sedative and toxic drugs
Culture

Cerebrospinal Fluid
Protein
Culture
Viral and fungal titers

HISTORY

Once vital functions have been protected and the patient's condition is stable, clues to the cause of coma must be sought by interviewing relatives, friends, bystanders, or medical personnel who may have observed the patient before or during the decline in consciousness. The history should include:

- Witnessed events—head injury; seizure; details of a motor vehicle accident; circumstances under which the patient was found.
- Evolution of coma—abrupt or gradual; headache; progressive or recurrent weakness; vertigo; nausea and vomiting.
- Recent medical history—surgical procedures; infections; current medication.
- Past medical history—epilepsy; head injury; drug or alcohol abuse; stroke; hypertension; diabetes; heart disease; cancer; uremia.

- Previous psychiatric history—depression; suicide attempts; social stresses.
- Access to drugs—sedatives; psychotropic drugs; narcotics; illicit drugs; drug paraphernalia; empty medicine bottles.

GENERAL PHYSICAL EXAMINATION

A systematic, detailed examination is helpful and necessary in the approach to the comatose patient who is in no condition to describe prior or current medical problems. This examination is an extension of the initial evaluation and includes the following:

- The repeated assessment of vital signs to determine efficacy of resuscitation measures
- External evidence of trauma
- Evidence of acute or chronic medical illnesses
- Evidence of ingestion or self-administration of drugs (needle marks, alcohol on breath)
- Evaluation for nuchal rigidity. Care is required if severe neck injury is possible or has not been excluded. (Nuchal rigidity may disappear in deeply comatose patients with meningeal infection/inflammation.)

NEUROLOGIC PROFILE

The establishment of the nature of coma is critical for appropriate management and requires the following:

- The correct interpretation of neurologic signs that reflect the integrity, or impairment, of various functional levels of the brain
- Determination whether the pattern and evolution of these signs are best explained by a supratentorial or infratentorial structural lesion, a metabolic-toxic encephalopathy, or a psychiatric cause (Tables 49-2 and 49-3)

The clinical neurologic functions that provide the most useful information in making a categorical diagnosis are outlined in Table 49-4. These indices are easily and quickly obtained. Furthermore, they have a high degree of interexaminer consistency and, when applied serially, they accurately reflect the patient's clinical course. Once the cause of coma can be assigned to one of these categories, specific radiographic, electrophysiologic, or chemical laboratory studies can be used to make a disease-specific diagnosis and to detect existing or potential complications.

TABLE 49–2. NEUROLOGIC PROFILE (A MODIFIED GLASGOW COMA SCALE)

Verbal Response
Oriented speech
Confused conversation
Inappropriate speech
Incomprehensible speech
No speech
Eye Opening
Spontaneous
Response to verbal stimuli
Response to noxious stimuli
None
Motor Response
Obeys
Localizes
Withdraws (flexion)
Abnormal flexion
Abnormal extension
None
Pupillary Reaction
Present
Absent
Spontaneous Eye Movement
Orienting
Roving conjugate
Roving dysconjugate
Miscellaneous abnormal movements
None
Oculocephalic Response
Normal (unpredictable)
Full
Minimal
None
Oculovestibular Response
Normal (nystagmus)
Tonic conjugate
Minimal or dysconjugate
None
Deep Tendon Reflexes
Normal
Increased
Absent

SPECIFIC MANAGEMENT

Supratentorial Mass Lesions

If the cause of coma is a presumed supratentorial mass, determine the severity and rate of evolution of signs. A stabilized patient next requires an emergency head CT or MRI. Carotid angiography is considerably less informative; a skull radiograph is a waste of time. The priority in deep coma or established/threatening transtentorial herniation is to apply successfully medical treatment of intracranial hypertension. Brief hyperventilation to a $PaCO_2$ between 25 and 30 mm Hg is the most rapid method to reduce intracranial hypertension. This is achieved by adjusting the ventilation rate to 10 to 16 breaths/min and tidal volume to 12 to 14 mL/kg. An osmotic agent must be administered concurrently. Sustained hyperventilation at less than 30 to 35 mm Hg removes all future value of this procedure. The preferred osmotic agent is a 20% mannitol solution as a 1g/kg intravenous bolus. Maximum reduction in ICP occurs within 20 to 60 minutes, and the effect of a single bolus lasts about 6 hours. Corticosteroids are not indicated in the emergent, empirical management of increased ICP, because full effects are observed only after a few hours. Furthermore, because corticosteroids are effective only for certain lesions (e.g., edema around a brain tumor or abscess), use can be delayed until a diagnosis has been made by head CT. After such initial ICP management, a head CT or MRI is required. The scan will demonstrate the nature of the supratentorial lesion and associated mass effect. Arrangements must be made to evacuate promptly an epidural or subdural hematoma. Intraparenchymal masses that acutely

TABLE 49–3. CORRELATION BETWEEN LEVELS OF BRAIN FUNCTION AND CLINICAL SIGNS

Structure	Function	Clinical Sign
Cerebral cortex	Conscious behavior	Speech (including any sounds) Purposeful movement Spontaneous To command To pain
Brainstem activating and sensory (reticular activating system) pathways	Sleep/wake cycle	Eye opening Spontaneous To command To pain
Brainstem motor pathways	Reflex limb movements	Flexor posturing (decorticate) Extensor posturing (decerebrate)
Midbrain CN III	Innervation of ciliary muscle and certain extraocular muscles	Pupillary reactivity
Pontomesencephalic MLF	Connects pontine gaze center with CN III nucleus	Internuclear ophthalmoplegia
Upper pons CN V CN VII	 Facial and corneal Facial muscle innervation	 Corneal reflex-sensory Corneal reflex-motor response Blink Grimace
Lower pons CN VIII (vestibular portion) connects by brainstem pathways with CN III, IV, and VI	 Reflex eye movements	 Doll's eyes Caloric responses
Pontomedullary junction	Spontaneous breathing Maintained blood pressure	Breathing and blood pressure do not require mechanical or chemical support
Spinal cord	Primitive protective responses	Deep tendon reflexes Babinski response

CN, cranial nerve.

produce deep stupor or coma initially are best managed nonsurgically. When corticosteroids are indicated for severe vasogenic edema, a dexamethasone bolus should be given (up to 100 mg i.v.), followed by 6 to 24 mg every 6 hours. Once signs of herniation have abated, the ventilator rate should be carefully reduced to achieve a $PaCO_2$ of 34 to 37 mm Hg.

The patient's vital signs and neurologic condition require repeated examination. The head should be kept slightly elevated (15 degrees). Mannitol may be repeated, if necessary, every 4 to 6 hours; serum electrolytes and fluid balance must be monitored.

When patients with presumed increased ICP do not respond clinically as expected to medical management, or when obstructive hydrocephalus complicates a supratentorial mass lesion, we favor placement of a ventriculostomy into the lateral ventricle. The ventriculostomy allows accurate measurement of intraventricular ICP and provides a method for CSF drainage, if necessary. The placement of a ventriculostomy allows calculation of cerebral perfusion pressure (CPP) (mean systemic arterial pressure minus ICP), a critical determinant of CBF and, therefore, of oxygen and substrate delivery. Monitoring of ICP also allows adjustment of therapeutic intervention before clinical deterioration occurs in patients with diminished intracranial compliance. Drainage of CSF aims to relieve raised ICP to maintain CPP (greater than 60 mm Hg) and to improve intracranial compliance. After increased ICP has responded to emergency management and the patient's condition has stabilized, definitive treatment of the mass lesion is required as deemed appropriate.

TABLE 49–4. CHARACTERISTICS OF CATEGORIES OF COMA

Supratentorial Mass Lesion Affecting the Diencephalon/Brainstem

Initial focal cerebral dysfunction
Dysfunction progresses rostral to caudal
Signs reflect dysfunction at one level
Signs often asymmetric

Infratentorial Structural Lesion

Symptoms of brainstem dysfunction or sudden-onset coma
Brainstem signs precede/accompany coma
Cranial nerve and oculovestibular dysfunction
Early onset of abnormal respiratory patterns

Metabolic-Toxic Coma

Confusion/stupor precede motor signs
Motor signs usually symmetrical
Pupil responses generally preserved
Myoclonus, asterixis, tremulousness, and generalized seizures common
Acid-base imbalance common with compensatory ventilatory changes

Psychogenic Coma

Eyelids squeezed shut
Pupils reactive or dilated, unreactive (cycloplegics)
Oculocephalic reflex unpredictable; nystagmus on caloric tests
Motor tone normal or inconsistent
No pathologic reflexes
(Awake-pattern EEG)

Infratentorial Lesions

The evolution of neurologic symptoms and signs and the neurologic examination generally give sufficient information to localize the lesion to the posterior fossa; the lesions themselves may be intrinsic or extrinsic to the brainstem.

Rapid neurologic deterioration of a patient suspected of harboring an infratentorial lesion sometimes demands emergency treatment before CT of the head is performed.

Treatment of a presumed extrinsic compressive lesion of the brainstem entails measures that decrease ICP as outlined earlier. Patients who are stuporous or showing signs of progressive brainstem compression from a cerebellar hemorrhage or infarction require urgent evacuation of the lesion. Intrinsic brainstem lesions are best treated conservatively; an incompleted stroke may benefit from thrombolysis and/or heparin anticoagulation. Posterior fossa tumors are managed initially with osmotic agents and corticosteroids; definitive treatment includes surgery and/or radiation. The placement of a ventricular catheter for acute hydrocephalus must be considered cautiously and in consultation with a neurosurgeon; the danger exists of potentially fatal upward transtentorial herniation.[12]

Metabolic Toxic Coma

The task of the physician in first contact with the patient in metabolic coma is to preserve and protect the brain from permanent damage. Metabolic and toxicologic studies must be performed on the first blood sample drawn (see Table 49-1). There are several treatable conditions that quickly and irreversibly damage the brain.

Hypoglycemia. As noted earlier, glucose (50 mL of a 50% solution i.v.) should be administered during emergency treatment before blood results return. Prolonged hypoglycemic coma that has considerably damaged the brain will not be reversed by a glucose load; a glucose bolus may transiently worsen hyperglycemic, hyperosmolar coma. In contrast, the osmolar load of intravenous glucose may transiently decrease elevated ICP and lighten nonhypoglycemic coma. A glucose infusion is needed to prevent recurrent hypoglycemia.

Acid-Base Imbalance. The hyperventilating comatose patient with acute, severe metabolic acidosis and threatening cardiovascular collapse requires emergency treatment. For accurate assessment an arterial blood gas is required. Administration of sodium bicarbonate (1 mEq/kg i.v.) can be life saving; simultaneously, a search for, and specific treatment of, the cause must be conducted.

Hypoxia. Carbon monoxide poisoning requires hyperoxygenation with 100% oxygen to facilitate excretion of this toxin. Closely monitor and correct blood pressure and cardiac rhythm abnormalities. Idiopathic and drug-induced methemoglobinemia is treated with methylene blue (1 to 2 mg/kg i.v. over a few minutes; repeat dose after 1 hour if needed). Anemia alone does not cause coma but exacerbates other forms of hypoxemia. Transfusion of packed red cells is appropriate for severe anemia (hematocrit < 25%). Cyanide poisoning causes histotoxic hypoxia of the brain. Treatment entails amyl nitrite (vapor or crushed ampule inhaled every minute), sodium nitrite (300 mg i.v.) followed by sodium thiosulfate (12.5 g i.v.).

Acute Bacterial Meningitis. A lumbar puncture must be considered in any unconscious patient with fever and/or signs of meningeal irritation. If possible, an emergency head CT should be performed before lumbar puncture on a comatose patient to rule out unexpected mass lesions. Increased ICP is present in all cases of bacterial meningitis, but a lumbar puncture is not contraindicated when this diagnosis is suspected. Cerebral herniation seldom, if ever, occurs except in small children.[20] Clinical correlates of impending herniation demand a more cautious approach to lumbar puncture: coma or rapidly deteriorating level of arousal, focal neurologic signs, and tonic or prolonged seizures. Papilledema is rare in acute bacterial meningitis. Should unexpected herniation occur after lumbar puncture, treatment with hyperventilation and intravenous mannitol is indicated. Appropriate antibiotic treatment can usually await the results of CSF Gram stain. If the Gram stain is negative yet a bacterial cause is suspected, empirical, broad-spectrum antibiotic treatment with a third-generation cephalosporin and vancomycin is appropriate.

Drug Overdose. Certain general principles apply to all patients suspected of having ingested sedative drugs.[21,22] Most drug overdose is treated by emergent and supportive measures (see Table 49-5). Once vital signs are stable, attempts should be made to remove, neutralize, or reverse the effects of the drug. Patients in coma from recent drug ingestion require gastric lavage after endotracheal intubation. A large, preferably double-lumen, gastric tube must be placed orally. The lavage is performed in the head-down position on the left side. Lavage is performed with 200 to 300 mL bolus of tap water or 0.45% saline and continued until the return is clear. After lavage, 1 or 2 tablespoons of activated charcoal is passed down the lavage tube. With meticulous supportive measures, patients with uncomplicated drug-induced coma should recover without neurologic deficit. The recovery from coma due to massive doses of barbiturates or glutethimide can be hastened by hemodialysis.

Constant vigilance and attention to the patient's condition, with timely and appropriate diagnostic and therapeutic evaluation, ensures the best possible outcome of metabolic coma. Effective care demands meticulous attention to the maintenance of tissue perfusion and oxygenation, the documentation and anticipation of acute neurologic events (particularly diminished cerebral perfusion, herniation, or seizures), aggressive, rapid treatment of initial or subsequent infections, and prevention of agitation. Deep venous thrombosis can be prevented with either subcutaneous heparin (5000 units q 12h) or full-length leg pneumatic compression boots. Enteral or parenteral feeding within 36 to 48 hours is required to satisfy nutritional needs. Corneal injury can be prevented by protecting the eyes with lubricants and taping the lids shut.

THE ROLE OF SPECIAL INVESTIGATIONS

NEURODIAGNOSTIC IMAGING

Once the patient with an altered mental status is appropriately resuscitated and stabilized, further investigation may be necessary to document the location and type of the lesion and to provide guidance for therapeutic intervention. CT and MRI provide an anatomic and/or functional assessment of the central nervous system (CNS) and provide helpful information for defining the localization of lesions that produce coma. For details on the use of these modalities in neurointensive care, see Chapter 48.

Cranial CT is currently the most expedient imaging technique in the comatose patient and gives the most rapid information about possible structural lesions with the least risk. The value of CT to demonstrate mass lesions, hemorrhage, and hydrocephalus is well established. CT shows tissue shifts due to intracranial intercompartmental pressure gradients but compared with MRI may underestimate the anatomy of herniation.[11] Certain lesions such as early infarction (less than 12 hours' duration), encephalitis, and isodense subdural hemorrhage may be difficult to visualize. Posterior fossa pathology may be somewhat obscured by bone artifact

TABLE 49–5. NEUROLOGIC MANIFESTATIONS OF COMMON DRUG POISONING

Drug	Signs and Symptoms	Diagnostic Test	Treatment
Carbon monoxide	Confusion, agitation, headache, convulsions, coma, respiratory failure, cardiovascular collapse	History Carboxyhemoglobin level	Remove patient from area; administer 100% oxygen until carboxyhemoglobin levels fall to < 5%. Administer hyperbaric oxygen if central nervous system affected. Treat cerebral edema with hyperventilation, diuretics, and cerebrospinal fluid drainage, if necessary.
Salicylate	Tinnitus, hyperpnea, confusion, convulsions, coma, hyperthermia	Blood	Provide supportive care, gastric lavage, charcoal, systemic alkalinization, hemodialysis for coma or seizures.
Cyanide	Agitation, confusion, headache, vertigo, hypertension, hypotension, seizures, paralysis, apnea, coma	Blood	Use amyl nitrate, sodium nitrate, sodium thiosulfate, 100% oxygen, or hyperbaric oxygen for refractory signs. Vitamin B12 injection.
Anticonvulsants: Phenytoin Carbamazepine Phenobarbital (see Barbiturates) Valproic acid Primidone Ethosuximide Felbamate Clonazepam (see Benzodiazepines)	Drowsiness, ataxia, nystagmus, tremulousness, coma. Dysrhythmias with carbamazepine or phenytoin overdose.	Blood Ammonia level in patients taking valproic acid.	Provide supportive care, gastric lavage, charcoal. Watch for withdrawal seizures.
Sedative hypnotics: Benzodiazepines Barbiturates Chloral hydrate Meprobamate Ethchlorvynol (Placidyl)	Confusion, lethargy, ataxia, nystagmus, hypothermia, dysarthria, respiratory depression, coma. Pupillary reactions preserved except in instances of deep barbiturate coma. Possible withdrawal seizures.	Blood	Provide supportive care, gastric lavage, flumazenil for benzodiazepine overdose, hemoperfusion for extreme barbiturate intoxication.
Methaqualone	Agitation, hypertonic, hyperreflexia, ataxia, hallucinations, convulsions	Blood	As above
Ethanol	Confusion, agitation, delirium, ataxia, nystagmus, dysarthria, coma	Blood, breath	Provide supportive care, lavage if within 1 hour of ingestion, thiamine, glucose.
Opioids	Lethargy; small reactive pupils; hypothermia; hypotension, urinary retention; shallow, irregular respirations; convulsions	Urine Response to naloxone	Administer naloxone, 0.4 mg IV or IM; continuous naloxone infusion, if necessary. Provide supportive care with intubation as necessary. Lavage if overdose is by ingestion.
Stimulants: Amphetamine Methylphenidate Cocaine	Hypervigilance, paranoia, violent behavior, tremulousness, dilated pupils, hyperthermia, tachycardia or arrhythmia, focal neurologic signs secondary to CNS stroke or hemorrhage, seizures	Blood, urine	Provide supportive care; sedation with benzodiazepines. Watch for rhabdomyolysis.
Psychedelics (LSD, mescaline, phencyclidine)	Delirium, delusions, marked agitation, hallucinations, hyperactivity, dilated pupils, hyperreflexia, nystagmus	Blood Measure phencyclidine levels in gastric juice.	Use gastric lavage, charcoal. Give benzodiazepines and haloperidol for sedation.
Antidepressants: Tricyclic antidepressants	Anticholinergic effects: dry mouth, agitation, restlessness, ataxia, tachycardia or arrhythmias, hyperthermia, hysteria, convulsions, mydriasis	Blood, urine	Use cardiac monitoring, gastric lavage, charcoal, mild systemic alkalinization. Administer physostigmine for refractory arrhythmias and anticonvulsants for seizures.
Monoamine oxidase inhibitors	Drowsiness, ataxia, seizures, hypertensive crisis; hypotension with severe overdose		Provide symptomatic care, gastric lavage; avoid narcotics.
Neuroleptics	Dystonia, drowsiness, coma, convulsions, hypotension, miosis, tremor, hypothermia, neuroleptic malignant syndrome	Urine	Use gastric lavage. Treat extrapyramidal signs with diphenhydramine or benztropine mesylate.
Lithium	Lethargy, tremulousness, weakness, polyuria, polydipsia, ataxia, seizures, coma	Blood	Perform hemodialysis for delirium, seizures, or coma.
Methanol, ethylene glycol	Drunkenness, hyperventilation, stupor, convulsions, coma. Blindness with methanol use.	Blood	Provide symptomatic care, gastric lavage, ethanol infusion, hemodialysis. For methanol intoxication, 4-methylpyrazole is under investigation.
Antihistamines	Anticholinergic effects: dry		Provide supportive care, gastric lavage;

TABLE 49–5. NEUROLOGIC MANIFESTATIONS OF COMMON DRUG POISONING—CONT'D

	mucosa, flushed skin, hyperthermia, dilated pupils, delirium, hallucinations, seizures, coma		control seizures with benzodiazepines; use physostigmine for life-threatening anticholinergic effects.
Organophosphates	Cholinergic crisis: cramps, excessive secretions, diarrhea, bronchoconstriction. Later tremulousness, fasciculations, weakness, convulsions, hypertension, tachycardia, confusion, anxiety, and coma.	RBC cholinesterase level	Provide symptomatic care, decontamination, atropine, and pralidoxime.

inherent in the CT technique. Raised ICP is suggested by effacement of cortical sulci, a narrow third ventricle, and obliteration of the suprasellar or quadrigeminal cisterns but cannot be otherwise quantified. MRI can be performed, depending on the clinical setting and the stability of the patient's condition. The use of MRI is limited in the urgent setting of coma evaluation because of the length of time required to perform the imaging, image degradation by even a slight movement of the patient, and the relative inaccessibility of the patient for emergencies that may occur during the imaging process. Nevertheless, MRI provides superb visualization of posterior fossa structures that is useful when intrinsic brainstem lesions are suspected as the cause of coma.[11] MRI images anatomic lesions, such as those resulting from acute stroke, encephalitis, central pontine myelinolysis, and traumatic shear injury with greater resolution and at an earlier time than CT. The injection of the paramagnetic substance, gadolinium, helps delineate areas of blood-brain barrier breakdown and may augment the sensitivity of this scanning technique. Diffusion-weighted imaging can demonstrate ischemic brain virtually immediately. Sagittal MRI views are particularly useful in the documentation of the degree of supratentorial or infratentorial herniations and may enable intervention before clinical deterioration (Fig. 49-1).[11] Newer MRI techniques allow functional imaging of the CNS by measurement of CBF to a particular region. Future application of this technique may allow rapid determination of diminished CBF, such as occurs in stroke or vasospasm, and will probably be useful in assessing the effect of therapeutic interventions.

ELECTROENCEPHALOGRAPHY

The EEG can sometimes gives useful additional information in the evaluation of the unresponsive patient. With metabolic and toxic disorders, the EEG changes generally reflect the degree and severity of altered arousal or delirium characterized by a decreased frequency of the background rhythm and the appearance of diffuse slow activity in the theta (4 to 7 Hz) and/or delta (1 to 3 Hz) range. Bilaterally synchronous and symmetrical, medium to high-voltage broad triphasic waves are seen in various metabolic encephalopathies, most often in hepatic coma. Rapid beta activity (greater than 13 Hz) in a comatose patient suggests the ingestion of sedative hypnotics, such as barbiturates and benzodiazepines. Acute, focally destructive lesions show focal slow activity; when periodic lateralized epileptiform discharges appear in one or both temporal lobes, herpes simplex encephalitis must be strongly considered. A nonreactive, diffuse alpha pattern in a comatose patient usually implies a poor prognosis and is most often seen after anoxic insults to the brain or acute, destructive pontine tegmentum damage.[23,24] A normally reactive EEG in an unresponsive patient suggests psychiatric disease; however, a relatively normal EEG can accompany the locked-in syndrome, some examples of akinetic mutism, and catatonia, all of which can be caused by structural brain lesions. Attempts to correlate the pattern and frequency spectra of a post-resuscitative EEG with neurologic outcome have been unsatisfactory because its predictive value is at best 88% accurate.[25] At present, the most useful information regarding patient prognosis is still obtained by the correct interpretation of physical signs.

Nonconvulsive generalized status epilepticus and repeated complex partial seizures may produce altered levels of awareness or arousal; the EEG is an indispensable tool in the diagnosis and management of both these disorders. Continuous EEG monitoring optimizes management of status epilepticus because clinical assessment is insufficiently sensitive to detect continued electrographic seizures. Furthermore, continuous EEG monitoring in the ICU has shown an unsuspected high incidence of electrographic seizure activity in critically ill neurologic patients.[26,27]

JUGULAR VENOUS OXIMETRY

Changes in jugular venous oxygen saturation measure the relationship between cerebral metabolic rate and CBF, and this monitoring tool is discussed in Chapter 48.[28] This form of monitoring offers the potential to minimize secondary insults after traumatic brain injury by providing warning of cerebral ischemia. It should be considered in comatose patients in conjunction with ICP monitoring (discussed later) to provide a logical approach to the treatment of brain injury.

TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

Transcranial Doppler imaging (see Chapter 48) allows noninvasive measurement of blood flow velocity in basal cerebral arteries.[29] The high dynamic resolution provided, and confirmed correlation with other hemodynamic modalities, encourages increasing numbers of neurointensivists to adopt the technique. Its importance in coma is in early detection of vasospasm in subarachnoid hemorrhage and at the time of brain death,[30] where an oscillating reverbatory

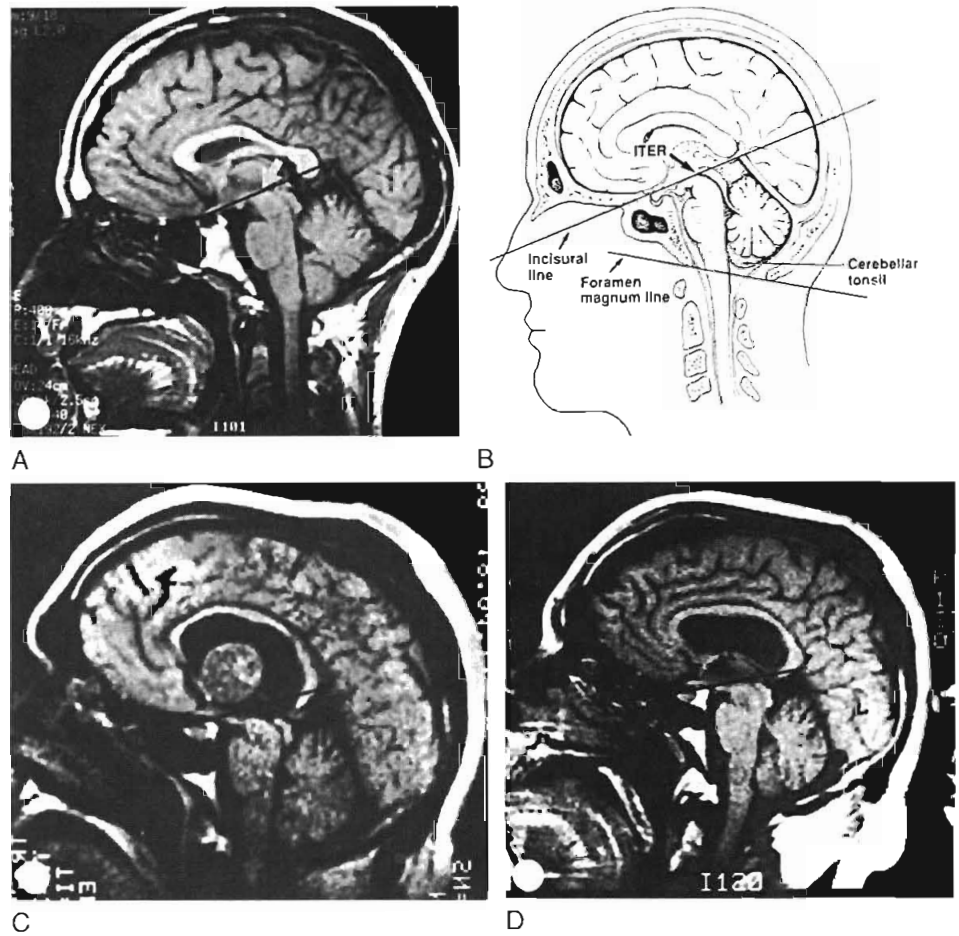

FIGURE 49–1. Midsagittal MRI views of a normal adult brain and of a brain with reversible downward transtentorial herniation. **A** and **B,** MRI view of a normal adult male brain and accompanying diagram. The opening of the tentorium of the cerebellum or anterior cerebellar notch lies along a line (incisural line) defined anteriorly by the anterior tubercle of the sella turcica and posteriorly by the junction of Galen's vein, the inferior sagittal sinus, and the confluence of the straight sinus. The proximal opening of the aqueduct of Sylvius, the iter ad infundibulum *(arrow),* lies within 2 mm of the incisural line. The foramen magnum line is defined between the inferior tip of the clivus anteriorly and the bony base of the posterior lip of the foramen magnum. **C,** A 47-year-old man who experienced 1 week of headache, nausea, vomiting, and gait ataxia presented with abrupt-onset coma, palsy of cranial nerve III, hyperreflexia, and bilateral extensor plantar responses. MRI revealed a third ventricular mass, obstructive hydrocephalus, and displacement of the iter ad infundibulum inferiorly by 6.5 mm. The cerebellar tonsils were not displaced. **D,** Subsequent MRI view in the patient in **C** at 2 weeks after surgical removal of a colloid cyst. The iter ad infundibulum is 1.2 mm below the incisural line. The patient had full neurologic recovery. (A, C, and D from Reich JB, Sierra J, Camp W, et al: Magnetic resonance imaging measurements and clinical changes accompanying transtentorial and foramen magnum brain herniation. Ann Neurol 1993;33:159-170.)

movement has been noted in the flow velocity waveforms. The diagnosis is suspected based on the finding of the reflux phenomenon during late systole after anterograde injection of blood into the vascular tree.

EVOKED POTENTIALS

Evoked potentials (EPs) are used to follow the level of CNS function in comatose patients.[31] Clinical use of brainstem auditory evoked potential (BAEP) and short latency somatosensory evoked potential (SEP) responses stem from the correlation between EP waveform and presumed generators within certain CNS structures. The SEP shows special promise in the ICU field because EP components generated supratentorially in the thalamus and primary sensory cortex can be identified and followed over time. Shifts of intracranial structures that lead to herniation syndromes are reflected in abnormalities in SEPs, whereas BAEPs are generated entirely at or below the lower midbrain and are less often affected. EPs are less affected than EEG readings by sedative medications and septic or metabolic encephalopathies, factors that frequently confound interpretations in comatose patients. Anatomic specificity and physiologic and metabolic immutability are the basis of clinical utility of EPs. Abnormal test results, however, are etiologically nonspecific and must be carefully integrated into the clinical situation by a physician familiar with their clinical use. Caution is needed in the interpretation of SEPs to ensure that absent responses are not due to technical problems. Repeat SEPs are useful in following patients' progress. A progressive decline in response amplitude appears to be associated with worsening prognosis. Studies have shown that all patients with anoxic coma and bilaterally absent SEPs had died or remained in persistent vegetative state.[32] In traumatic coma, absent SEPs may be a less definitive prognostic indicator, because recovery of consciousness has been reported in some patients.[33] Furthermore, comatose patients, especially those with motor response of flexor posture or better, with an initial poor prognostic EEG pattern but normal SEPs, may have the potential for recovery and should be supported until the patient's condition has

changed to a more prognostically definitive category.[34] BAEPs and median SEPs obtained within 24 hours of coma onset had a 3-month predictive outcome (compared with Glasgow outcome score) in patients with head injury, brain hemorrhage, or neoplasm.[35] Diagnostic sensitivity for an unfavorable outcome was low for both parameters, although specificity and positive predictive value was equally high for abnormal wave VI of BAEPs and median SEPs.

MONITORING OF INTRACRANIAL PRESSURE

Monitoring of ICP in neurointensive care is discussed in detail in Chapter 47. A review of published randomized controlled studies of real-time ICP monitoring by invasive or semi-invasive means in acute coma (traumatic or nontraumatic etiology) versus no ICP monitoring (i.e., clinical assessment of ICP) looked at outcome measures of all-cause mortality and severe disability at the end of a given follow-up period.[36] The conclusion drawn is that there are insufficient data to clarify the role of routine ICP monitoring in all severe cases of acute coma. However, it is of value in traumatic brain injury and should be considered on a case-by-case basis in other cases of coma.

PROGNOSIS

A complete evaluation of the comatose patient must include an estimate of prognosis. The outcome in a given comatose patient cannot be predicted with absolute certainty. Available serial data are not sufficiently specific or selective to help in establishing the prognosis in an individual patient. Guidelines on the outcome of coma have been compiled based on serial examinations. Although the status of the comatose patient on admission is valuable in providing early, informed discussion with relatives of patients and medical colleagues, that moment in most instances does not provide sufficient information to withhold immediate therapy. However, the early establishment of a highly probable poor outcome ideally should be made within 24 hours after hospital admission to ration intensive care services and protect families from false hope in futile cases. A logical and sensible approach to prognostication includes an etiologic subcategorization into medical, drug-induced, and traumatic coma.

Numerous prehospital descriptive scoring systems are used in an attempt to assess the severity of illness and predict outcome of patients. A 2-year prospective study compared severity of illness scoring systems (Acute Physiology and Chronic Health Evaluation [APACHE] II and Mainz Emergency Evaluation System [MEES]) to mental status measurement (Glasgow Coma Score [GCS]) in predicting outcome of 286 consecutive adult patients hospitalized for nontraumatic coma.[37] There were no statistically significant differences among the scoring systems to correctly predict outcome. APACHE II and MEES should not replace GCS. For the prediction of mortality, the GCS score provides the best indicator also in nontraumatic comatose patients (it is simple, less time consuming, and accurate in an emergency situation). Factors that are useful in determining the outcome of medical coma include the cause, the depth, and the duration of coma. Clinical signs reflecting brainstem, motor, and verbal function are the most helpful and best validated predictors (confidence interval 0.95).[38-41] Overall, only 15% of patients in established medical coma for 6 hours will make a good or moderate recovery; others will die (61%), remain vegetative (12%), or become permanently dependent on others for daily living (11%). Prognosis depends on etiology of medical coma. Patients in coma due to a stroke, subarachnoid hemorrhage, or cardiorespiratory arrest have only about a 10% chance of achieving independent function. Thirty-five percent of patients will achieve moderate to good recovery if coma is due to other metabolic reasons, including infection, organ failure, and biochemical disturbances. As noted earlier, almost all patients who reach hospital after sedative overdose or other exogenous agents will recover moderately or completely. The depth of coma affects the individual prognosis. Patients who open their eyes in response to noxious stimuli after 6 hours of coma have a 20% chance of making a good recovery versus 10% if the eyes remain closed. The longer coma persists, the less likely are the chances for recovery; 15% of patients in coma for 6 hours make a good or moderate recovery compared with only 3% who remain unconscious at 1 week.[38,39] Coma after head trauma has a somewhat better prognosis (see later).

The severity of signs of brainstem dysfunction on admission inversely correlates with the chance of good recovery in medical coma. Absent pupillary responses at any time after onset and absent caloric-vestibular reflexes 1 day after onset indicate a poor prognosis (<2% recovery except in barbiturate or phenytoin poisoning). Except for sedative drug poisoning, no patient with absent pupillary light reflexes, corneal reflexes, oculocephalic or caloric responses, or lack of a motor response to noxious stimulation at 3 days after onset is likely to ever regain independent function. In a prospective study of 500 patients in medical coma, a uniform group of 210 patients suffered anoxic injury: 52 of these had no pupillary reflex at 24 hours, all of whom died. By the third day, 70 were left with a motor response worse than withdrawal and all died. By the seventh day, the absence of roving eye movements was seen in 16 patients, all of whom died.[38,39]

Patients likely to recover to functional independence will within 1 to 3 days speak words, open their eyes to noise, show nystagmus on caloric testing, or have spontaneous eye movements. More than 25% of patients with anoxic injury who show roving conjugate eye movements within 6 hours of the onset of coma or who show withdrawal responses to pain or eye opening to pain will recover independence and make a moderate or good recovery. The use of combinations of clinical signs helps to improve the accuracy of prognosis: at 24 hours the absence of a corneal response, pupillary light reaction, or caloric or doll's eye response is not compatible with recovery to independence.

Postanoxic convulsive status epilepticus and/or myoclonic status epilepticus reflect a poor prognosis. Occasional patients recover consciousness but remain handicapped. Most die or become vegetative.[42,43] Associated clinical findings, such as loss of brainstem reflexes or eye opening at the onset of myoclonic jerks, and sinister EEG patterns, such as suppression or burst-suppression, confirm a grim neurologic outcome in this group. Autopsy studies show that cerebral and cerebellar damage can be ascribed to the initial ischemic hypoxic event; there is no evidence that status epilepticus further contributes to this damage. We initially treat patients with an intravenous loading dose of a major anticonvulsant (phenytoin, 13 to 18 mg/kg at 25 mg/min, and/or phenobarbitol, 20 mg/kg at 50 mg/min). Myoclonic status epilepticus is generally resistant to therapy; we give intermittent doses of benzodiazepines (lorazepam, 2 to 4 mg, or clonazepam, 0.5 mg i.v.) as needed to suppress particularly severe

myoclonus that interferes with ventilatory support. Anesthetic agents are rarely indicated and are unlikely to alter outcome.

A meta-analysis of prognostic studies in anoxic-ischemic coma examined the value of biochemical markers of brain damage in CSF or serum.[44] Only concentrations of CSF markers (creatine kinase brain isoenzyme, neuron-specific enolase, lactate dehydrogenase, and glutamate oxaloacetate) reached 0% false-positive rate. Because of small numbers of patients involved in studies (wide confidence levels) and methodologic limitations of studies the results available are not sufficiently accurate to provide a solid basis for management decisions of patients in coma.

The most accurate prediction of outcome in a patient in medical coma is obtained from the use of a combination of clinical signs and there is little to be added by more sophisticated testing other than in identifying the cause of the coma.[38,39] Within the first week, it is hard to justify the withdrawal of therapy from patients in medical coma unless they are already brain dead or lack all signs of brainstem function. After that, the probability of being able to predict the quality of life increases steadily. A multisociety task force of neurologists and neurosurgeons obtained a large number of data concerning the persistent vegetative state that provides guidelines to outcomes in patients remaining vegetative 1 month after severe head trauma or coma-producing medical illness (mostly anoxic).[15]

Among adults with head trauma who were in a vegetative state at 1 month (n = 434), 33% died, 15% remained vegetative, and 28% suffered severe disability at 1 year. Among children vegetative for 1 month after trauma (n = 106), 9% died, 29% remained in a persistent vegetative state, and 35% were severely disabled at 1 year; only 27% attained moderate/good recovery.

Nontraumatic (medical) coma results were even worse. Among 169 adults with nontraumatic brain injury and vegetative at 1 month, 53% died within a year, 32% remained vegetative, and only 14% made a moderate/good recovery. Outcome of 45 children in similar circumstances showed 22% dead, 65% still vegetative, and only 6% who made a moderate/good recovery at 1 year.

It is possible in a fraction of patients to predict within the first week those who will recover, those who will die in coma or enter a vegetative state, and those who will survive with severe disability. It is well established that patients in anoxic coma who are in a vegetative state at 1 month will never recover their full preanoxic physical or cognitive function.

Patients in coma due to *exogenous agents* (except carbon monoxide poisoning) carry an overall good prognosis provided that circulation and respiration are protected by avoiding or correcting cardiac dysrhythmia, aspiration pneumonia, and respiratory arrest. Despite absent brainstem reflexes (electrocerebral silence on EEG), patients with deep sedative drug intoxication have the potential for complete recovery. Therefore, in the emergent situation, patients in coma of uncertain etiology should be supported vigorously until the precise cause of coma has been fully established.

The outcome of *traumatic coma* is generally better than that of medical coma, and prognostic criteria are somewhat different[15,33,45]:

1. Many patients with head injury are young.
2. Prolonged, post-traumatic unconsciousness of up to several months does not always preclude a satisfactory outcome.
3. Compared with the initial degree of neurologic abnormality, patients in traumatic coma improve more than patients in medical coma. Patients in coma for longer than 6 hours after traumatic brain injury have a 40% chance to recover to moderate disability or better at 6 months.

The most reliable predictors of outcome at 6 months are:

1. Patient age (worse outcome especially after 60 years).
2. Depth and duration of coma (an inverse correlation with GCS score).
3. Pupil reaction and eye movements (absence at 24 hours predicts death or a vegetative state in 90%).
4. Motor response in the first week of injury (Table 49-6).

An independent poor prognostic indicator is sustained, uncontrollably increased ICP (greater than 20 mm Hg). Additional factors play a role in the eventual outcome from traumatic coma. Specific lesions, such as subdural hematoma, that result in coma can have a less than 10% recovery rate.[46] In studies with blunt trauma, comatose patients with increased plasma glucose, hypokalemia, or elevated blood leukocyte counts were associated with lower GCS scores and an increased probability of death.[47] There are some reports of patients who have suffered coma as a result of traumatic brain injury in whom an improvement from the vegetative state has been recognized after months, but these anecdotal cases of recovery are difficult to validate, and it seems possible that such patients were not truly vegetative, rather in a

TABLE 49–6. TRAUMA SCALE: TOTAL TRAUMA SCORE (SUM OF INDIVIDUAL SCORES)*

Glasgow Coma Scale	
14-15	5
11-13	4
8-10	3
5-7	2
3-4	1
Respiratory Rate	
10-24/min	4
25-35/min	3
>35/min	2
1-9/min	1
None	0
Respiratory Expansion	
Normal	1
None	0
Systolic Blood Pressure	
>89 mm Hg	4
70-89 mm Hg	3
50-69 mm Hg	2
0-49 mm Hg	1
No pulse	0
Peripheral Perfusion (Capillary Refill)	
Normal	2
Delayed	1
None	0

*Scores less than 10 represent less than 60% chance of survival.

state of profound disability but with cognition, at the beginning of the observation.[48]

A systematic review of trials reporting on multisensory stimulation programs in patients with traumatic brain injury in coma or the vegetative state found no reliable evidence of the effectiveness of such techniques when compared with standard rehabilitation.[49] Outcome measures included duration of unconsciousness (time between injury and response to verbal commands), level of consciousness (GCS), level of cognitive functioning, functional outcomes (GCS), or disability rating scale. The overall methodologic quality was poor, and studies differed widely in design and conduct. Because of the diversity in reporting of outcome measures a meta-analysis was not possible.

The prognostic guidelines for medical and traumatic coma should be applied with care. One must be sure that evaluation and interpretation of clinical signs are correct. The prognostic signs, however, predict general outcomes in large patient groups and cannot be applied with absolute precision to every individual comatose patient. In addition, the effect of anticholinergic agents, used during resuscitation, on pupillary reactivity and the effect of paralytic agents on motor response must be excluded.

The ability to predict prognosis after coma can benefit the patient, family, and physician. Families can be spared both the emotional and financial burdens of caring for individuals with an insignificant chance of independent function and quality life. Physicians can then properly allocate limited resources to patients with the potential to benefit from advanced medical care.

There are recognized difficulties in interpreting the outcome of studies of coma prognosis: the lack of prospective studies, failure to state confidence intervals, and the fact that patients in coma may die of a non-neurologic disease. The self-fulfilling nature of poor prognoses is difficult to eliminate: the care of a patient will reflect the treating physicians' impressions and opinions on patient outcome. Ideally, prognostic studies should only be performed on patients who will receive maximal life support for as long as possible, but this is inconsistent with the humane and sensitive management of patients and their relatives.

A recent analysis used data from the SUPPORT (Study to Understand the Prognoses and Preferences for Outcomes and Risks of Treatments) trial to estimate the cost-effectiveness of aggressive care for patients in nontraumatic coma.[50,51] Patients with reversible metabolic causes of coma were excluded. The incremental cost-effectiveness was calculated for aggressive care versus withholding cardiopulmonary resuscitation and ventilatory support after day 3 of coma. The incremental cost-effectiveness of the more aggressive strategy was $140,000 (1998 dollars) per quality-adjusted life year for high-risk patients and $87,000/quality-adjusted life year for low-risk patients (five risk factors were age older than 70 years, absent verbal response, absent withdrawal to pain, abnormal brainstem response, and serum creatinine value greater than 1.5 mg/dL). Earlier decisions to withhold life-sustaining treatments for patients with very poor prognoses may yield considerable cost savings. On moral and ethical grounds physicians may object to consideration of the cost factor when it comes to treatment decisions of more-or-less sick patients. Financial constraints imposed on the medical fraternity from "top down" by politicians and the business culture may no longer afford such "luxury" even in a country as wealthy as the United States.

ANNOTATED REFERENCES

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This textbook on neurocritical care gives concise access to causes and treatment of medical and neurologic coma. It is easy to access because topics are discussed in short, easy to read chapters with a short list of references.

Jennett B, Teasdale G, Braakman R, et al: Prognosis of patients with severe head injury. Neurosurgery 1979;4:283-301.

This article helps guide physicians to focus on the important clinical prognostic factors when managing severely head-injured patients. Because the prognosis of traumatic coma is better than medical coma, these guidelines potentially minimize management errors in patients with other severe injuries.

Levy DE, Bates D, Caronna JJ, et al: Prognosis in non-traumatic coma. Ann Intern Med 1981;94:293-301; and Levy DE, Caronna JJ, Singer BH, et al: Predicting outcome from hypoxic-ischemic coma. JAMA 1985;253: 1420-1426.

These two articles recognize the value/importance of the bedside evaluation in the prediction of outcome of medical (hypoxic-ischemic) coma. This bedside knowledge helps clinicians orient patient care in an increasingly high-tech hospital environment.

Plum F, Posner JB: The Diagnosis of Stupor and Coma. Philadelphia, FA Davis, 1980.

This book is a convenient "one-stop" reference to stupor/coma. It is an excellent source of information about the pathophysiology and etiology of altered consciousness.

Synek VM: Prognostically important EEG coma patterns in diffuse anoxic and traumatic encephalopathies in adults. J Clin Neurophysiol 1988;5:161-174.

The EEG is often used by clinicians (and requested by family) to help establish cause and prognosis of stupor and coma. This article usefully categorized EEG patterns according to a severity scale that can be incorporated into the bedside evaluation of a patient with altered consciousness.

Chapter 50
CARDIOPULMONARY-CEREBRAL RESUSCITATION

Clifton W. Callaway

KEY POINTS

1. **Improvement in outcome after cardiac arrest** requires attention both to the reversal of cardiopulmonary arrest at the scene and to restoration of consciousness in the intensive care unit. Isolated attention to only the heart or only the brain is unlikely to improve outcomes for many patients (see Fig. 50-8).
2. **Increased emphasis on the basic mechanics of artificial circulation**, specifically uninterrupted vigorous chest compressions, may increase the number of individuals reaching the intensive care unit.
3. It is necessary to **prioritize the various adjunct tools for cardiac resuscitation.** For example, time devoted to endotracheal intubation may delay drug therapy and interrupt chest compressions without altering overall hemodynamics.
4. **The cornerstone of drug therapy during resuscitation** attempts is the administration of vasoconstrictor drugs that will increase coronary perfusion pressure developed by chest compressions.
5. Induction of mild hypothermia, optimal management of blood pressure and serum glucose level, and a prothrombotic state, along with proper treatment of the root cause of the cardiac arrest may **increase the number of initially comatose patients who awaken.**
6. **Neurologic prognosis** is best established by serial clinical examinations over the first 48 to 72 hours after restoration of circulation. Constant reassessment of the likelihood of meaningful recovery can guarantee that continued care and interventions are appropriate.

Cardiopulmonary arrest may occur as the endpoint or consequence of many diseases. Examples include acute dysrhythmias, cardiac pump failure, hypoxemia, sepsis, hemorrhage, drug toxicity, and metabolic disturbances. Often the mechanism is unknown when treatment is initiated, and an algorithmic approach titrated to real-time monitoring (electrocardiography, capnometry, oximetry, blood pressure) is used. When the cause is known or suspected, therapy may be individualized and directed at that cause. In all cases, management has two priorities: (1) rapid restoration of cardiopulmonary function and (2) minimization of ischemic damage to end organs, primarily the brain. Restoration of circulation is composed largely of mechanical and electrical treatment. In contrast, brain injury involves primarily cellular and molecular events that are treated with specific and detailed intensive care. Meaningful survival is unlikely without attention to both heart and brain.

Previously, there has been little consensus on intensive care management of the patient resuscitated from cardiac arrest, but there is increasing evidence that differences in post-resuscitation management influence final outcomes.[1,2] Despite decades of attention to acute cardiac resuscitation, there has been little or no change in long-term survival.[3,4] Meaningful improvements in outcome will require an integrated approach to the patient that includes not only immediate resuscitation but also intensive care management after restoration of circulation (Fig. 50-1). The epidemiology of cardiac arrest, the initial approach for reversing cardiopulmonary arrest, modifications of this approach appropriate for specific disease states, and post-resuscitation care designed to minimize brain injury are reviewed.

EPIDEMIOLOGY

In the United States, heart disease is the overall leading cause of death. Cardiopulmonary arrest outside the hospital has an age-adjusted incidence of 100 to 120 events per 100,000 people per year.[5,6] Overall survival after out-of-hospital cardiac arrest in the United States is estimated at 6.4%,[7] with several large U.S. cities reporting a survival rate less than 2%.[8,9] The incidence of cardiac arrest in the hospital is about 0.17 event per hospital bed per year.[10] For inpatients experiencing cardiac arrest, survival to hospital discharge is estimated at 17%. Fewer than one half of cardiac arrests occur in an intensive care unit (ICU) setting, and survival does not appear to be related to the location of collapse.[11]

Demographic features of sudden cardiac death are similar to the characteristics of cardiovascular disease. Sudden cardiac death is more common in males than females both outside of the hospital[6] and in the hospital.[10] However, the incidence of cardiac arrest is higher in women (6.0%) than in men (4.4%) who are admitted to the hospital for acute myocardial infarction.[12] Cardiac arrest outside the hospital affects blacks more than whites or Asians.[6,8] Whereas sudden death can affect patients of all ages, the mean age for sudden cardiac arrest is between 65 and 70 years in most studies.[6,10]

Two temporally and mechanistically separate processes contribute to mortality: (1) cardiopulmonary collapse and (2) neurologic injury. In evidence of the first process, only one third of patients who collapse outside the hospital have

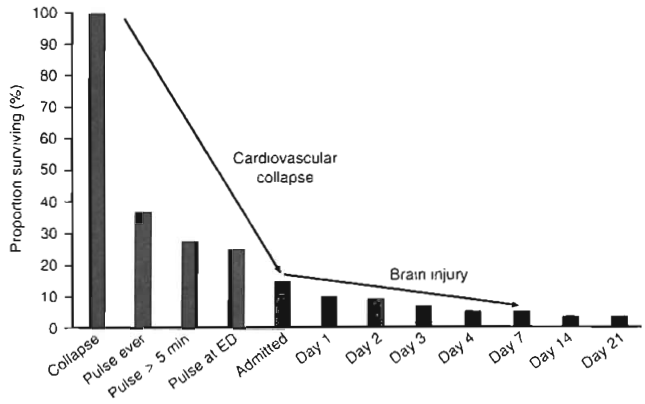


FIGURE 50–1. The survival curve for patients treated for out-of-hospital cardiac arrest in one city illustrates that risk of death occurs in two phases. Early death after cardiac arrest results from irreversible cardiopulmonary collapse, precluding survival to hospital admission for 70% to 80% of patients. Death during the first few days after hospital admission is usually related to brain injury and failure to awaken, precluding long-term survival for an additional 10% to 15% of patients. (Unpublished data from City of Pittsburgh.)

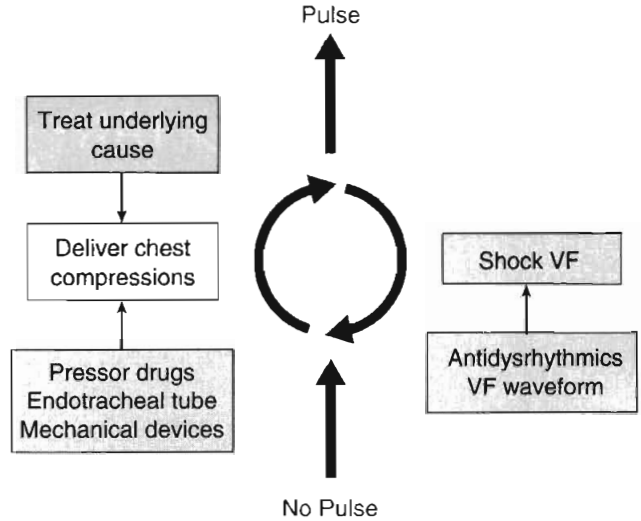


FIGURE 50–2. Prioritization of activities must occur during cardiac resuscitation. The central circle emphasizes that the core activity of artificial perfusion should be interrupted only to provide rescue shocks when appropriate. All drugs, airway devices, and other interventions are designed to augment either artificial circulation or defibrillation. None of these adjuncts should interrupt or detract from performing the two core activities.

restoration of circulation long enough to be admitted to the hospital (see Fig. 50-1). Likewise, only 44% of patients who collapse in the hospital have return of circulation.[10] In evidence of the second process, two thirds of patients admitted to the hospital after out-of-hospital collapse die before discharge from the hospital.[13] Likewise, over 60% of patients initially resuscitated from cardiac arrest in the hospital do not survive to hospital discharge.[10] The most common reason for death among patients after restoration of circulation is post-ischemic brain injury. Failure to awaken leads to withdrawal of care and in-hospital death for as many as 44% to 68% of subjects after initial restoration of circulation.[10,14]

RESTORING CIRCULATION

Acute treatment of cardiac arrest consists of two essential, goal-directed activities: (1) artificial circulation (usually chest compressions augmented by peripheral vasoconstrictors) to circulate oxygenated blood to heart and brain and (2) electrical shock to terminate ventricular fibrillation (VF) and unstable tachyarrhythmias. Of these two procedures, artificial circulation (including ventilation) occupies most of the time and electrical rescue shock is invoked only when appropriate. Rescue shock is the only procedure for which interruption of artificial circulation is absolutely necessary and justified.

The recommended division of time and prioritization of activities is depicted in Figure 50-2. All other activities, including antidysrhythmic medications and advanced airway maneuvers, are designed to supplement these two core activities. Optimization of resuscitation requires that any interruption in the two core activities, especially artificial circulation, be minimized. In addition, continuous reassessment of the patient can be reduced to constant awareness of two parameters (Fig. 50-3). The organization of the electrocardiogram (ECG) and the presence of pulses will prompt appropriate selection of therapy.

The American Heart Association (AHA) and European Resuscitation Council provide consensus scientific statements about the acute management of cardiac arrest.[15] Those guidelines have a detailed review of specific drugs and procedures. The following section provides an overview of airway management, circulation support, rescue shock for defibrillation, and drug therapy during cardiac arrest.

AIRWAY AND VENTILATION

Obstruction of the airway can occur in any patient with impaired consciousness, including cardiac arrest.[16] If uncorrected, this obstruction prevents oxygenation and

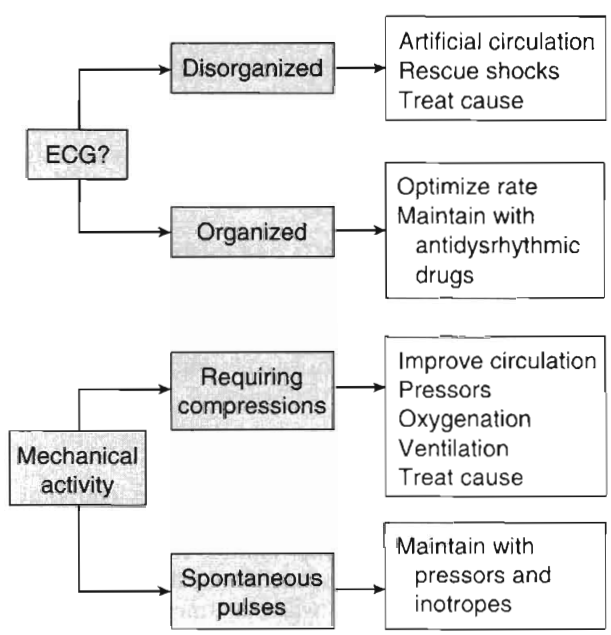


FIGURE 50–3. Continuous reassessment of the patient during cardiac resuscitation can focus on the electrocardiogram (ECG) and on the presence of cardiac activity (pulses). If an organized ECG is not present, interventions should be undertaken to restore an organized ECG. If mechanical cardiac activity is not present, interventions should be undertaken to improve mechanical cardiac activity.

ventilation, leading to or perpetuating cardiopulmonary collapse. In patients who are comatose because of primary cardiac arrest, the airway usually is not patent. Animal models typically do not mimic ventilation through the human airway because the most common research animals (dogs and swine) have straight orotracheal passages.

Agonal respirations occur after acute cardiac arrest for an additional 1 to 2 minutes.[17] These respirations may confuse lay people, delaying recognition of cardiac arrest. It is unclear whether these agonal respirations can generate sufficient ventilation to support life. The presence of gasping is associated with survival, but it also may be a surrogate marker for brief collapse-to-resuscitation intervals.[18] Regardless, the amplitude and frequency of agonal respirations declines over 1 to 2 minutes, necessitating artificial ventilation for all patients requiring more than momentary resuscitation efforts.

Simple maneuvers can establish patency of the human airway. Extension of the neck (head tilt) and forward displacement of the mandible (chin lift) straightens and opens the pharynx. The tongue can be displaced from the posterior pharynx by insertion of an oropharyngeal airway. With these steps, positive-pressure ventilation can be provided using mouth-to-mouth or bag-valve-mask ventilation. A positive-pressure breath of 10 to 15 mL/kg delivered over 2 to 3 seconds will fill the lungs. Ventilation with as little as 400 mL in adults (6 to 7 mL/kg) will cause the chest to rise.[19] While that volume is inadequate for conscious subjects, it is unclear what tidal volume is necessary to provide adequate gas exchange during cardiac arrest.

The minute ventilation required to accomplish resuscitation in humans has not been established. The need for gas exchange must be balanced against the fact that interrupting chest compressions lowers coronary perfusion (Fig. 50-4).[20] Comparison of different ratios of chest compressions to ventilation in swine suggests that two breaths per 50 chest compressions or more may be optimal for resuscitation.[21] An extreme point of view is that chest compressions without any artificial ventilation may be sufficient to accomplish resuscitation in certain individuals.[22] This position is contrary to early work demonstrating that the human airway collapses in most unconscious subjects and that compressions alone are unable to provide ventilation.[16] Therefore, the optimal ratio of chest compressions to ventilations remains to be established but may be greater than the 15:2 currently recommended in the AHA guidelines.

Ventilation can be confirmed with capnometry. During cardiac arrest, end-tidal CO_2 measurement is related to cardiac output and pulmonary blood flow.[23] Therefore, CO_2 levels may be very low (<10 mm Hg) at the onset of resuscitation. Adequate artificial circulation will cause CO_2 levels to increase, and these levels may be used as a feedback to improve or modify chest compressions. Data from emergency department patients suggest that an end-tidal CO_2 level greater than 15 to 16 mm Hg is associated with successful cardiac resuscitation.[24,25] Conversely, end-tidal CO_2 less than 10 mm Hg after 20 minutes of resuscitative efforts predicts nonsurvival.[26] However, drugs commonly used during resuscitation can disrupt the association between capnography readings and pulmonary blood flow. For example, epinephrine infusion reduces CO_2 levels and sodium bicarbonate infusion produces a transient, but profound, elevation of CO_2 levels. An abrupt increase in end-tidal CO_2 levels, usually to levels greater than 35 mm Hg, accompanies the return of spontaneous circulation.

AIRWAY DEVICES

The most common ventilation device used by rescue personnel, paramedics, and other health care providers is a self-inflating bag attached to a facemask (bag-valve-mask), which has several pitfalls. First, it is difficult to maintain an air-tight seal between the mask and the face of the patient, particularly when simultaneously performing head-tilt, chin-lift maneuvers. Adequate training and practice increases ventilation success by a single provider, but two providers achieve more reliable airway management. One provider squeezes the bag, while the second provider uses two hands to hold the mask on the face and position the head.

A second difficulty with bag-valve-mask ventilation is insufflation of the stomach.[27] Excessive air in the stomach can promote emesis, and the abdominal distention may impair venous return and lung compliance.[28] The esophagus prevents air entry into the stomach unless upper airway pressures exceed 15 to 20 cm H_2O.[29] However, during cardiac arrest, esophageal muscle tone declines, and air will enter the stomach with upper airway pressures greater than 5 to 8 cm H_2O.[30] If the upper airway is not patent, providers may try to ventilate with increased pressure to achieve chest rise. Furthermore, rapid squeezing of the bag during the excitement of the situation results in too high upper airway pressures. By avoiding these problems, mechanical ventilators with regulated flow rates and peak pressures may perform better than bag-valve-mask during resuscitation.

Endotracheal intubation can secure the airway definitively. A cuffed endotracheal tube protects from emesis and maintains airway patency. However, laryngoscopy requires an interruption in chest compressions and the endotracheal tube by itself does not correct cardiac arrest. Therefore, endotracheal intubation must be considered an adjunct to initial resuscitation that should not delay or interrupt more definitive interventions. Obviously, any patient with restoration of circulation and subsequent coma will require endotracheal intubation, but the interruption in artificial circulation required for this procedure should be carefully considered.

Alternative airway adjuncts, such as double-lumen, combination endotracheal-esophageal tubes (Combitube) or laryngeal mask airways can be used to temporarily manage the airway during resuscitation.[31,32] The Combitube and laryngeal mask airways have the advantage that they can be inserted blindly in seconds without laryngoscopy, thereby minimizing any interruption of chest compressions.[27] The degree to which these devices can protect from aspiration is debated.

ARTIFICIAL CIRCULATION

In the patient without pulses, circulation of blood can be accomplished by mechanical compression of the heart and chest. The critical parameter for restoring spontaneous circulation is the development of adequate coronary perfusion pressure (CPP). The CPP is quantified by the pressure gradient between the aorta and the inside of the ventricles (usually approximated by the pressure in the right atrium or the central venous pressure [CVP]). Measurement of CPP in clinical practice is difficult unless the patient has invasive monitoring before cardiopulmonary collapse. CVP can be estimated from a central line, and peripheral arterial pressures can be developed from approximate aortic pressures. In the spontaneously beating heart, most blood flows through the ventricular walls

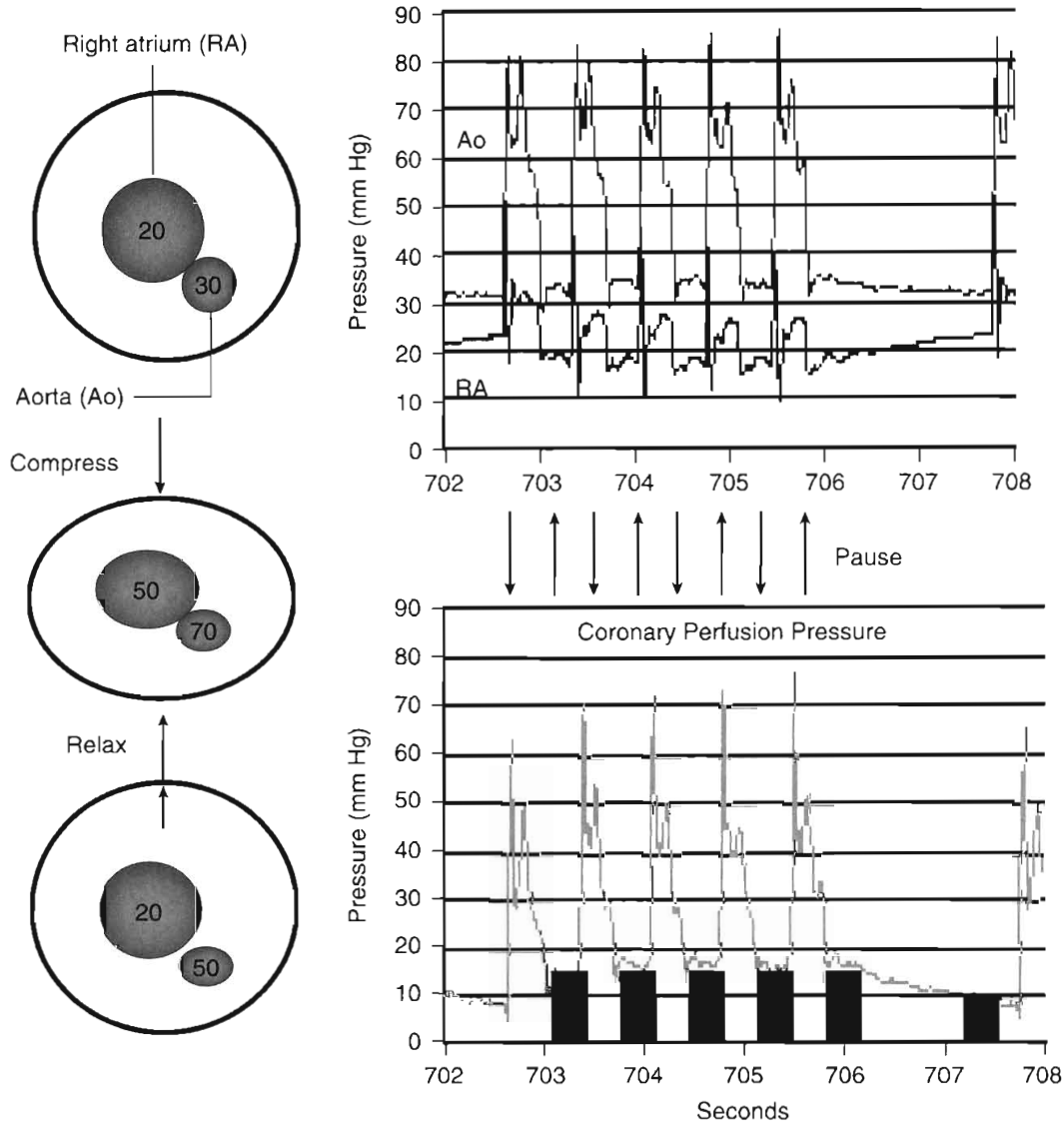


FIGURE 50–4. Chest compressions provide coronary perfusion by creating a pressure gradient between the aorta (Ao) and the inside of the ventricles (approximated by the right atrium [RA]). The gradient between these sites is the coronary perfusion pressure (CPP). During chest compression *(down arrows)* pressure increases in both Ao and RA. During relaxation *(up arrows)*, pressure persists in Ao more than RA. Thus, myocardial blood flow is most related to CPP during the relaxation phase of chest compressions. Note that the CPP declines within 1 to 2 seconds when compressions are interrupted for ventilation. (Unpublished laboratory data.)

during diastole, when the ventricular pressure is lowest. With mechanical compression of the heart and chest during resuscitation, the primary perfusion of the heart occurs during the relaxation phase (see Fig. 50-4).

CPP is highly correlated with myocardial perfusion, and consequently with the likelihood of resuscitation.[33] In humans, return of circulation requires that the developed CPP exceeds 15 to 20 mm Hg. It is likely that with CPP less than 15 mm Hg, perfusion is inadequate to replete the energy state of the myocardium during cardiac arrest. It is important to recognize that peak arterial pressure or palpable pulses measured during chest compressions do not necessarily represent CPP because ventricular pressures are simultaneously elevated. Consequently, it is more useful to follow the "diastolic" or relaxation phase arterial pressure. If unable to follow these pressures, the clinician must rely on indirect evidence of myocardial perfusion, such as improved electrical and mechanical activity or increased pulmonary CO_2 excretion.

Direct cardiac compression via a thoracotomy is more effective than external chest compressions, producing roughly threefold increases in CPP.[34] This approach also allows recognition of cardiac tamponade and treatment by pericardiotomy. Mechanical activity and fibrillation are immediately visible, and electrical rescue shocks or pacing can be applied directly to the heart. In the setting of cardiopulmonary collapse due to exsanguination, thoracotomy also allows aortic compression to shunt blood to heart and brain, as well as the potential for direct control of intrathoracic bleeding. Until the 1960s, thoracotomy was the standard approach for treatment of sudden cardiac arrest, but this procedure has now been supplanted by closed-chest compressions. Case series describe how cardiac massage continues to be successful, and its use should be considered when closed-chest compressions are ineffective.[34] Open-chest cardiac massage is most likely to succeed if initiated early during resuscitation.[35]

Delivery of chest compressions is often inadequate, and uninterrupted chest compressions are critical for restoration of circulation.[20,36,37] A variety of mechanical devices have been developed to provide more consistent and continuous chest compressions.[38] Some of these devices exploit

circumferential compression or active compression-decompression of the chest to increase the efficiency of artificial circulation. However, none has gained widespread use because of their weight and cost. Whereas no current device is poised to solve this challenge, the constant attention of industry to this area illustrates the need for strategies to improve delivery of chest compressions.

Extracorporeal perfusion for restoration of circulation is highly effective and can be used to resuscitate subjects for whom chest compressions have failed.[39,40] With extracorporeal support, more time becomes available to address the primary cause for cardiac arrest. However, this approach requires specialized technical skill and has increased cost and increased risk. Logistical issues include limited availability of perfusion equipment, increased set-up time for circuit priming, and delays in establishing adequate venous and arterial access. Development of portable cardiopulmonary bypass devices that can be primed quickly along with improved techniques for rapid vascular access could broaden the use of this technology.

ECG MONITORING

Continuous three-lead ECG monitoring provides information that can be used to titrate resuscitation. A practical division of the ECG is to divide rhythms into organized and not organized. Organized rhythms include supraventricular rhythms or ventricular tachycardia. Disorganized rhythms include VF and asystole. Disorganized rhythms cannot support the pumping of blood, regardless of volume status, cardiac muscle state, and vascular integrity. Therefore, restoring cardiac electrical activity to an organized rhythm is an essential step in resuscitation. Organized rhythms can support pumping of blood unless they are too slow (<30 to 40 complexes per minute) or too fast (>170 to 180 complexes per minute). An organized rhythm in the absence of pulses is termed *pulseless electrical activity* (PEA).

Any organized complex that is not associated with perfusion should be considered PEA. The absence of perfusion in the presence of organized electrical activity may result from damage to heart muscle (as in massive myocardial infarction) or from uncoupling of electrical and mechanical activity (as in prolonged circulatory arrest). Perfusion may be so poor that pulses are absent in ventricular tachycardia, supraventricular tachycardia, and atrial fibrillation with rapid ventricular response that are unresponsive to the filling of the heart. These tachyarrhythmias should be corrected by electrical cardioversion. Outside of these tachyarrhythmias, the rate of complexes in PEA is related to the ischemic state of the heart and may be used to monitor resuscitation efforts. With increasing ischemia, energy depletion will occur in the electrical system and the rate of PEA will slow. If resuscitation is improving the energy state of the heart, the rate of PEA will accelerate. Anecdotally, narrow complexes reaching rates of 80 to 100 beats/min often herald the return of pulses. Falling rates of complexes in PEA reflect unsuccessful resuscitation efforts, probably because of inadequate perfusion of the cardiac conduction system.

VF and asystole lie along a continuum of disorganized ECG. Arbitrary peak-to-peak amplitude of the ECG is usually used to distinguish asystole (amplitude < 0.1 to 0.2 mV) from VF (amplitude > 0.2 mV).[41] However, VF also exhibits temporal structure that may be absent in asystole.[42] VF is a chaotic electrical activity formed by multiple interacting waves of activation within the heart.[43] VF emerges from broken wave fronts that result from an area of ischemia (as in myocardial infarction), an area of prolonged refractoriness (as in drug-induced or inherited prolonged QT intervals), or too rapid succession of activation potentials (as in tachycardia or an R-on-T premature beat). As the organization and amplitude of these waves decline, because of ischemia or hypoxemia, the amplitude of the ECG also declines. Reperfusion of the heart in asystole may restore VF. Furthermore, the amplitude and organization of the VF increase with reperfusion, providing a marker of adequate artificial perfusion.

RATIONAL USE OF RESCUE SHOCKS FOR DEFIBRILLATION

Delivery of immediate transthoracic electrical (rescue) shocks to patients in VF can convert it into an organized cardiac rhythm (Fig. 50-5). Rescue shocks are highly effective when VF is of very brief duration (<1 to 2 minutes). These shocks may work by depolarizing the heart, canceling the original wave fronts, or by prolonging the refractory periods.[43] Although rescue shocks can successfully restore an organized rhythm, repeated shocks may directly damage the myocardium. The precise magnitude of this damage is still unclear.[44] Nevertheless, optimal therapy should provide rescue shocks at the lowest effective energy while minimizing the number of unsuccessful rescue shocks.

Rescue shocks are more likely to fail when cardiac arrest has lasted more than a few minutes. In the out-of-hospital setting, only 9% of rescue shocks restore an organized ECG if the collapse was not witnessed by the paramedic.[45] Furthermore, resuscitation is less likely after rescue shocks that convert VF into asystole.[46] In one model for defibrillation, a "critical mass" of the heart must be depolarized by

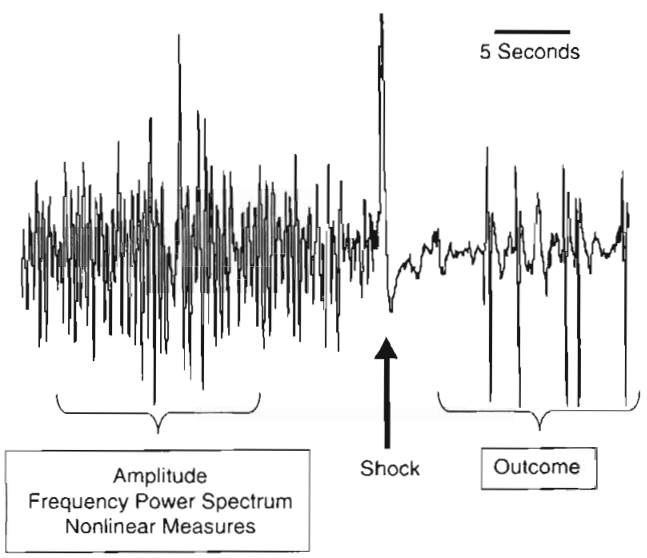


FIGURE 50–5. Rescue shock converts ventricular fibrillation into an organized rhythm. Note that several seconds pass between the rescue shock and the first appearance of complexes. Quantification of the waveform of ventricular fibrillation before shock using amplitude, frequency components, or nonlinear measures can predict the likelihood that the outcome will be an organized rhythm. The appearance of an organized rhythm does not guarantee pulses, and continued reevaluation is essential. (Unpublished data from City of Pittsburgh.)

a rescue shock to ensure that VF activation potentials are extinguished.[43] If a critical mass is not defibrillated, chaotic activity in the remaining regions will spread throughout the heart, rekindling VF. However, even when the entire heart is depolarized by the shock, VF may recur, perhaps because of heterogeneous areas of refractoriness or persistent foci.[47] Regardless, shocks must be of sufficient intensity to deliver depolarizing current to the majority of the heart.

Several maneuvers can facilitate electrical defibrillation. Increased pressure of paddles from 0.5 to 8.0 kg on the chest will decrease transthoracic impedance by as much as 14%, increasing delivery of current to the heart.[48,49] This advantage of paddles must be weighed against the increased safety and convenience afforded by hands-free adhesive defibrillation pads. Multiphasic shock waveforms that produce more effective depolarization of individual myocytes (e.g., biphasic waveforms) tend to accomplish defibrillation with less energy.[43] In the past, multiple shocks would be delivered in rapid succession to decrease chest impedance. However, repetitive shocks decrease chest impedance only about 8% in actual patients.[48] Rescue shock energy can be increased by much greater amounts, and this modest decrease in impedance afforded by repetitive shocks probably does not justify prolonging the interruption of artificial circulation. Together, these data suggest that rescue shocks of sufficient energy with multiphasic waveforms should be delivered singly to the patient in VF using firm paddle pressure on the chest.

For VF that has lasted more than 3 to 4 minutes, delaying rescue shocks until after a few minutes of chest compressions can improve the rescue shock success. In animals, reperfusion before rescue shocks appears to be preferable to immediate rescue shock after more than 5 minutes of untreated VF.[50-53] Researchers in two clinical studies have found that either 90 seconds or 3 minutes of chest compressions before delivery of the initial rescue shock improved resuscitation rates for subjects with VF outside the hospital, particularly when rescuer response intervals are longer than 4 minutes.[4,54] Thus, defibrillation should be provided immediately for VF shortly after a witnessed collapse, but a brief period of artificial circulation should precede any shock delivery to VF that has lasted longer.

Quantitative analysis of the VF waveform can distinguish early VF from late VF and may be useful for estimating the likelihood of rescue shock success (see Fig. 50-5).[55] Larger amplitude of VF suggests early VF and is associated with more successful resuscitation.[56] However, amplitude can be affected by body habitus and other recording conditions. Frequency-based measures, as well as nonlinear dynamic measures, also can be used to quantify VF and to estimate the probability of rescue shock success and are less dependent on recording conditions.[57-60] All of these measures, or some combination of these measures, are likely to be implemented in future generations of defibrillators. These devices will provide real-time, semi-quantitative estimates of the probability that a rescue shock will succeed in restoring an organized rhythm. Using this information, the clinician will be able to choose to shock VF when the probability of shock success is high or to concentrate on improving the situation with artificial perfusion when the probability of shock success is low.

DRUG THERAPY

All drug therapy in cardiac arrest can be divided into three categories: pressors, antidysrhythmics, and metabolic drugs. There is good evidence that pressors improve artificial circulation, making resuscitation more likely. Antidysrhythmic drugs are effective for preventing dysrhythmias and therefore have a role in stabilizing the heart once circulation is restored. The value of an antidysrhythmic drug for terminating VF or reversing asystole is less clear. Metabolic drugs, primarily bicarbonate, can be used to reverse acidosis or other electrolyte problems when they are recognized. However, there are no data to support the routine use of these drugs for all patients.

Pressors used during resuscitation include epinephrine and vasopressin. Both of these drugs can increase CPP through actions on alpha-adrenergic (epinephrine) or vasopressin receptors (Fig. 50-6).[61,62] Epinephrine is usually administered in 1 mg (~0.015 mg/kg) increments. In laboratory studies, the pressor effects of epinephrine during cardiac arrest are brief (~5 minutes). Vasopressin has been administered as 40-unit boluses (~0.5 unit/kg) and produces a longer-lasting increase in CPP (~10 minutes). Both drugs should be titrated to improvement in clinical indicators (ECG waveform, mechanical activity, changes in end-tidal CO_2 or coronary perfusion pressure).

The 1-mg dose of epinephrine is widely believed to be subtherapeutic in the setting of circulatory arrest lasting more than a few minutes. Trials in out-of-hospital patients comparing higher initial boluses of epinephrine (15 mg vs. 1 mg) found a higher rate of restoration of pulses (13% vs. 8%) and admission to the hospital (18% vs. 10%).[63] However, overall survival was not different. Comparison of a lower dose (7 mg vs. 1 mg) of epinephrine in both in-hospital and out-of-hospital cardiac arrest found no change in restoration of pulses or survival.[64] Likewise, comparison of 0.02 mg/kg versus 0.2 mg/kg epinephrine found no change in restoration of pulses or survival.[65]

It is possible that the beta-adrenergic effect of these higher doses of epinephrine produces toxicity that limits long-term survival. Post-resuscitation impairment of cardiac index and oxygen delivery has been related to epinephrine dose.[66] No trial has completed a direct comparison of epinephrine with more selective alpha-adrenergic agents such as phenylephrine. However, one trial found no advantage from administration of 11 mg of norepinephrine.[63]

Vasopressin can increase coronary perfusion pressure without complicating beta-adrenergic effects. Resuscitation rates and survival are identical for inpatients resuscitated with vasopressin and standard doses of epinephrine.[67] For out-of-hospital cardiac arrest, vasopressin appears to be superior for resuscitation and survival of patients whose first ECG rhythm is asystole.[68] Post hoc analyses suggest that vasopressin may be superior for those subjects requiring multiple doses of vasopressors. At present, use of either drug is justified in the setting of cardiac arrest. None of the studies on these pressors standardized post-resuscitation care, and therefore all are limited in their ability to define drug effects on neurologic recovery.

The role of antidysrhythmic drugs during cardiac arrest is equivocal.[69,70] Atropine may relieve bradycardia when it is vagally mediated. However, nervous system influences on the heart are largely eliminated after more than 1 to 2 minutes of circulatory arrest. Lidocaine, procainamide, and bretylium have a long history of use in the treatment of VF. The basis for this use is principally the observation that these drugs can suppress dysrhythmias before cardiac arrest. Once VF is established, lidocaine can actually increase the electrical energy required

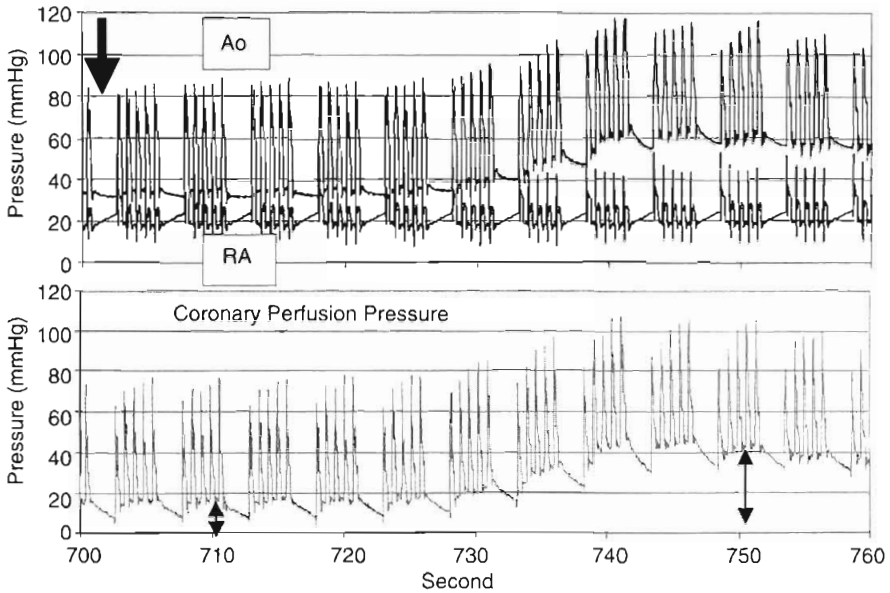


FIGURE 50–6. Administration of a pressor drug *(arrow)*, in this case vasopressin, can increase coronary perfusion pressure (CPP) produced by chest compressions. Note that the CPP generated by chest compressions alone (at ~710 seconds) is below the 15 to 20 mm Hg believed necessary for restoration of circulation. However, at 40 to 60 seconds after drug administration (at ~750 seconds) CPP increases above this threshold *(long, double-headed arrow)*. When treating cardiac arrest, it is unreasonable to expect physiologic responses to pressor drug administration until after at least 60 more seconds of chest compressions. (Unpublished laboratory data.)

to defibrillate by more than 50%.[71] This effect is not true for agents that are less potent as sodium channel antagonists. For example, administration of amiodarone (5 mg/kg) is superior to placebo[72] and to lidocaine[73] for restoration of pulses in out-of-hospital patients with VF that is not terminated by three rescue shocks. These studies did not control subsequent critical care and are thus not designed to determine any effect on long-term survival. In summary, antidysrhythmic drugs are commonly used during resuscitation, but only amiodarone use has supporting human data.

Empirical treatments of metabolic disturbances during cardiac arrest are not supported by prospective human data. Bicarbonate or other buffers may improve acidemia resulting from ischemia, but no efficacy study of human administration is available.[74] Aminophylline has been proposed as an antagonist of adenosine released during ischemia. Adenosine is hypothesized to suppress cardiac electrical activity. Two prospective studies of aminophylline administration to subjects with PEA or asystole failed to demonstrate any improvement in resuscitation.[75,76] Use of dextrose-containing fluids versus dextrose-free fluids did not alter outcome for out-of-hospital cardiac arrest.[77] Other metabolic therapies including calcium and magnesium also lack supporting data.[78,79] However, specific use of these agents for specific causes of cardiac arrest, such as known hyperkalemia, calcium channel blocker overdose, torsades, or hypomagnesemia remains appropriate.

Taken together, data support a simple pharmacologic approach to treatment of cardiac arrest. First, the vasopressors epinephrine and vasopressin are useful for augmenting CPP generated during chest compressions. Other vasopressors should also be useful but lack prospective data. Second, antidysrhythmic drugs are useful for maintaining organized rhythms but not for terminating VF. Only amiodarone has clinical data supporting its use during VF that persists after rescue shocks. All other drug therapy should be based on the clinical situation and the response of the patient.

ASPECTS OF CARDIAC ARREST IN SPECIFIC SITUATIONS

The original cause of cardiac arrest may not be known during acute resuscitation. However, if this information is available, treatment and prognosis can be individualized to the specific patient. Among out-of-hospital patients, as many as 66% have primary cardiac disturbances.[80] For in-hospital patients experiencing cardiac arrest, dysrhythmia and cardiac ischemia account for 59% of events.[10] This section reviews unique features of cardiac arrest resulting from both cardiac and noncardiac causes.

PRIMARY CARDIAC EVENTS

Cardiac arrest is most commonly attributable to cardiac disease. A primary dysrhythmia or cardiogenic shock is the most common proximate cause of cardiac arrest.[80,81] Patients undergoing angioplasty have 1.3% incidence of cardiac arrest, and survival in these patients resembles survival in other populations.[82] Among patients admitted to the hospital with acute myocardial infarction, cardiac arrest occurs in 4.8%.[12] Dysrhythmias are common during the hours after reperfusion therapy,[82] although reperfusion therapy reduces the overall risk of cardiac arrest.[83] During acute myocardial infarction, cardiac arrest is most likely in patients with lower serum potassium levels, more than 20 mm of total ST segment elevation, and a prolonged QTc interval during the first 2 hours of their event.[83] With a mean follow-up of 43 months, 3.3% of subjects surviving acute myocardial infarction suffered sudden cardiac death.[84] Abnormalities of the heart are present in most cases of cardiac arrest, with coronary artery disease present in at least 65% of autopsies.[85] Taken together, these data suggest that most patients with cardiac arrest will have contributing cardiovascular disease.

An acute coronary syndrome is present in more than one half of patients presenting with primary cardiac arrest outside the hospital. When angiography was performed on

consecutive patients resuscitated from cardiac arrest, coronary artery occlusion was identified in 48%.[86] Similarly, 51% of initially resuscitated outpatients exhibited cardiac enzyme elevation or ECG evidence of acute myocardial infarction.[87] In one series, troponin T was elevated in 40% of out-of-hospital patients undergoing cardiopulmonary resuscitation (CPR), regardless of whether circulation was restored.[88] The direct myocardial injury from defibrillation and CPR may cause spurious elevations of creatine kinase that are unrelated to cardiovascular disease.[89] However, cardiac troponin elevations are believed to reflect acute myocardial infarction rather than injury from electrical shocks.[90] Thus, the 40% of subjects undergoing CPR with elevated troponin probably suffered myocardial injury before collapse.

The high likelihood of an acute coronary syndrome in the patient suffering cardiac arrest should prompt consideration of antiplatelet therapy, anticoagulation, beta blockade, and nitrates during the post-resuscitation care. Unless a clearly noncardiac etiology for cardiac arrest is evident, acute coronary angiography may reveal an indication for angioplasty, thrombolysis, or other reperfusion therapy. Early angioplasty or reperfusion therapy is associated with improved survival and outcome.[12,86,91]

Primary ventricular tachyarrhythmias are rapidly reversible and may be more likely than PEA or asystole for patients with a primary cardiac cause of collapse. Ventricular tachyarrhythmias are the initially recorded rhythm in 38% to 41% of out-of-hospital cardiac arrests[6,92] and in 25% of in-hospital cardiac arrests.[10] Because VF is rapidly reversible, patients with this rhythm comprise the majority of survivors of cardiac arrest. Data collected over three decades in one city noted that the prevalence of VF in out-of-hospital cardiac arrest has declined since 1978.[10] This trend may reflect a change in preventive medicine or in the epidemiology of cardiovascular disease over time. Once defibrillation is accomplished, short-term suppression of ventricular dysrhythmias with infusions of lidocaine, amiodarone, procainamide, or other antidysrhythmics is reasonable for these patients.

For subjects who survive sudden cardiac arrest and have decreased left ventricular function, long-term antidysrhythmia treatment should be considered.[93] Subjects surviving a life-threatening ventricular dysrhythmia had a 15% to 20% risk of death during a mean of 16 months of follow-up, even when a reversible cause of the dysrhythmia, such as electrolyte disturbance or hypoxemia, could be identified.[94] Implantable defibrillators have been found to be superior to antidysrhythmic drugs for reducing this risk of subsequent death.[95] This benefit is primarily in subjects with a left ventricular ejection fraction less than 0.35.[96] Implantable defibrillators were not better than antidysrhythmic drugs in a European trial that enrolled subjects resuscitated from cardiac arrest secondary to ventricular dysrhythmia without regard to left ventricular ejection fraction.[97] Nevertheless, these devices offer significant hope of preventing sudden cardiac death, and identification of patients whom they may benefit is an active area of research. At present, implantable defibrillators should be discussed for patients with left ventricular ejection fraction less than 0.35 and prior evidence of ventricular arrhythmias, particularly after acute myocardial infarction.

ASPHYXIA

Asphyxia-induced cardiac arrest can result from drowning, choking, asthma, progressive respiratory failure with hypoxemia, or traumatic coma with hypoventilation. Acute asphyxia causes transient tachycardia and hypertension, followed by bradycardia and hypotension, progressing to PEA or asystole. This period of blood flow with severe hypoxemia before cardiac arrest may make asphyxiation a more severe injury than VF or other rapid causes of circulatory arrest.[98] Brain edema was more common on computed tomography after resuscitation when cardiac arrest was caused by pulmonary rather than cardiac causes.[99]

During cardiac arrest, pulmonary edema develops from redistribution of blood into the pulmonary vasculature.[100] Thus, oxygenation is only worsened in the asphyxiated patient. Attention to the primary cause of asphyxia, as well as to maneuvers that will increase oxygenation, such as increased end-expiratory pressure or increased inspiration to expiration time ratios may be necessary.

PULMONARY EMBOLISM

Pulmonary emboli may occur in the postsurgical patient, as well as in medical patients with impaired mobility.[101] In one series, pulmonary emboli were present in 10% of in-hospital deaths,[102] and the prevalence among out-of-hospital deaths was similar.[103] Pulmonary emboli can result in rapid cardiopulmonary collapse and should be considered as a possible cause of cardiac arrest in the proper clinical setting or when collapse is preceded by sudden shortness of breath, hypoxemia, and/or pleuritic chest pain.

Physiologically, pulmonary emboli can result in cardiac arrest if a large thrombus obstructs right ventricular outflow into the pulmonary arteries. This situation results in a dilated, distended right ventricle and an empty left ventricle. Right ventricular dilation is sufficiently profound that it can be seen on transthoracic echocardiogram. Circulation cannot be restored unless this obstruction is relieved. Because the primary disturbance is hypoxemia and decreased cardiac output, cardiac arrest from pulmonary embolism should present as an initial rhythm of PEA or asystole.

Administration of bolus fibrinolytic drugs (tissue plasminogen activator, streptokinase, or urokinase) may help acutely during resuscitation of a patient with a suspected pulmonary embolism. Smaller pulmonary emboli can lead to cardiac arrest because of hypoxemia, and resuscitation may be possible before fibrinolysis if adequate oxygen exchange can be restored. Thrombolytic drugs have been used in a nonrandomized trial during resuscitation of undifferentiated patients with some success.[104] However, a randomized clinical trial of tissue plasminogen activator to patients with out-of-hospital cardiac arrest and an initial rhythm of PEA failed to demonstrate any benefit, although drug administration was late during resuscitation.[105]

ELECTROLYTE DISTURBANCES

Potassium disturbances are the most likely electrolyte disturbance to result in cardiac arrest. In cardiac patients, hypokalemia has been linked to the incidence of VF after myocardial infarction.[83,106] Hypokalemia also may account for the increased incidence of sudden death in patients taking large doses of diuretics. VF is rare in patients where the serum potassium concentration is maintained greater than 4.5 mEq/L. Conversely, hyperkalemia can prolong repolarization, increasing the likelihood of VF initiation. Hyperkalemia may also suppress automaticity in the myocardial electrical

system, leading to bradycardic PEA or asystole. Cardiac arrest occurring during hemodialysis is not associated with high or low potassium levels but is more common when patients are dialyzed against a low (0 or 1.0 mEq/L) potassium dialysate.[107] These data suggest that rapid changes in potassium rather than the absolute value are important triggers of cardiac arrest in this population. Derangements of calcium and magnesium may produce similar or synergistic changes in cardiac conduction.

The clinical setting of cardiac arrest may suggest a primary electrolyte disturbance. Heavy diuretic use or intestinal fluid loss, for example, suggests potassium depletion. Suspected hypokalemia will not change acute resuscitation but must be addressed promptly in the post-resuscitation stabilization of the patient. Cardiac arrest in a patient with renal failure or during potassium infusion suggests hyperkalemia. Widened ventricular complexes with repolarization abnormalities on ECG would heighten this suspicion. If hyperkalemia is suspected, the usual acute resuscitation maneuvers can be supplemented by bolus injection of calcium carbonate (1 mg), bicarbonate (1 mEq/kg), and perhaps insulin (0.1 units/kg) with glucose (0.5 to 1 g/kg). These drugs may improve cardiac electrical stability, facilitating restoration of circulation.

POISONING

Cardiac arrest can result from drug overdose. Therapy does not change except when specific antidotes or countermeasures to the poison are available. For example, calcium channel blocker overdose may be countered by administration of intravenous calcium.[108] Beta-blocker toxicity may require large doses of inotropic agents[109] or may respond to glucagon.[110] Digoxin overdose may respond to digoxin-binding antibodies.[111] In the case of narcotic-induced respiratory depression, subsequent cardiac arrest is a specific result of asphyxia. One principle of poisonings is that the patient was often healthy before the event and may recover well once the poison is eliminated. This potential for a better outcome may justify longer and more aggressive efforts at resuscitation.

SEPSIS

Cardiac arrest can develop from sepsis for several reasons. Direct myocardial depression occurs, probably owing to humoral factors.[112,113] Vasodilation results in apparent hypovolemia. Finally, impaired oxygen extraction, shunting, and mitochondrial depression can produce cellular hypoxia. Because pump and vascular failure are the principal physiologic derangements, the most common initial ECG rhythm would be expected to be a rapid PEA that slows to asystole with ischemia. When these processes have progressed to cardiac arrest, large doses of inotropes, vasoconstrictors, and volume may be needed to restore circulation. Because the underlying sepsis physiology will still be present if pulses are restored, these patients may prove exceedingly unstable during the subacute recovery period and have a reduced chance for survival.[18,114-116]

TRAUMA/HEMORRHAGE

Hypovolemic cardiac arrest occurs after severe trauma, gastrointestinal hemorrhage, or other blood loss. Absence of venous return results in an empty heart, which cannot produce cardiac output despite normal inotropic state and normal or increased vascular tone. As with sepsis, this situation would most likely present with a rapid PEA that slows to asystole, but VF can develop in response to the global ischemia. Because cardiac function and vascular function are initially normal, inotropes and vasoconstrictors are unlikely to benefit hypovolemic cardiac arrest. Rapid replacement of volume with crystalloid infusion is indicated. Colloid or blood infusion should correct the situation more rapidly.[117] After restoration of circulation, patients with hemorrhagic cardiac arrest are likely to develop multisystem organ failure.[117]

During hypovolemic cardiac arrest the empty cardiac ventricles render external chest compressions ineffective. If blood loss is ongoing or if massive volume replacement cannot be instituted rapidly, thoracotomy allows clamping or compression of the aorta, perhaps retaining sufficient blood in the proximal aorta to perfuse the coronary and cerebral arteries. This procedure has produced success in the treatment of penetrating traumatic injuries[118] but not in blunt trauma.[119] Survival is better if thoracotomy occurs in the operating room after brief loss of pulses and best if the penetrating injury has created cardiac tamponade that is directly relieved by pericardotomy. Restoration of circulation must be accompanied by repair of the site of hemorrhage.

HYPOTHERMIA

Hypothermia represents an important situation in which prolonged resuscitative efforts are justified. If hypothermia develops before circulatory arrest, the tolerance of the heart and brain to ischemia is greatly prolonged. Survival with favorable neurologic recovery has been reported after cold-water submersion or exposure with cardiac arrest and resuscitation efforts lasting several hours.[120,121] Although all data are retrospective, subjects in whom circulatory arrest occurs because of hypothermia appear to be more salvageable than subjects who asphyxiate or have circulatory arrest before becoming cold.[122]

Treatment should be based on the initial temperature of the patient. Between 32°C and 37°C, no change in drug or electrical treatment is required, and this level of hypothermia may be beneficial for resuscitation of both brain and heart.[123,124] Between 29°C and 32°C, cardiac activity may be preserved, and external warming (warm air, heating lights, warm blankets) and warm intravenous fluids should accompany usual resuscitation efforts. The likelihood of generating sufficient perfusion to rewarm the body declines as temperature decreases from 32°C to 29°C, and more invasive warming should be considered if there is not a rapid response with external warming. More invasive and aggressive treatment will almost certainly be required for cooler patients, because both mechanical and electrical activity of the heart are disrupted at temperatures below 28°C. Patients below this temperature may exhibit PEA, VF that is refractory to defibrillation attempts, or asystole. Repetitive rescue shocks in such patients are not justified and may be detrimental. Efficacy of most resuscitation drugs may be impaired.

Several techniques for active rewarming during resuscitation of victims of severe hypothermia are available. Given the potentially prolonged tolerance of the cold patient to ischemia, there may be sufficient time to establish arterial and venous access for partial or complete cardiopulmonary bypass. Extracorporeal circulation is particularly useful in these subjects because it can provide artificial circulation at the same time as rewarming.[122,125,126] In the absence of extracorporeal

circulation, placement of thoracostomy tubes and lavage of the chest with warm fluids is an option.[127] Thoracostomy is intuitively preferable to peritoneal lavage because the heart will be directly warmed. Warm air forced over the body surface can rewarm a patient, although this technique may provide the least heat exchange.[128] In any case, it is difficult to determine whether circulation can be reestablished in the profoundly hypothermic patient until near physiologic core temperatures (33°C to 37°C) are restored.

OTHER MEDICAL CONDITIONS

Comorbidities have a tremendous influence on the outcome from cardiac arrest.[81,129,130] In some cases, cardiac arrest may be an expected progression of the patient's disease but guidelines about limiting resuscitation were not defined. For example, no survivors were reported among cancer patients with expected cardiac arrest.[130] Therefore, it may be appropriate to set limits on resuscitation efforts in certain medical conditions before cardiopulmonary collapse. Ideally, discussion about the expectations for resuscitative efforts should be held with the patient, the family, or the patient representatives before cardiac arrest. If those discussions did not occur before the first cardiac arrest, they should follow promptly any initially successful resuscitation.

POST-RESUSCITATION CARE TO MINIMIZE BRAIN INJURY

Management of the patient after restoration of circulation affects ultimate outcome. For example, long-term survival differed for comparable patients treated by a single ambulance service but delivered to separate hospitals.[1,2] Institutional differences in in-hospital management, particularly in the permitted frequency of hyperthermia and hyperglycemia, were identified that may have accounted for these differences. Despite the apparent importance of post-resuscitation critical care, there are few guidelines for treatment.

Brain injury appears not to be acute neuronal necrosis during ischemia but instead to be an active process that develops over hours to days after resuscitation. Multiple cellular and molecular mechanisms contribute to neurologic injury after global brain ischemia.[131] These are discussed in greater detail in Chapter 46. Germane to cardiac arrest, during brain ischemia and immediately after reperfusion, studies have detected increased release of excitatory amino acids, free radicals, and energy failure. Protein synthesis is inhibited at the level of translation initiation for several hours.[132] There are focal disturbances of cerebral blood flow.[133] Specific intracellular and extracellular signaling pathways are activated for several hours after brain ischemia,[134,135] which may lead to specific changes in gene transcription. Finally, activation of specific proteases between 24 and 72 hours after reperfusion is associated with appearance of histologic signs of neuronal death.[136] The relative contribution of each of these processes to neuronal injury is unknown, and all may contribute synergistically to brain injury. All represent potential targets for therapeutic intervention.

Despite detailed knowledge of the mechanisms involved with brain ischemia, drugs that target specific pathways provide modest effects in laboratory studies, and no drug to date has demonstrated clear benefit in human trials. Randomized clinical trials have examined thiopental, the calcium-channel blocker lidoflazine, magnesium, and diazepam.[137-139] One explanation for this failure is that multiple mechanisms contribute simultaneously to the process of ischemic neuronal death. Antagonizing one pathway leading to neuronal death may leave other mechanisms unaffected. Less-specific therapies or multifaceted therapies that affect multiple pathways may prove more effective.

In support of this idea, prospective randomized clinical trials confirm that induction of mild hypothermia (33°C to 34°C) for 12 to 24 hours after resuscitation improves survival and neurologic recovery.[123,140] Observational data also support avoidance of fever, hypotension, and hyperglycemia.[1,141-143] Therefore, systematic brain-oriented intensive care rather than a single therapeutic drug or intervention is required to improve outcome (Table 50-1).

TABLE 50–1. POST-RESUSCITATION INTENSIVE CARE

Temperature
Avoid fever for 48 hours
Induce mild hypothermia of 33°C to 34°C for 12-24 hours
Rewarm slowly (<1°C/hr)
Cardiovascular
Mean arterial pressure > 100 mm Hg for first day
Inotropic and vasopressor support as needed
Invasive monitoring as needed
Must be balanced by concern for injured heart
Suppress dysrhythmias
Reperfusion therapy for acute myocardial infarction
Medical management for acute coronary syndromes
Beta blockade, antiplatelet drugs, anticoagulation
Nitrates as tolerated
Pulmonary
Usual care
Pneumonia common
Gastrointestinal
Usual care
Consider early refeeding to reduce translocation
Fluids/Electrolytes
Monitor central venous pressure and urine output with hypothermia/rewarming
Monitor potassium/electrolytes during temperature changes
Keep potassium ≥4.5 mEq/L
Monitor glucose concentration frequently, and avoid hyperglycemia
Hematologic
Prothrombotic state is common
Anticoagulation is of unproven benefit but reasonable
Infection
Bacteremia and pneumonia are common
Prophylactic antibiotics are of unproven benefit
Antipyretics are reasonable
Neurologic
Sedation as needed for hypothermia induction
Most clinical improvement occurs over first 72 hours
Clinical examination for prognosis
Electroencephalography and evoked potentials may add to clinical examination for selected patients

TEMPERATURE CONTROL

Meticulous avoidance of fever is important during the first 24 to 48 hours after ischemic brain injury. Temperature control after cardiac arrest may be confounded by the fact that the occurrence of bacteremia and spontaneous fever is common in the resuscitated patient.[144,145] The benefit of lower temperatures for injured brain tissue has been demonstrated after traumatic brain injury, stroke, and cardiac arrest.[141,146,147] Mechanistically, temperature probably affects more than brain metabolic rate. For example, manipulations of temperature that improve neurologic recovery in laboratory studies produce no effect on jugular venous lactate or oxygen uptake.[148] Recent laboratory investigations suggest that a variety of signaling pathways and cellular responses are sensitive to relatively small (1°C to 2°C) changes in brain temperature.[134,135]

Induction of mild hypothermia for resuscitated patients produces a 24% to 30% relative risk reduction for death or poor neurologic outcome (Fig. 50-7).[149] Mild hypothermia (33°C to 34°C) maintained for 12 or 24 hours significantly improved the odds of survival and good neurologic outcome for subjects resuscitated from VF cardiac arrest.[123,140] There is no reason to believe that this neurologic benefit of induced hypothermia is specific to patients with one type of cardiac rhythm, and use in all post-resuscitation patients seems reasonable. At the time of resuscitation, many patients are already mildly hypothermic with core temperatures between 35°C and 35.5°C.[123,140,150] This spontaneous cooling may result from equilibration of core and peripheral blood compartments during circulatory arrest. Subsequent to restoration of circulation, patients will rewarm within a few hours unless specific interventions are instituted.[141]

The optimal duration of cooling, the maximum delay in achieving target temperatures, the optimal target temperature, and the preferred rate of rewarming are unknown. Laboratory studies suggest that cooling to between 32°C and 35°C for 12 to 24 hours is beneficial, particularly if cooling is achieved within 6 hours after resuscitation. These studies also suggest that temperature is less important more than 48 hours after resuscitation and that rewarming should be performed slowly (<1°C/hr). Clinical data to answer these practical questions are likely to become available over the next few years as the use of therapeutic hypothermia becomes widespread.

After cardiac arrest, mild hypothermia can be induced by a variety of techniques. Surface cooling with ice packs and cooling blankets is tolerated by the comatose patient.[140,151] Neuromuscular blockade and sedation can help prevent shivering or other compensatory reflexes. However, surface cooling alone is slow and may require 4 to 6 hours to reach 34°C.[123,146,152] Lavage of the stomach with ice-cold water can accelerate cooling but is labor intensive. Local cooling of the head is unlikely to produce brain hypothermia when there is adequate perfusion by warm core blood,[150] although the head can be an effective site for removing heat from the body.[153] Intravascular devices can provide direct cooling of blood in the vena cava, but these devices are expensive and invasive.[124] Rapid infusion of 30 mL/kg cold (4°C) crystalloid produces a rapid decrease in core temperature and is tolerated by the post-resuscitation patient.[154] The volume required may limit this intervention to those patients without renal failure or pulmonary edema. Taken together, these data support the rapid induction of mild hypothermia by surface cooling and bolus

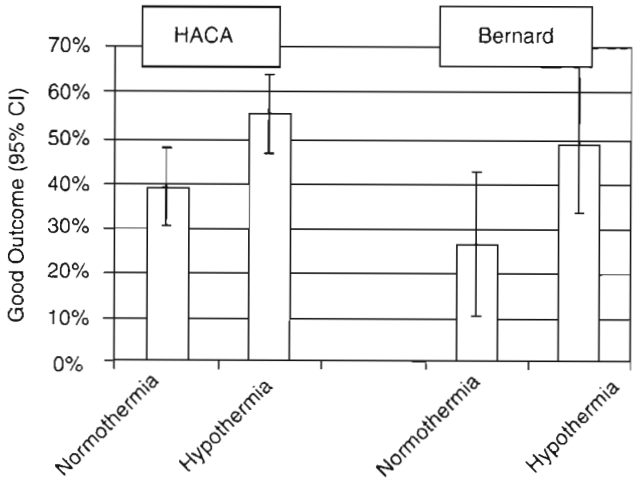


FIGURE 50-7. Improvement in good neurologic outcome was reported in two randomized clinical trials of therapeutic hypothermia. HACA[123] studied 275 subjects, with 137 receiving 24 hours of cooling to 32°C to 34°C. Bernard and colleagues[140] studied 77 subjects, with 43 receiving 12 hours of cooling to 33°C.

infusion of cold intravenous fluids (unless contraindicated), followed by maintenance of hypothermia by surface cooling, neuromuscular blockade, and sedation (Fig. 50-8.)

Fluid and electrolyte shifts are the primary management concerns during induction of hypothermia. Induction of cooling can result in peripheral vasoconstriction, with an apparent reduction in vascular volume.[155] CVP will increase, followed by diuresis. Conversely, at the time of rewarming, vessels will dilate, CVP will decrease, and the patient may become relatively hypovolemic. Volume status should be followed closely, and a need for additional volume infusion to maintain blood pressure and urine output should be anticipated at the time of rewarming. Inattention to this fluid shift was cited as a pitfall in trials of therapeutic hypothermia for traumatic brain injury.[155] The initial diuresis, along with shifts between intracellular and extracellular compartments, can result in hypokalemia, hypophosphatemia, and hypomagnesemia at cooling, followed by hyperkalemia at rewarming.[156,157] Frequent monitoring and correction of electrolytes during these transitions is warranted.

Cardiovascular complications of hypothermia are rare with temperatures greater than 30°C. Cooling from 37°C to 31°C actually has a positive inotropic effect, increasing stroke volume to a greater extent than it decreases heart rate.[158] Systemic vascular resistance does not appear to change greatly. Clinical data report a transient 18% decline in cardiac index with cooling to 33°C.[159] Conscious patients undergoing angioplasty for acute myocardial infarction tolerate mild hypothermia.[124] In these patients, cooling did not interfere with defibrillation when it was required.

Other complications of mild hypothermia are few when the cooling period lasts less than 24 hours. Infections do become more common if cooling is prolonged for more than 24 hours. There is a suggestion that infections were slightly more common in post-resuscitation patients cooled for 24 hours,[123] but not in those cooled for 12 hours.[140] Although mild hypothermia can inhibit platelet function and coagulation,[160] these changes are of small magnitude, leading to no bleeding complications in studies to date. These studies included subjects with concurrent trauma or administration of heparinoids

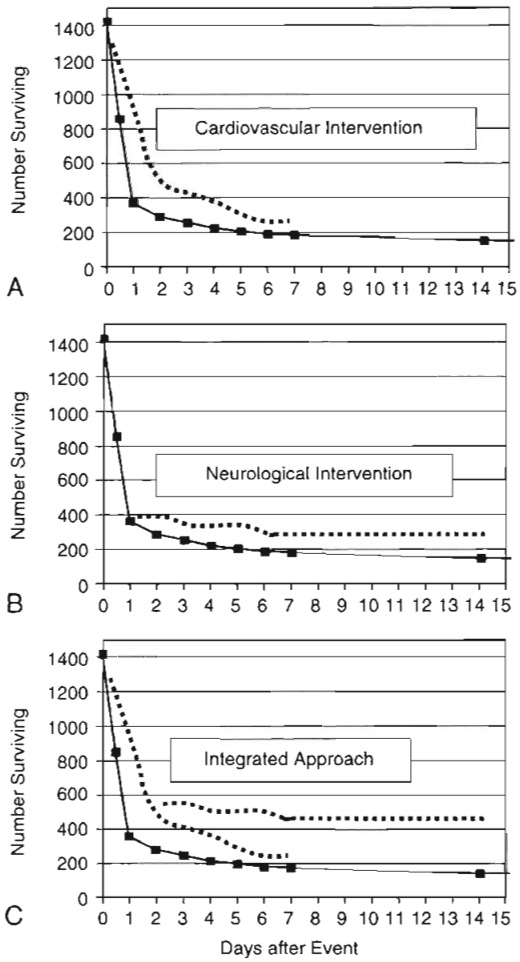


FIGURE 50–8. An integrated approach to cardiopulmonary-cerebral resuscitation is most likely to generate significant changes in patient survival after cardiac arrest. Hypothesized benefits are superimposed on recent survival curves from one city. **A,** Compared with current care, an intervention that improves cardiovascular resuscitation may increase admission to the hospital without preventing later death due to brain injury. **B,** An intervention that improves neurologic recovery may improve the proportion of subjects who awaken from coma, but the magnitude of this benefit for the population is obscured by the large number of deaths due to cardiopulmonary collapse. **C,** Combined care directed at both cardiopulmonary and neurologic injury may provide more than additive increases in meaningful survival.

and glycoprotein IIb/IIIa inhibitors.[124,146] Elevations of pancreatic enzymes have been reported in cooled patients, but these changes resolve with rewarming.[123,159] Creatinine clearance and platelet count may decrease during cooling, but both parameters normalize with rewarming.[159]

BLOOD PRESSURE AND CEREBRAL BLOOD FLOW

After cardiac arrest, the heart experiences a reversible period of decreased mechanical function.[161] The biochemical basis for this dysfunction is an active area of study. Moreover, reperfusion at the time of resuscitation includes oxidative stress or other triggers that can lead to myocyte death.[162] From a clinical standpoint, inotropic support will almost certainly be necessary for any patient resuscitated from cardiac arrest lasting more than 3 or 4 minutes. This dependence on inotropes should decline over the subsequent 24 to 48 hours.

Autoregulation of cerebral blood flow is disturbed after cardiac arrest. Measurement of oxygen saturation in the jugular bulb venous blood allows calculation of brain oxygen extraction. Furthermore, cerebral blood flow can be estimated using transcranial Doppler ultrasound or nuclear imaging. During the first day after resuscitation from cardiac arrest, patients exhibit increased cerebral vascular resistance[163] and impaired cerebral autoregulation.[164,165] When autoregulation is present, it is right shifted such that brain perfusion declines when mean arterial pressure declines below 80 to 120 mm Hg. When blood pressure is maintained, clinical PET studies suggest that regional perfusion remains matched to metabolic activity after cardiac arrest.[166]

Therefore, after cardiac arrest, relative hypertension (mean arterial pressure greater than 100 to 110 mm Hg) should be maintained to prevent brain hypoperfusion. Maintaining this level of hypertension will require infusions of inotropes and/or pressors. In support of this recommendation, hypotension during the first 3 hours after resuscitation is associated with poor neurologic recovery in patients admitted to the hospital after cardiac arrest.[142] Future research is needed to develop hemodynamic support strategies that optimize both cerebral and cardiac perfusion and metabolism during ICU care after cardiac arrest.

GLUCOSE CONTROL

Elevated serum glucose is associated with poor outcome after cardiac arrest[77] and may be a marker of prolonged or difficult resuscitation. Both epinephrine and physiologic stress can elevate serum glucose levels. However, multivariate models that accounted for resuscitation time and medication usage still show an effect of serum glucose on admission and during the first 48 hours of intensive care on long-term outcome.[1,167] Despite this association, both studies noted that monitoring of glucose in nondiabetic patients was infrequent. Because no randomized clinical trial has been performed, it remains unclear whether aggressive management of serum glucose concentration will improve outcome.

HEMATOLOGIC CHANGES

Cardiac arrest is associated with activation of coagulation that is not balanced by fibrinolysis. This hematologic profile is reminiscent of DIC and may contribute to subsequent end-organ dysfunction. Markers of thrombogenesis that have been reported include increased thrombin-antithrombin complexes and fibrinopeptide A.[168,169] These increases are not balanced by fibrinolytic factors for at least 24 hours. The cause of these changes is unknown and may be related to ischemic injury to the endothelium.

At present, use of anticoagulation is variable and there are no prospective trials evaluating the effect of anticoagulation after resuscitation. Anticoagulation and even fibrinolytic drugs are safe after CPR.[169,170] A retrospective series noted a univariate relationship between anticoagulation and 6-month survival that was not significant in a multivariate model.[167] In a series of patients with cardiac arrest related to VF and cardiac ischemia, administration of thrombolytic drugs was associated with better neurologic outcome.[171] Given the

hematologic evidence of active thrombogenesis, these data suggest that at least anticoagulation should be considered immediately after resuscitation.

INFECTION

The physiology of the post-resuscitation patient resembles that of systemic inflammatory response syndrome. Bacteremia has been noted in 39% of patients during the first 12 hours after resuscitation.[144] Fever is common in patients within 48 hours after resuscitation from cardiac arrest. Potential causes include contamination during emergent line placement, aspiration or transient bacteremia during airway management, and mesenteric ischemia contributing to bacterial translocation from the gut. Endotoxin and various cytokines are increased in serum after resuscitation.[172] Whereas an intestinal origin of endotoxin was suspected, pulmonary infections were more common than bacteremia. When they develop, severe infections are associated with mortality.[145] Despite these observations, the role of routine antibiotics and antipyretics has not been examined.

PREDICTING NEUROLOGIC RECOVERY

The goal of clinical practice always is to restore the patient to full consciousness and function.[173] All subjects with circulatory arrest of more than a 1 or 2 minutes will be comatose at initial presentation, but some of these same patients can recover and awaken. Therefore, signs of neurologic activity immediately after restoration of circulation are encouraging, but their absence does not preclude eventual recovery. Unfortunately, many cardiac arrest survivors fail to completely awaken and may meet criteria for a persistent vegetative state.[174,175] The status of patients who do not quite meet these criteria but are not awake has been described as a minimally conscious state.[176] Assessment of neurologic prognosis after resuscitation becomes increasingly reliable over the first 3 days of recovery.[177-179]

Several clinical signs have been used to assess awakening after cardiac arrest. A classic case series found that pupillary reaction to light, corneal reflexes, and motor activity can change over the first 72 hours after resuscitation.[179] By 72 hours, absence of eye reflexes and failure to have a localizing response to pain are highly predictive of permanent coma. A systematic review of literature since that initial report confirms the value of these clinical findings.[177] For individual patients who remain in coma, these series show how specific clinical signs can provide quantitative estimates of the probability of awakening.

NEUROPHYSIOLOGY

It is common for electroencephalography (EEG) to be done for prognostic purposes. However, the predictive value of EEG after resuscitation from cardiac arrest is unclear, and the timing of this test in relation to the ischemic event is rarely standardized. A burst-suppression pattern or an isoelectric electroencephalogram during the first week after resuscitation is associated with poor neurologic prognosis.[177] Recovery of longer-latency event-related potentials or evoked potentials (EPs) is associated with awakening.[180-182] Absence of early somatosensory EPs is very specific for poor neurologic outcome.[177] Both EEG and EPs vary with the elapsed time since resuscitation.[182] There are no data about the influence of induced hypothermia or other treatments on EEG and EPs.

BLOOD MARKERS

Several neuronal peptides appear in the blood after injury to the brain, including neuron-specific enolase (NSE) and S-100B. After cardiac arrest, NSE reaches a maximum level in serum at 72 hours. High NSE levels at 48 to 72 hours after resuscitation are associated with poor outcome.[181,183,184] Serial NSE levels that continue to rise over the first 72 hours also predict poor outcome.[184] In contrast to NSE, peak levels of S-100B in serum occur during the first 24 hours after resuscitation.[183] Higher S-100B levels are also associated with poor neurologic outcome.[183,185]

These data suggest that initial S-100B levels and the change in NSE over the first 72 hours after resuscitation may provide blood markers to follow brain injury. For example, in subjects treated with induced hypothermia, S-100B levels were not altered but decreasing NSE levels were more common.[186] More research is necessary to determine whether initial S-100B can be used to select patients for specific therapies or whether those therapies could be titrated to the changes in NSE.

IMAGING STUDIES

Imaging of the brain is important to exclude injury incurred at the time of collapse and to exclude intracranial causes of collapse. Cranial CT to exclude hemorrhage may be prudent in the comatose resuscitated patient before beginning anticoagulation or fibrinolytic therapy. Experience with more advanced imaging for making neurologic prognoses is limited. Cortical abnormalities on fluid-attenuated inversion recovery (FLAIR) MRI are associated with poor neurologic outcome.[187] In the long-term, cognitive deficits are associated with global brain volume loss after cardiac arrest.[188] At present, use of brain imaging beyond the cranial CT scan remains largely investigational.

WITHDRAWAL OF SUPPORT AND REHABILITATION

For adults who are neurologically devastated after cardiac arrest in North America, it is more common to die in the hospital than to receive long-term care. An estimated 44% of patients who are initially resuscitated from cardiac arrest in the hospital have withdrawal of care later during their hospitalization.[10] For patients resuscitated from out-of-hospital cardiac arrest, 68% have do not resuscitate (DNR) status established in the hospital, perhaps representing a comparable outcome.[14] These decisions are often based on the neurologic prognosis of the patient, and these decisions limit the number of neurologically impaired individuals who are discharged from the hospital. Quality of life for those patients who do leave the hospital is generally high.[13,189,190]

The role of rehabilitation or other therapy in recovery from neurologic impairment after cardiac arrest is relatively unstudied. It is clear that both patients and their caregivers have complex needs if neurologic injury is severe.[191] Unfortunately, long-term improvement is less common when neurologic devastation follows a medical cause, like cardiac arrest, than when it results from traumatic brain injury.[175] Popular reports

of awakening after long coma may cause inappropriate optimism for families of patients or surrogate decision makers. Partial awakening of the patient into a persistent vegetative state or minimally conscious state can further confuse their expectations. These individuals should receive information about these syndromes, expectations of recovery, and any specific considerations for the patient. Religious, cultural, and personal beliefs will contribute to their decisions, and appropriate social service and pastoral support should be provided.

ANNOTATED REFERENCES

HACA—Hypothermia after Cardiac Arrest Study Group: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549-556.

This prospective multicenter trial found that induction of mild hypothermia (33°C to 34°C) for 24 hours after restoration of circulation improved survival and neurologic recovery. Mild hypothermia reduced the relative risk of poor outcome by 26%.

Langhelle A, Tyvold SS, Lexow K, et al: In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest: A comparison between four regions in Norway. Resuscitation 2003;56:247-263.

This cohort study examined survival of patients in the hospital after initial resuscitation from out-of-hospital cardiac arrest. Survival varied between regions, and survival was independently associated with lower temperature and lower serum glucose. While not a prospective trial, these data suggest that control of these parameters may be important.

Paradis NA, Martin GB, Rivers EP, et al: Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. JAMA 1990;263:1106-1113.

This prospective study placed central monitors in 100 subjects during chest compressions. Failure to develop coronary perfusion pressures of more than 15 mm Hg guaranteed the failure of resuscitation.

Wik L, Hansen TB, Fylling F, et al: Delaying defibrillation to give basic cardiopulmonary resuscitation to patients with out-of-hospital ventricular fibrillation. JAMA 2003;289:1389-1395.

In this prospective, randomized trial, subjects with ventricular fibrillation outside the hospital received either immediate rescue shocks or 3 minutes of chest compressions before rescue shocks. The subgroup of subjects for whom response intervals were longer than 5 minutes had better outcomes if chest compressions were performed first. Immediate rescue shocks may be appropriate for brief ventricular fibrillation, but reperfusion first may be better for prolonged ventricular fibrillation.

Zandbergen EG, de Haan RJ, Stoutenbeek CP, et al: Systematic review of early prediction of poor outcome in anoxic-ischaemic coma. Lancet 1998;352:1808-1812.

This paper reviews studies of prognostic tests for predicting neurologic outcome after cardiac arrest. The literature suggests that by the third day of recovery, pupillary response and motor response to pain are predictive of outcome and that, during the first week of recovery, somatosensory evoked potentials are also predictive. Other diagnostic tests are less specific.

Chapter 51

MANAGEMENT OF ACUTE ISCHEMIC STROKE

Lawrence R. Wechsler • Carol A. Barch

KEY POINTS

1. The success of acute stroke management begins with a patient's family member or bystander recognizing the symptoms of stroke (see Table 51-1) and calling 911 immediately.
2. On arrival, the prehospital team should complete a quick assessment. The assessment includes following the basics of the *ABCs-N: a*irway, *b*reathing, *c*irculation, and *n*eurology evaluation. Oxygen saturation should be maintained at least 96% to provide adequate oxygenation to the brain tissue. Continuous monitoring of the electrocardiogram is recommended because almost 30% of ischemic stroke patients have arrhythmias (e.g., atrial fibrillation). Blood pressure should be determined, but treatment should be considered only if blood pressure is greater than 220/120 mm Hg.
3. A stroke team consists of individuals from multiple disciplines with specialized knowledge and interest in acute stroke care. The team approach brings together the necessary skills to administer emergently whatever care is best suited to the situation and divides the workload so that tasks can be performed simultaneously rather than sequentially.
4. Studies do not support a reduced recurrence rate or improved outcome with anticoagulation when administered within 24 to 48 hours of stroke onset. There is little value in anticoagulating all patients with acute stroke.
5. In June 1996, the U.S. Food and Drug Administration (FDA) approved intravenous tissue plasminogen activator (tPA) for treatment of stroke within 3 hours of onset.
6. A growing body of evidence suggests a small benefit of intravenous tPA up to 4.5 hours after stroke onset, but the earlier treatment is initiated, the greater the likelihood of a good clinical outcome.
7. Patients receiving antiplatelet therapy usually are not excluded from thrombolytic therapy, although additional studies are needed to clarify the relative risk of thrombolysis in these patients.
8. Good outcomes have been reported with intra-arterial thrombolysis of basilar thrombosis well beyond the usual 6-hour time limit. Intravenous tPA also may result in improvement, but the large clot burden favors the intra-arterial approach.
9. Surgical decompression for hemispheric infarction should be considered for younger patients with a greater potential for recovery from massive stroke and particularly for nondominant strokes.
10. The availability of effective treatment to alter outcome within the first few hours after stroke onset necessitates dramatic changes in the evaluation of stroke. Patients with symptoms suggesting cerebral ischemia must be treated emergently from the prehospital encounter to the emergency department and the treating physicians. Imaging must be performed rapidly and provide useful information for the decision-making process.

Stroke is a medical emergency. The rationale for acute stroke treatment is based on the concepts of the ischemic penumbra. When an arterial occlusion occurs, an area of infarcted brain is surrounded by a region that has reduced blood flow impairing function, but not sufficiently severe to result in irreversible infarction. If adequate blood flow can be restored within a critical time frame, this area at risk may return to normal function. Experimental models of stroke indicate that lower levels of blood flow are tolerated for brief periods, whereas slightly higher blood flow can be maintained for several hours without developing infarction.[1] The precise relationships between blood flow levels and duration for human stroke are not known, but the more quickly flow is restored, the greater the likelihood that the tissue will be spared.

In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) tPA study[2] was published showing for the first time in a randomized controlled trial a reduction in stroke morbidity with acute treatment. Other treatments, such as intra-arterial thrombolytics, clot disruptive devices, and neuroprotective agents, continue to be investigated. At present, intravenous tPA is approved by the FDA for treatment of acute stroke within 3 hours of onset.

New medical-surgical advances in stroke led to the development of acute stroke teams and stroke centers. The NINDS Stroke Group initiated the conceptual groundwork during the NINDS Stroke Trial to facilitate recruitment. The Brain Attack Coalition[3] published recommendations for the organization of these teams and health care delivery systems to facilitate a rapid response. The American Heart Association and the Joint Commission of Health Organizations support disease-specific stroke certification to measure the standards necessary to deliver high-quality

stroke care. Stroke specialists, stroke centers, and future clinical trials will continue to drive advances in acute stroke management.

STROKE MECHANISMS

Appropriate treatment of ischemic stroke depends on identification of the mechanism of stroke. The duration of symptoms and the time course are not as important as the underlying etiology of the ischemic syndrome. Ischemic strokes generally are classified as large vessel thrombotic, small vessel thrombotic, or embolic. An embolic occlusion of a major intracranial artery may require a different therapeutic approach than an atherosclerotic occlusion. Similarly, small vessel thrombosis has different implications for treatment and a better prognosis than large vessel thrombosis.

In the first few hours after stroke, identification of stroke mechanisms may be difficult or impossible. Even distinguishing ischemic from hemorrhagic stroke may be hazardous based on clinical evaluation alone. Information obtained from history and rapid examination provides clues to pathophysiology,[3] but definitive diagnosis usually requires additional testing, such as ultrasound and imaging. Large vessel thrombotic strokes are often preceded by transient ischemic attacks or a stepwise progression of deficits. Risk factors include hypertension, smoking, diabetes, and elevated serum cholesterol level. Clinical deficits typically correspond to the territory of major cerebral arteries or their border zones. In embolic strokes, the onset is usually sudden, although in occasional cases a stepwise progression occurs in the first few hours. The presence of atrial fibrillation, rheumatic heart disease, or a recent myocardial infarction increases the probability of embolism. Several clinical syndromes are attributable to small vessel thrombotic or lacunar stroke, including pure motor stroke involving the face, arm, and leg; pure sensory stroke; ataxia hemiparesis; and dysarthria–clumsy hand syndrome. Other syndromes also may be due to lacunar strokes, but in such cases the mechanism is less certain, illustrating the hazards of deciding on stroke mechanism from clinical findings alone.

Pathophysiologic diagnosis is enhanced greatly by imaging modalities, including computed tomography (CT) and magnetic resonance imaging (MRI). These studies take time to complete, delaying administration of acute stroke therapy and potentially leading to irreversible brain injury before the diagnosis can be established. The time needed for imaging studies must be weighed against the benefit of the information obtained. Studies need to be performed rapidly with minimal delay, and the results must be used to decide on optimal treatment. Acute stroke treatment is likely to differ depending on stroke mechanism, and rapid imaging modalities should become increasingly important in acute stroke management.

PREHOSPITAL EVALUATION OF STROKE

The success of acute stroke management begins with a patient's family member or bystander recognizing the symptoms of stroke (Table 51-1) and calling 911 immediately. When there was no acute treatment for stroke, only primary and secondary preventive measures, health care professionals did little to educate the public on recognizing stroke, identifying risk factors, or promoting stroke prevention.

TABLE 51–1. STROKE RECOGNITION

Sudden onset of:
Numbness or weakness of the face, arm, or leg
Slurred speech or difficulty with speech
Blurred or loss of vision in one or both eyes
Onset of severe headache
Onset of clumsiness or loss of balance

On average, across the United States, stroke patients arrive at the hospital 24 hours after symptom onset. A huge effort is under way to educate the public at large of the warning signs of stroke, especially in individuals at risk and their family members (Table 51-2). The key message is how to recognize stroke, to take action, and to get to the hospital immediately.

In recent years, prehospital systems across the United States have begun to implement an acute stroke protocol. The protocol is published in the American Heart Association's *Advanced Cardiac Life Support 1997-1999* manual.[4] An algorithm for acute stroke was developed from the experience of conducting acute stroke trials.[5-7] Similar to the concept of time-focused field management of myocardial infarction, acute stroke now is being approached as a medical emergency. Rapid identification of the problem as a stroke, determining onset to be less than 6 hours, appropriate field assessment and management, rapid transport, and prenotification of the incoming stroke patient to the receiving emergency department are the key elements for prehospital personnel.

The process begins at dispatch. Any calls with complaints of "weakness, numbness, changes in speech, headache, confusion, found down, or unconscious," are considered a possible stroke. A crew is sent immediately to the scene.

On arrival, the prehospital team should complete a quick assessment, which includes following the basics of the *ABCs-N: a*irway, *b*reathing, *c*irculation, and *n*eurology evaluation. Oxygen saturation should be maintained at least 96% to provide adequate oxygenation to the brain tissue. Continuous monitoring of the electrocardiogram is recommended because almost 30% of ischemic patients have arrhythmias (e.g., atrial fibrillation). Blood pressure should be determined, but treatment should be considered only if it is greater than 220/120 mm Hg. Intravenous access should be established if this does not delay transport to the emergency department. If administering intravenous fluids, only isotonic solutions, such as normal saline or lactated Ringer's solution, should be used. Glucose should be avoided in intravenous fluids because it may be detrimental to ischemic brain tissue and can lead to unnecessary cerebral edema. Hypoglycemia can mimic stroke symptoms, and serum glucose should be checked. Glucose should be administered if hypoglycemia is found. Hyperglycemia needs to be treated on arrival to the emergency department.

TABLE 51–2. RESOURCES FOR PUBLIC STROKE EDUCATION

National Stroke Association (NSA)	1-800-STROKES
American Heart Association (AHA)	1-800-AHA-USA1
National Institute of Neurological Disorders and Stroke (NINDS)	www.nih.gov

TABLE 51-3. CINCINNATI PRE-HOSPITAL STROKE SCALE

Facial droop—have patient show teeth or smile	Normal—both sides of face move equally Abnormal—one side of the face does not move as well as the other side
Arm drift—patient closes eyes and holds both arms out	Normal—both arms move the same or both arms do not move at all Abnormal—one arm does not move or one arm drifts down compared with the other
Speech—have patient say "you can't teach an old dog new tricks"	Normal—patient uses correct words with no slurring Abnormal—patient slurs words, uses inappropriate words, or is unable to speak

It is important for the prehospital personnel to gather information about the onset of stroke symptoms. First, it is crucial to determine the time of onset of the symptoms; this is important because the emergency department may not have access to individuals who were present at the onset. Time of onset is determined by when the patient was last seen without a neurologic defect. When the deficit is present on awakening, the time of onset is considered the previous night before going to bed. If thrombolytic treatment is considered, it is important to obtain a history of trauma or falling when the symptoms occurred. The examiner should check for any signs of ecchymosis or laceration. Also, a history of seizure activity after the onset of symptoms should be obtained. Todd's paralysis, a syndrome that occurs after a seizure, often is confused with stroke symptoms.

To assess the patient's neurologic status, the best tool to use in the field is the Pre-hospital Stroke Scale developed by the University of Cincinnati (Table 51-3). This quick screen allows for uniformity in assessing stroke deficits that clarify communication of the results to the receiving team at the hospital.

Information that should be communicated to the receiving hospital includes age, sex, past medical history, current medications, presenting problem, onset time, neurologic status, vital signs, estimated time of arrival to hospital, and any concerns while in transport. Fieldwork can save precious minutes of additional work in the emergency department. The importance of care given by paramedics should not be underemphasized.

EMERGENT STROKE EVALUATION

GENERAL ASSESSMENT

Emergent assessment of the stroke patient begins immediately on arrival at the emergency department. If prenotification is obtained from emergency medical services, a physician should meet the patient at triage and begin the evaluation. Initial concerns include assessment of respiratory function, cardiovascular stability, and level of consciousness. An adequate airway must be established to ensure proper ventilation, particularly in obtunded or comatose patients. Aspiration is a serious concern and leads to subsequent pneumonia and is a major cause of morbidity and mortality during hospitalization.[8] Supplemental oxygen is often administered, but the benefit is uncertain when oxygenation is already adequate. Hypoxemia should be corrected immediately, however, and its source aggressively investigated. Arrhythmias are common in acute stroke. Bradycardia may signal underlying increased intracranial pressure or cardiac ischemia. Atrial fibrillation associated with rapid ventricular response often impairs cardiac output requiring immediate treatment. Atrial fibrillation also may be an embolic source for stroke. Ventricular tachycardia or fibrillation rarely occurs with stroke[9] and when present usually is due to coexistent myocardial infarction. Hypotension should be corrected with intravenous fluids. Seizures should be controlled with anticonvulsants. The initial physician evaluation should be completed within 15 minutes.

BLOOD PRESSURE MANAGEMENT

Hypertension commonly accompanies ischemic and hemorrhagic stroke.[10] In most cases of ischemic stroke, abrupt lowering of blood pressure is not advised because of the risk of causing further impairment of perfusion in the ischemic region.[11] When a systemic or cardiac reason for reducing blood pressure is present, such as aortic dissection or acute myocardial infarction, the relative importance of the systemic and neurologic issues must be considered. Hypertensive encephalopathy is a syndrome of extreme hypertension, papilledema, altered mental status, microangiopathic hemolytic anemia, and renal insufficiency that responds to lowering blood pressure. In the absence of papilledema or systemic features, it is unlikely that acute neurologic deficits are due to hypertensive encephalopathy, and acutely lowering blood pressure is more likely to worsen deficits rather than improve them.

When thrombolytic therapy is considered, reducing blood pressure within limits is necessary. Before thrombolytic therapy is administered, systolic blood pressure should be less than 185 mm Hg and diastolic less than 110 mm Hg.[12] Labetalol typically is administered in increasing doses every 5 to 10 minutes to control blood pressure. If beta blockers cannot be used, enalapril is a reasonable alternative. Sublingual nifedipine should be avoided because of the potential to lower blood pressure precipitously. If these agents do not provide adequate control, thrombolytic therapy probably should be avoided. Although some authors recommend limiting treatment to one or two doses of labetalol before excluding the patient from thrombolytics, we generally proceed with treatment as long as the blood pressure is controlled within the time frame for treatment with thrombolytic therapy.

TRIAGE AND LABORATORY STUDIES

The immediate concern for the emergency department evaluation after initial cardiovascular stabilization is confirming the diagnosis of stroke, excluding stroke mimics, and establishing whether acute stroke intervention is appropriate for the patient. It is crucial to establish the time of onset with certainty. The time of onset should be considered the time

the patient was last seen without a neurologic deficit, rather than the time the patient was found with a deficit. If deficits were present on awakening, the onset time should be considered the previous night when the patient was last seen neurologically normal. This time of onset may exclude some patients who otherwise would benefit, but it avoids the risk of causing hemorrhages in patients with long established infarction. For intravenous tPA, the window for treatment is currently 3 hours. The evaluating physician must allow for time needed for CT scanning and interpretation and preparing and administering tPA. Completion of CT scanning should take no more than 25 minutes from arrival, and interpretation should be completed within 45 minutes. tPA treatment should be initiated within 1 hour of arrival in the emergency department.

Conditions other than stroke that cause acute neurologic deficits must be considered before proceeding with acute stroke treatment. Occasionally, intracranial mass lesions present with acute deficits. Migraine, seizures, and metabolic aberrations such as hypoglycemia may present with focal neurologic signs. A brief history obtained from the patient or family usually excludes these possibilities. Two intravenous catheters should be established as soon as possible. Blood glucose should be checked and corrected if needed. Additional blood tests obtained immediately include coagulation studies, complete blood count, and electrolytes.

GLUCOSE

Evidence from animal models of stroke suggests that hyperglycemia increases the severity of ischemic injury.[13] Increased glucose concentration in the area of ischemia causes higher lactate concentrations and local acidosis; this increases generation of oxygen free radicals damaging neurons. Hyperglycemia also may increase ischemic edema, release excitatory amino acid neurotransmitters, and weaken blood vessels in the ischemic area.

Studies of stroke in humans show an inconsistent association between stroke outcome and initial blood glucose; however, admission glucose concentration correlates with initial stroke severity. Initial hyperglycemia also has been associated with higher mortality rates after stroke. Some authors have suggested that hyperglycemia in acute stroke is a stress reaction, but the relationship between initial blood glucose concentration and outcome is independent of initial stroke severity, arguing against a stress phenomenon.

Although a relationship exists between hyperglycemia and stroke outcome, no study has examined the effect of lowering glucose acutely on outcome. At least one randomized trial is currently in progress,[14] and others are planned.[15] In the absence of such data, it seems prudent to lower blood glucose in the first few hours after stroke when it is markedly elevated. Glucose levels greater than 200 mg/dL should be treated with insulin on a sliding scale to keep the level less than 200 mg/dL (ideally <150 mg/dL).

TEMPERATURE

Fever also has been associated with worse outcomes after stroke.[16] It is unclear, however, whether fever is a response to the stroke or a cause of neurologic worsening. Hypothermia reduces stroke severity in animal models of stroke,[17] but no randomized trials have been completed in humans with stroke to test the benefits of this therapy. Despite the uncertainty of benefit, maintenance of normothermia is advised after stroke. Cooling blankets and antipyretics should be used to treat temperature elevations. Intravascular cooling devices currently are being tested. These devices rapidly reduce body temperature and allow the temperature to be maintained within a narrow range.

Although "central" fever occasionally occurs after stroke, most temperature elevations are due to infection. A thorough search for the cause of fever is paramount. Appropriate antibiotic treatment must be instituted as quickly as possible.

FLUID MANAGEMENT

Most patients with acute stroke are volume depleted. Intravenous fluids should be replaced with either normal saline or lactated Ringer's solution. In patients with large strokes in danger of developing brain edema, fluid administration should be titrated carefully, and free water must be limited. Mild hyponatremia need not be treated acutely. More severe hyponatremia should be corrected slowly and usually reverses with infusion of normal saline.

STROKE TEAM

A stroke team consists of individuals from multiple disciplines with specialized knowledge and interest in acute stroke care. The team approach brings together the necessary skills to administer emergently the care best suited to the situation and divides the workload so that tasks can be performed simultaneously rather than sequentially. Ideally, a stroke team consists of a neurologist, neuroradiologist, nurse coordinator, and neurosurgeon. Not all hospitals have the resources necessary to provide a complete stroke team at all times, but at least one individual should be available with the ability to evaluate acutely the neurologic status of a stroke patient, interpret the CT scan, and institute acute stroke therapy in appropriate cases. The more components of the team involved in acute stroke care, the more rapidly treatment can be initiated. The stroke team is usually responsible for confirming the onset time, evaluating the CT scan, establishing the diagnosis, reviewing the inclusion/exclusion criteria for thrombolytic therapy, and making the final decision to proceed with treatment.

IMAGING OF ACUTE STROKE

Evaluation of patients with acute stroke depends heavily on imaging. Although CT and MRI of stroke is a component of standard stroke care, emergent imaging of stroke raises several new issues. For additional details on neuroimaging in intensive care, see Chapter 48. It is paramount to differentiate ischemic from hemorrhagic stroke before deciding on the use of thrombolytics. In the future, selection of appropriate neuroprotective agents also may depend on the presence of hemorrhage. Although still investigational, it is likely that identification of an arterial occlusion and information about cerebral blood flow would help triage acute stroke patients to a treatment regimen most likely to produce benefit, while limiting the potential for complications.

At present, selection of patients for thrombolytics or other acute stroke therapy is based entirely on clinical evaluation

and historical time of onset. It is likely, however, that some patients within the 3-hour time window already have established infarction that would not reverse with thrombolysis and may result in hemorrhage owing to reperfusion of infarcted brain. In contrast, others may have salvageable brain tissue despite a greater than 3-hour interval since onset. A physiologic estimate of tissue viability would be preferable to a fixed time interval, if a study were found that reliably predicted viability of brain after stroke.[18] CT and MRI have the potential to provide this measurement.

COMPUTED TOMOGRAPHY

CT has been the imaging procedure of choice for patients with recent stroke to exclude hemorrhage as the etiology. CT has the potential to provide a great deal more information, however, in an acute stroke patient. Subtle parenchymal abnormalities show evidence of early edema or infarction. Spiral CT allows CT angiography and imaging of the intracranial and extracranial circulation. Cerebral perfusion can be examined with stable xenon CT and mapped to the arterial distribution of the major cerebral arteries. This battery of tests is performed without moving the patient from the CT scanner, minimizing the time delay before deciding on optimal treatment.

Not all patients can complete the entire battery of tests. CT angiography requires contrast administration and cannot be performed in patients with renal failure or contrast allergies. There is a potential problem in patients undergoing angiography for possible intra-arterial therapy after CT angiography because the dye load is increased by the combination of procedures. If digital angiography is used and arterial injections of contrast material are minimized, however, the contrast load should not be prohibitive. Xenon CT has few limitations, but excessive movement reduces the accuracy of the acquired blood flow information. Blood flow data may not be reliable in agitated patients. Vomiting occasionally occurs after xenon inhalation, and care must be taken to avoid aspiration.

Early Computed Tomography Changes

It previously was thought that parenchymal changes did not occur on CT for at least 6 hours after ischemic stroke. More recent studies indicate, however, that early changes of ischemia frequently occur within a few hours of stroke onset and have been seen 1 hour after stroke.[19] These changes include reduced attenuation in the basal ganglia,[1] loss of gray-white differentiation particularly in the insular region,[20] low density in the cortex and subcortical white matter, and loss of sulcal markings suggesting early mass effect and edema (Fig. 51-1A and B).[21] A hyperdense middle cerebral artery occurs in 20% to 37%,[22] indicating acute thrombus within the artery, but rarely occurs without at least one other early CT abnormality. Hyperdensity in the basilar artery associated with thrombosis also has been reported.[23] In 100 patients studied within 14 hours of stroke onset (mean 6.4 hours), multiple early CT abnormalities correlated with size of subsequent infarct and poor outcome.[22] In the ECASS trial of tPA for acute stroke (see later), early CT changes correlated with larger subsequent infarct volume[24] and a greater likelihood of hemorrhagic conversion after tPA.[25] Based on these results, some experts recommend withholding thrombolytic therapy in patients with extensive early CT changes[26]; however, whether these abnormalities represent irreversible brain infarction is controversial. A report of a patient with hypodensity in 60% of the middle cerebral artery territory and clinical and CT resolution after reperfusion with intra-arterial urokinase suggests this is not always the case.[27] In the NINDS recombinant tPA trial of intravenous treatment within 3 hours of stroke onset, early ischemic changes did not predict symptomatic hemorrhage or response to treatment.[28] CT scanners used in this study from the early 1990s are likely less sensitive than modern-day scanners. In addition, the association of early CT changes with infarction, and risk of hemorrhage may be greater with longer intervals from stroke onset. Half of the patients in the NINDS trial were treated within 90 minutes. Extensive hypodensity may have greater predictive value than other early ischemic changes.

Computed Tomography Angiography

CT angiography can be performed using spiral CT technology adding only 15 to 20 minutes to the routine CT examination. Either the intracranial or the extracranial circulation may be imaged. In a patient with acute stroke, the intracranial study may be sufficient to diagnose proximal arterial occlusion. When extracranial carotid disease is suspected, both parts of the circulation can be studied. A single bolus of contrast material similar to that used for a contrast CT scan is given for this examination, limiting use in patients with renal failure or contrast hypersensitivity. In acute stroke, CT angiography has been shown to be highly reliable for diagnosis of intracranial occlusions and correlates with other imaging modalities (Fig. 51-1C and D).[29,30] Examination of the carotid bifurcation with CT angiography provides a three-dimensional view of carotid lesions and shows eccentric lesions or ulceration not seen by conventional angiography.[31] When used in combination with conventional CT and xenon CT, the major limitation is tube heating. The studies must be sequenced properly and the area of interest on CT angiography selected carefully to minimize the number of slices needed to obtain the necessary anatomic information. CT angiography in acute stroke patients provides important information about arterial occlusions and possibly collateral blood flow[32] and may be useful to triage patients with large proximal occlusions to thrombolytic therapy and avoid interventions in patients without demonstrable arterial occlusions. It is hoped that future acute stroke trials will incorporate these imaging modalities to assess the value of triaging patients based on anatomic evidence of occlusion.

Computed Tomography Perfusion

In addition to imaging the parenchyma with CT and the cerebral vasculature with CT angiography, CT perfusion adds assessment of cerebral blood flow and blood volume. Using a helical scanner during a bolus of intravenous contrast, the time-dependent concentration curve of contrast in each pixel can be acquired (see Chapter 48). Mean transit time and subsequently cerebral blood flow can be calculated. In patients with acute stroke, perfusion-weighted CT images, similar to cerebral blood volume, correlate with final infarct size and outcome, particularly after recanalization.[33] CT perfusion maps combining cerebral blood flow and cerebral blood volume information identify tissue that progresses to infarction if not reperfused, consistent with ischemic penumbra.[34]

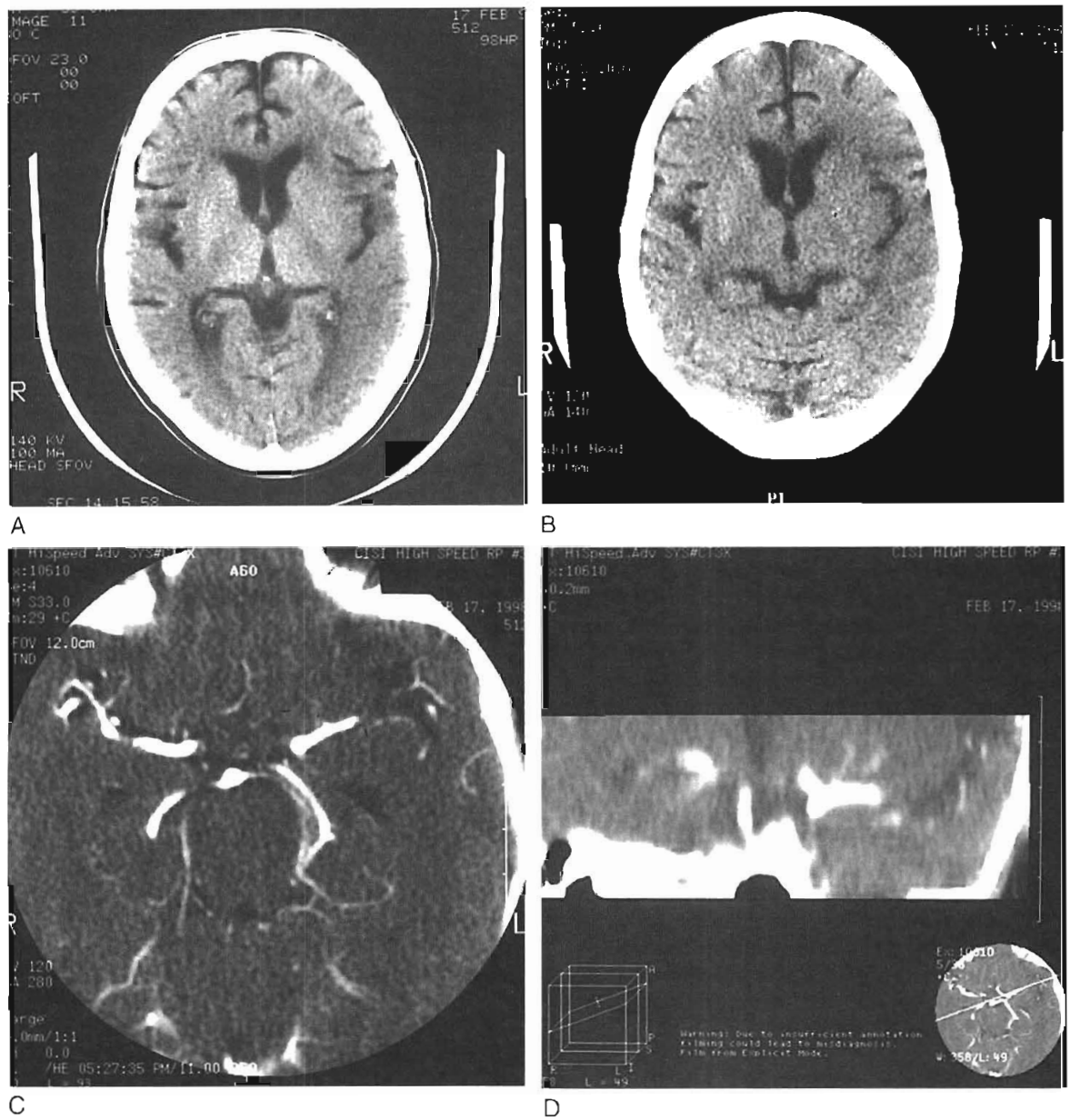


FIGURE 51–1. A, Normal computed tomography (CT) scan of brain 2 hours after onset of aphasia and left hemiparesis. **B,** Repeat CT scan at 5 hours after stroke onset shows early CT changes, including basal ganglia hypodensity, loss of the insular ribbon, and slight effacement of the sulci on the left. **C,** CT angiogram at 5 hours after stroke onset shows complete occlusion of the left middle cerebral artery. **D,** Rapid reconstruction of the CT angiogram again shows occlusion of the left middle cerebral artery.

Xenon Computed Tomography

Measurement of brain perfusion should be particularly beneficial in patients with stroke. Several methods of measuring cerebral blood flow are available; however, quantitative blood flow can be obtained only with xenon CT or positron emission tomography. Positron emission tomography has the advantage of providing corresponding metabolism data, but is more difficult to perform, particularly in acutely ill patients with stroke.

Stable xenon is an inert gas that is inhaled as a mixture of 27% xenon and 73% oxygen. During a 4-minute inhalation, rapid scanning is performed, and pixel-by-pixel blood flow values are calculated at three brain levels. Corresponding brain CT sections allow anatomic correlation. Xenon CT cerebral blood flow studies require about 15 minutes for completion. Reconstruction of images is accomplished within 5 minutes. In acute stroke patients, xenon CT identifies ischemic regions in patients without acute changes on CT. Patients with occlusion of the proximal middle cerebral artery have significantly lower cerebral blood flow in the middle cerebral artery distribution than patients with more distal occlusion (Fig. 51-2).[35] In addition, normal cerebral blood flow in a patient with an acute ischemic deficit is associated with rapid clinical improvement.[36] In a series of patients with middle cerebral artery occlusion studied with xenon CT, penumbral values of cerebral blood flow were present in all patients, and the percentage of middle cerebral artery territory in the penumbral range (cerebral blood flow 8 to 20 mL/100 g/min) remained relatively constant across the group. In contrast, the percentage of middle cerebral artery territory with cerebral blood flow values representing infarcted tissue (cerebral blood flow <8 mL/100 g/min) varied greatly.[37] Outcome was highly correlated with the area of infracted middle cerebral artery territory, not the amount

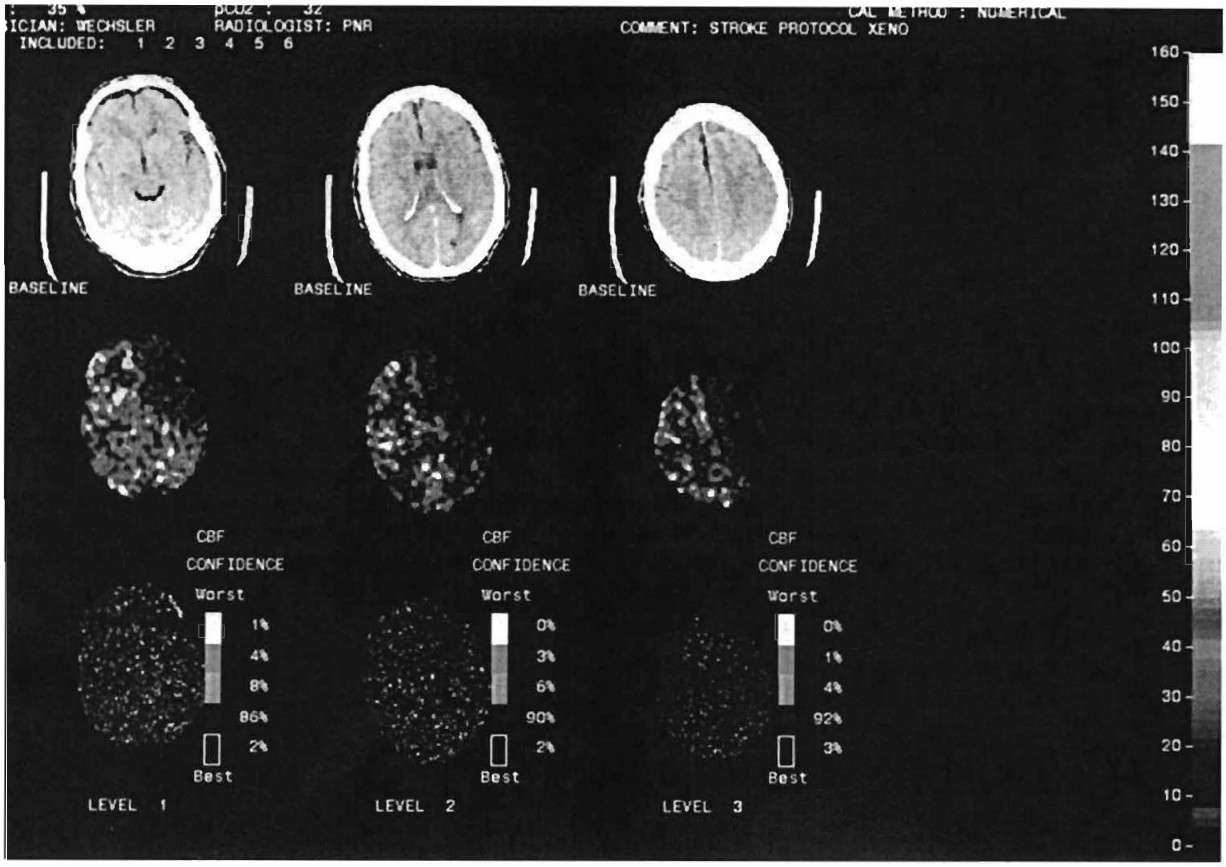


FIGURE 51-2. Xenon computed tomography blood flow study from a patient with large left hemisphere stroke 3 hours after onset of symptoms. Flow is nearly absent throughout the middle cerebral artery territory on the left.

of penumbra. These results suggest that after the first few hours, the size of the already infarcted tissue, not the amount of penumbra, may be the most important imaging parameter to determine suitability for acute stroke therapy.

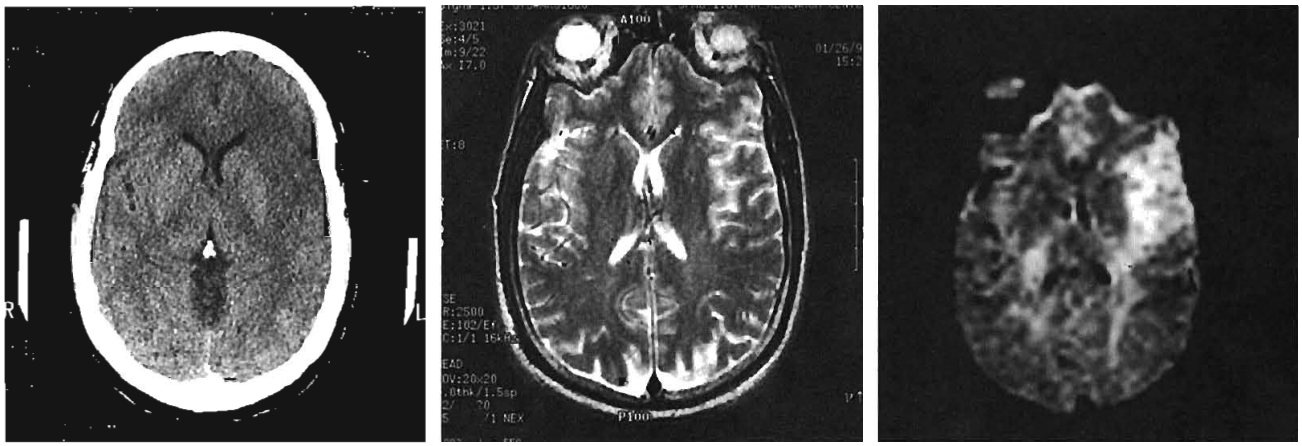
The combination of CT, CT angiography, and CT perfusion or xenon CT represents a battery of tests easily and rapidly performed with the CT scanner and capable of providing important data for decision making regarding acute stroke interventions.[38] Patients with large vessel occlusion on CT angiography, minimal early CT changes, and the presence of penumbra with small areas of cerebral blood flow in the infarction range should be optimal candidates for reperfusion therapy.

MAGNETIC RESONANCE IMAGING

In many hospitals, MRI is available on an emergent basis and reliably identifies cerebral ischemia. Compared with CT, MRI is more sensitive to cerebral infarction, particularly in the brainstem and deep white matter.[39-41] Most comparisons preceded the recognition of early CT changes, however, and may favor MRI unfairly for diagnosis of cortical infarction. Absence of flow void in major cerebral arteries suggests occlusion or slow flow in that artery; this provides important information about arterial occlusion even without angiography that may be valuable particularly in the setting of acute stroke. The major drawback of MRI is the difficulty identifying hemorrhage. MRI signal abnormalities vary depending on the age of the hemorrhage.[42] Knowledge of the signal characteristics of hemorrhage of varying ages on specific imaging sequences is necessary for accurate diagnosis. More knowledge, experience, and skill are needed for MRI interpretation of hemorrhage compared with CT. There is uncertainty about the reliability of MRI for detection of hyperacute hemorrhage and subarachnoid hemorrhage, although it is likely that experienced readers would make few mistakes.[43,44] Results of studies comparing modalities suggest that MRI is at least as sensitive as CT for detection of hemorrhage in patients with acute stroke. As MRI is more commonly used for multimodality imaging in acute stroke, the need for CT to detect hemorrhage should diminish.

Diffusion Weighted Imaging and Perfusion Imaging

Diffusion weighted imaging (DWI) shows parenchymal abnormalities earlier than conventional T2-weighted images in patients with acute stroke.[45] Perfusion imaging is based on transit times for contrast material through brain parenchyma. DWI detects the diffusion of water in the brain and shows hyperintensity in areas of reduced diffusion (Fig. 51-3). As water moves from the extracellular to the intracellular space, there is less movement of water and loss of signal resulting in hyperintensity.[46] DWI has potential advantages in the evaluation of acute stroke. First, early detection of lesions helps differentiate cerebral ischemia from other conditions that mimic stroke, such as seizures or toxic-metabolic states.[47] Hyperintensity on DWI may not be entirely specific for ischemia,[48] however, and at least one false-negative DWI scan has been reported (although a perfusion abnormality was present).[49] Second, combining DWI with perfusion imaging may identify reversibly ischemic tissue. In some cases, the area of perfusion abnormality is larger than the



A B C

FIGURE 51–3. A, Computed tomography scan of the brain in a patient with sudden onset of expressive speech difficulty and right arm weakness 2.5 hours after onset of symptoms. There is early low density and sulcal effacement in the perisylvian region. **B,** T2-weighted magnetic resonance imaging study of the same patient 5 hours after stroke onset. Subtle increased signal intensity is seen in the perisylvian region. **C,** Diffusion-weighted image also at 5 hours after stroke onset. A larger area of signal abnormality is present in the left hemisphere.

DWI abnormality, indicating a region of brain that has impaired flow but has not yet become ischemic. Expansion of DWI abnormalities between the first few hours after stroke and repeat studies many hours later also suggests the existence of tissue at risk.[50] Several studies found that the size of DWI abnormalities correlated with clinical outcome.[51] Abnormal DWI does not always represent irreversible ischemia, however. In animal models of stroke, reduction in the size of DWI abnormalities after treatment has been shown,[52,53] and similar findings have been reported in humans after treatment with intra-arterial thrombolysis[54] and neuroprotective agents.[55] Progression to infarction is a complex phenomenon that depends on many factors in addition to cerebral blood flow.[56] The total DWI abnormality seen in the first few hours after stroke likely represents the core infarction and a portion of the penumbra.

In patients with stroke, the size of the diffusion abnormality and the growth of areas of abnormal DWI are strong predictors of outcome. Lesion growth may be an effective surrogate marker to be used in clinical trials of acute stroke therapy, particularly neuroprotective agents.[57] In acute stroke, a marker of tissue viability is needed, and some authors have suggested that the extent of mismatch between perfusion and diffusion abnormality can be used in this manner. Patients with a large mismatch might be more likely to respond to reperfusion therapy, whereas patients without mismatch have little to gain.[58] Patients without mismatch and with large areas of DWI abnormality may be at greater risk for hemorrhage. These concepts currently are undergoing testing in clinical trials. In some trials, only patients with DWI/perfusion imaging mismatch are selected for treatment expecting that they are most likely to respond. In others, after MRI all patients are treated to compare the response to treatment between patients with and without mismatch at baseline. These trials should add to understanding of the ability of a mismatch to select patients for acute stroke therapy.

Magnetic resonance angiography provides a noninvasive method of imaging the intracranial and extracranial circulation. Several techniques are available; most require no contrast and are based on time-of-flight techniques.[59] The arteries comprising the circle of Willis and the extracranial vertebral and carotid arteries can be examined, allowing detection of occlusions in acute stroke. Occlusions of small peripheral branch arteries may not be detected by magnetic resonance angiography. Gadolinium-enhanced magnetic resonance angiography allows visualization of the intracranial and the extracranial circulation. Patients with claustrophobia or implanted metal devices, such as pacemakers, cannot undergo magnetic resonance angiography. Artifacts in some cases obscure proper identification of arterial pathology. Signal dropout may occur at the site of arterial stenosis owing to the effects of turbulent flow. If an artery is tortuous, it may extend out of the imaging section and appear occluded. In addition, construction of maximal intensity projections is subject to a variety of errors.[60] Experience and careful examination of studies typically avoids these pitfalls. In patients with stroke, magnetic resonance angiography correlates well with angiographic evidence of stenosis or occlusion of arteries in the intracranial[61,62] and the extracranial circulation.[63,64] In patients undergoing MRI and particularly DWI and perfusion imaging, the addition of magnetic resonance angiography to the battery provides evidence of arterial pathology and may add important diagnostic information when considering treatment options.

TREATMENT OF ACUTE STROKE

ANTICOAGULATION

The use of anticoagulants in acute stroke is controversial, although several randomized clinical trials provide information regarding its efficacy. Retrospective data previously suggested a significant incidence of early recurrences after ischemic stroke with reported rates of 20%. These studies also suggested that anticoagulation with heparin reduced recurrences. Hemorrhagic complications were acceptably low, particularly when patients with large strokes and uncontrolled hypertension were excluded from treatment. The results of more recent randomized clinical trials have challenged these findings and call into question the value of anticoagulation for treatment of acute stroke.[65]

The randomized studies completed to date include trials of low-molecular-weight heparin, heparinoid, and

subcutaneous heparin. All have serious flaws in design that limit the ability to make definitive conclusions. The major results of these studies are summarized in Table 51-4. The studies do not support a reduced recurrence rate or improved outcome with anticoagulation when administered within 24 to 48 hours of stroke onset. Hemorrhage rates ranged from 1% to 2.5%. These results suggest that there is little value in anticoagulation for all patients with acute stroke, but it remains possible that some subgroups benefit. The TOAST study suggested that patients with large vessel disease may achieve better functional outcome.[66] The relatively high hemorrhage rate in some studies also may have obscured some benefit. In the International Stroke Trial (IST), a significant reduction in recurrent strokes from 3.8% in the control group to 2.9% in patients treated with subcutaneous heparin ($P < .01$) was offset by an increase in hemorrhagic stroke from 0.4% in controls to 1.2% in patients receiving heparin ($P < .00001$).[67] Even in patients with atrial fibrillation, the value of early anticoagulation is uncertain with studies showing benefit and lack of benefit in reducing recurrent stroke.[65]

Antiplatelet Therapy

There is less uncertainty about the benefit of aspirin in acute stroke. Two large randomized controlled trials, the Chinese Aspirin Stroke Trial (CAST)[68] and the IST,[67] showed a small but significant improvement in outcome in patients treated with aspirin. In the IST, patients received 300 mg of aspirin daily for 14 days. There was a significant reduction in stroke recurrence within 14 days in the aspirin group (2.8%) versus avoid-aspirin groups (3.9%) and a significant decrease in the risk of death or nonfatal recurrent stroke in the aspirin group (11.3%) versus avoid-aspirin groups (12.4%). In the CAST trial, 160 mg of aspirin was given per day for 4 weeks or until hospital discharge. In the aspirin group, there was a significant reduction in death within 4 weeks (3.3%) versus placebo (3.9%) and a significant reduction in death or nonfatal stroke during hospitalization. There also was a significant reduction in recurrent ischemic strokes in the aspirin group (1.6%) versus placebo (2.1%), which was offset only by a nonsignificant trend of excess of hemorrhagic strokes (aspirin 1.1% versus placebo 0.9%).

The CAST and IST were designed to be considered together and include more than 40,000 patients. Combining the results of both studies shows a significant reduction in recurrent stroke of 7 per 1000 ($P < .000001$) and reduction of death or dependency of 12 per 1000 ($P = .01$).[69] The risk of aspirin in the absence of thrombolytics is minimal, and the small but significant benefit argues in favor of routine treatment.

INTRAVENOUS THROMBOLYSIS

Trials of intravenous thrombolytic agents in acute stroke date back to the early 1960s. At that time, several trials of streptokinase,[70] fibrinolysin,[71] and urokinase[72] were performed and showed either no effect or higher mortality in patients treated with thrombolysis. These studies preceded CT scanning, and patients with hemorrhage were not excluded. The discouraging results inhibited further acute stroke trials until the 1980s, when several reports appeared showing favorable outcomes with intra-arterial thrombolytic therapy within a few hours of stroke onset.[73,74] These reports led to small randomized trials and feasibility studies of intravenous thrombolytics.[75,76] The results of two multicenter randomized controlled trials of intravenous tPA for acute ischemic stroke have been published more recently, with one showing for the first time a beneficial effect of acute stroke treatment when given within 3 hours of onset.

Tissue Plasminogen Activator within 3 Hours

The NINDS acute stroke study showed the benefit of intravenous tPA for patients within 3 hours of onset of stroke. This study was performed in two parts and included more than 600 patients with acute ischemic stroke.[77] All patients were treated within 3 hours, and half were treated within 90 minutes. Patients were randomly assigned to receive either intravenous tPA, 0.9 mg/kg to a maximum of 90 mg, or intravenous placebo. Primary outcome measures were favorable outcomes at 90 days measured by the National Institutes of Health stroke scale, Barthel index, Glasgow outcome scale, and Rankin scale. By all four measures, significantly more patients had a favorable outcome at 90 days in the tPA group compared with placebo. Treatment with tPA resulted in an 11% to 13% absolute increase in good outcomes and a slight, nonsignificant decrease in mortality at 3 months. The benefit was sustained at 12 months.[78] Intracerebral hemorrhage with clinical deterioration occurred in 6.4% of tPA-treated patients but only 0.6% of placebo patients. Despite the increase in hemorrhages, there was no significant increase in mortality or severe disability in the tPA group compared with placebo. The relationship between benefit and time from onset suggested there was little to be gained by treatment beyond 3 hours and possibly beyond 2.5 hours.

When strokes were classified according to initial impression of stroke subtype, all types of strokes had more favorable outcomes with tPA. There were no clear factors that predicted response to tPA.[79] Patients with large strokes as measured by the National Institutes of Health Stroke Scale (NIHSS, >20) and evidence of early low density or edema on CT had a higher rate of hemorrhage after tPA.[80]

TABLE 51–4. RANDOMIZED TRIALS OF ANTICOAGULATION IN ACUTE STROKE

Study	Treatment	Patients	Recurrence: Treatment Versus Control	Favorable Outcome: Treatment Versus Control	Hemorrhage: Treatment Versus Control
FISS	Nadroparin	308	1% vs. 4.7%	48% vs. 35%	0% vs. 1%
IST	Subcutaneous heparin	19,435	1.6% vs. 2.2%	17% vs. 17%	1.8% vs. 0.3%
TOAST	Danaparoid	1281	1.1% vs. 1.1%	49% vs. 47%	2.9% vs. 0.9%
HAEST	Daleparin	449	8.5% vs. 7.5%	23% vs. 21%	2.8% vs. 1.8%
TAIST	Tinzaparin	1486	3.3% vs. 3.1%	38% vs. 43%	1.4% vs. 0.2%

On the strength of the NINDS study results, in June 1996 the FDA approved intravenous tPA for treatment of stroke within 3 hours of onset. Since then, reports of small groups of patients suggest similar efficacy can be obtained at community hospitals without an increase in hemorrhages as long as the NINDS protocol is used for patient selection.[81] Not all patients respond to intravenous tPA. In a dose escalation trial of intravenous tPA (Duteplase, Burrows-Welcome), angiography was performed before thrombolysis in all patients documenting the site of arterial occlusion and repeated 2 hours later.[82] Only 31% of arterial occlusions recanalized. Proximal occlusions in the middle cerebral artery opened less frequently than distal branch occlusions, and only 8% of carotid occlusions recanalized. The resistance of carotid occlusion to intravenous thrombolysis also has been noted by others.[83]

Tissue Plasminogen Activator beyond 3 Hours

Several other tPA trials attempted to extend the window for treatment beyond 3 hours (Table 51-5). ECASS I and II[84,85] and the ATLANTIS study[86,87] treated patients with intravenous tPA 6 hours after stroke onset but failed to show a significant benefit compared with placebo. Several design differences between these studies and the NINDS trial could have contributed to the different results, but the major factor was likely the longer time to treatment. In these studies, few patients were treated within 3 hours, and most were 4 to 6 hours from onset of stroke.

Combined Analysis

Although no individual trial showed a statistically significant benefit of intravenous tPA beyond 3 hours based on the primary prespecified analysis, several post-hoc analyses suggest that a small benefit might exist. ECASS II did not find a significant benefit based on the prespecified endpoint of modified Rankin score 0 to 1 at 90 days; however, a significant benefit would have been shown had the endpoint of modified Rankin score 0 to 2 been used,[88] similar to the Prolyse in Acute Cerebral Thromboembolism (PROACT) II study of intra-arterial thrombolysis.[89] The latter endpoint encompasses independent functioning rather than normal or near-normal neurologic status. For studies with moderate-to-severe strokes and longer time windows, functional independence may be a more appropriate endpoint. In addition, a meta-analysis of eight intravenous tPA trials including more than 2800 patients found a significant reduction in death and disability (modified Rankin score 3 to 6) in patients treated 6 hours after stroke onset.[90] This finding translates into 57 fewer patients dead or disabled for every 1000 treated.

More recently, a combined analysis of intravenous tPA trials has been performed, including NINDS, ECASS I and II, and ATLANTIS A and B.[91] In contrast to a meta-analysis, the combined study pooled original patient information from all trials into a single database. A total of 2776 patients were analyzed for outcomes and hemorrhage rates. The odds ratio for good outcome (modified Rankin score 0 to 1) was greatest for treatment within 90 minutes but remained significant for treatment between 91 and 180 minutes (Table 51-6). In contrast to the individual trials, the combined analysis also showed a statistically significant benefit for treatment between 181 and 270 minutes. The odds ratio was only slightly lower than for between 91 and 180 minutes. No treatment effect was observed beyond 270 minutes. It is likely that the greater number of patients in the later time-to-treatment group allowed detection of a small but significant benefit between 3 and 4.5 hours. In patients treated between 3 and 4.5 hours, 37% reached the endpoint of modified Rankin score 0 to 1 at 90 days, whereas only 32% of controls achieved this outcome. There was no difference in mortality for treatment up to 4.5 hours, although mortality was increased beyond 4.5 hours in the tPA group. Overall symptomatic hemorrhage rate was 5.8%, and there was no relationship between time to treatment and the rate of symptomatic hemorrhage 6 hours after stroke onset. A growing body of evidence suggests a small benefit of intravenous tPA 4.5 hours after stroke onset, but the earlier treatment is initiated, the greater the likelihood of a good clinical outcome.

SITS-MOST and ECASS III

Approval for intravenous tPA (Actilyse) was granted in Europe for treatment within 3 hours, but was conditional on review of a safety monitoring study (Safe Implementation of Thrombolysis in Stroke [SITS-MOST]) of patients treated and a new randomized controlled trial of patients treated 3 to 4 hours after stroke onset (ECASS III). SITS-MOST is a mandatory registry of patients treated in Europe with intravenous tPA under the conditional approval. The goal of the registry is to confirm the rate of symptomatic intracerebral hemorrhage, mortality, and independence at 3 months equal or better than the data from randomized controlled trials. All patients treated throughout Europe will be entered into this registry for future analysis.

In addition to SITS-MOST, the European authorities mandated a randomized controlled trial of intravenous tPA for patients 3 to 4 hours from stroke onset. This placebo-controlled trial is expected to enroll 800 patients at 110 sites in 15 European countries and help settle the issue of benefit for intravenous tPA 4 hours after stroke onset. Patients with NIHSS greater than 24 are excluded. The primary efficacy endpoint is modified Rankin score 0 to 1 at 90 days.

TABLE 51-5. INTRAVENOUS TISSUE PLASMINOGEN ACTIVATOR TRIALS BEYOND 3 HOURS

Study	Design	Time To Treatment (h)	Symptoms On Hemorrhage: tPA/PL (%)	Good Outcome: tPA/PL (%)	Results
ECASS I	Intravenous tPA vs. PL	6	19.8/6.5	41/29	No benefit
ECASS II	Intravenous tPA vs. PL	6	8.8/3.4	40/36	No benefit
ATLANTIS A	Intravenous tPA vs. PL	6	11.3/0	47/49	No benefit
ATLANTIS B	Intravenous tPA vs. PL	3-5	7/1.1	34/32	No benefit

PL, placebo; tPA, tissue plasminogen activator.

TABLE 51–6. ODDS RATIOS FOR MODIFIED RANKIN SCORE 0-1 IN THE COMBINED TPA ANALYSIS

Time	N	Odds Ratio	95% CI
0-90	311	2.83	1.77, 4.53
91-180	618	1.53	1.11, 2.11
181-270	801	1.40	1.06, 1.85
271-360	1046	1.16	0.91, 1.49

CI, confidence interval.
Data from The ATLANTIS, ECASS and NINDS rt-PA Study Group Investigators: Association of outcome with early stroke treatment: Pooled analysis of ATLANTIS, ECASS and NINDS rt-PA stroke trials. Lancet 2004;363:768-774.

Other Thrombolytic Agents

At present, only tPA is approved by the FDA for treatment of acute stroke. Many other thrombolytic agents are in various stages of investigation, however. These alternative treatments offer the potential for greater efficacy with lower hemorrhage rates and improved convenience of administration. Whether these advantages are clinically relevant and sufficient to replace tPA for stroke therapy awaits the results of future clinical trials.

Desmoteplase is a plasminogen activator with higher selectivity and far greater specificity for fibrin than tPA. Additional advantages over tPA include a long half-life that allows bolus administration and the lack of hypofibrinogenemia. Desmoteplase is currently in phase 2 clinical trials. Tenecteplase is a modification of human tPA designed to achieve more effective thrombolysis. The half-life of tenecteplase is significantly longer, allowing administration as a single bolus. Similar to desmoteplase, tenecteplase has greater fibrin specificity and less fibrinogen depletion than tPA.[92] A pilot safety study of tenecteplase for acute ischemic stroke is currently in progress.[93] Reteplase is another genetically modified form of human tPA. It also has been shown to be effective in treatment of acute myocardial infarction. Because of a longer half-life, reteplase is administered as two bolus injections 30 minutes apart. A small trial of intra-arterial reteplase for acute ischemic stroke was reported.[94] Sixteen patients were treated 9 hours after stroke onset with complete recanalization in 88% and clinical improvement in 44% at 24 hours. Only one symptomatic hemorrhage occurred. An ongoing study (ROSIE) combines abciximab and intravenous reteplase treatments in patients 24 hours after stroke onset with an endpoint of MRI-based reperfusion at 24 hours. Abciximab alone has been studied in a phase 2b trial.[95] A glycoprotein IIb and IIIa inhibitor, abciximab may improve outcome through its powerful antiplatelet effects or by direct thrombolytic activity. The AbBEST study included 400 patients randomized to treatment with intravenous abciximab or placebo 6 hours after stroke onset. Based on a responder analysis, outcomes at 3 months were improved with abciximab in patients with mild or moderate strokes but not in patients with NIHSS greater than 15. The effect also was greater in patients treated within 5 hours of symptom onset. Symptomatic hemorrhage occurred in 3.6% of patients treated with abciximab. A larger phase 3 randomized controlled trial is under way.

Tissue Plasminogen Activator in Specific Subgroups

Further analysis of the results of the NINDS study did not identify any specific subgroups of patients with a greater or lesser likelihood of responding to tPA. The number of patients treated in many subgroups was quite small, however. Clinical experience has raised questions about treatment of several patient subgroups with conflicting evidence concerning the advisability of treatment with thrombolytics.

Age and Risk of Thrombolysis

One group of concern is elderly patients, in whom the incidence of cerebral amyloid angiopathy is greater and might predispose to hemorrhage after tPA. Some studies of anticoagulation with warfarin indicate a higher rate of intracerebral hemorrhage in the elderly.[96] In the NINDS study, older patients were less likely to have a favorable outcome but fared better with tPA than without.[97] In ECASS II, older patients had a greater risk of severe hemorrhagic transformation.[98] In contrast, a retrospective survey of patients treated with intravenous tPA at multiple centers did not find any difference in outcome or hemorrhage rate in 30 patients older than age 80 compared with 159 younger patients.[99] Advanced age should not be considered a contraindication to thrombolysis, but requires consideration of a lower probability of good outcome after treatment and possibly a higher rate of intracerebral hemorrhage.

Computed Tomography Findings on Baseline Scan

Another point of controversy is the significance of early CT abnormalities as a predictor of hemorrhage after thrombolysis for acute stroke. Before the randomized controlled tPA trials, several studies suggested that the presence of early changes in CT predicted a greater likelihood of hemorrhagic transformation.[100,101] In ECASS I, hypodensity greater than one third of the middle cerebral artery territory was an exclusion; however, many patients were entered despite such findings on CT. These patients had an increased mortality and showed no benefit from tPA.[84] In ECASS II, additional training of investigators reduced the number of protocol violations; however, in a subsequent analysis, the extent of hypodensity on baseline CT was found to be an independent risk factor for intracerebral hemorrhage.[98] The STARS study, a multicenter registry of 389 consecutive patients treated with intravenous tPA, found that the absence of extensive hypodensity on initial CT predicted a favorable outcome.[102,103] Quantitative assessment of CT changes using the ASPECTS scoring system in patients treated with intravenous tPA also showed a relationship between early CT hypodensity (ASPECTS <8) and hemorrhage.[104]

The NINDS group examined the association between early CT changes and hemorrhage and arrived at a different conclusion. Although outcomes were worse in patients with mass effect or edema on initial CT scan, more such patients had good outcomes if treated with tPA. The odds ratio of symptomatic hemorrhage was increased (2.9 versus 1.5) with hypodensity greater than one third of the middle cerebral artery territory. Few patients had this finding on baseline CT scan, however, and the difference did not reach significance.[105] Analysis of the Australian Streptokinase study including patients treated within 4 hours of stroke onset also failed to show any significant relationship between early ischemic changes and intracerebral hemorrhage.[106] The significance of early CT changes as a risk for hemorrhage and poor outcome after intravenous tPA therapy is unclear. At present, most tPA protocols continue to exclude patients from treatment with extensive low density

on initial CT. In the future, MRI or cerebral blood flow measurement might allow more appropriate exclusion of patients with high risk of hemorrhage.

Stroke on Awakening

Frequently, patients arrive in the emergency department after awakening with a new neurologic deficit due to stroke. Because the time of onset cannot be established with certainty, these patients usually are excluded from thrombolytic therapy. Some of these patients may be within the time window for acute stroke treatment, however, and might benefit from thrombolysis.[107,108] Stroke-on-awakening patients may be an ideal group to undergo physiologic imaging studies to select patients appropriate for acute stroke treatment.

Aspirin Pretreatment

Many individuals at risk for stroke are treated with aspirin or other antiplatelet agents. Others take aspirin on the way to the hospital after onset of stroke symptoms. Whether aspirin pretreatment increases the risk of thrombolytic therapy is unclear. In the MAST-I study, patients treated with aspirin and streptokinase had a higher incidence of death from intracranial hemorrhage.[109,110] In ECASS II, there was a higher incidence of symptomatic hemorrhage in patients pretreated with aspirin. In the multicenter recombinant tPA Acute Stroke Survey, aspirin therapy was associated with a higher risk of symptomatic hemorrhage, but did not remain significant after adjustment for other factors. In contrast, a report of 300 patients treated with intravenous tPA failed to find any association between pretreatment with aspirin and hemorrhagic complications.[111] Aspirin pretreatment also was not associated with intracerebral hemorrhage in the NINDS intravenous tPA trial.[112] Patients receiving antiplatelet therapy usually are not excluded from thrombolytic therapy, although additional studies are needed to clarify the relative risk of thrombolysis in these patients.

Severe Stroke

In most studies of thrombolysis, prognosis and risk of hemorrhage are strongly related to initial severity of stroke as measured by the NIHSS score. In the NINDS trial, at 3 months 48% of patients with NIHSS greater than 20 were dead, and 21% were severely disabled. Symptomatic hemorrhage occurred in 17% compared with 6% in the entire cohort.[112] Despite the poor outcomes and increased hemorrhage rate, more patients had good outcomes with tPA than without (10% tPA versus 4% placebo). Severe stroke should not be considered a contraindication to thrombolytic therapy, although the overall poor prognosis and increased hemorrhage rate must be considered in deciding on treatment in individual cases.

INTRA-ARTERIAL THROMBOLYSIS

An alternative approach to intravenous thrombolysis is direct delivery of thrombolytic agents by a microcatheter embedded in the clot (Fig. 51-4).[113] The advantage of the intra-arterial approach is direct visualization of the occluded artery and knowledge of the recanalization status as thrombolysis proceeds. Delivery of the thrombolytic agent to the site of the clot should be more effective than intravenous infusion. The disadvantage is the additional time needed to bring the patient to angiography, prepare the groin, catheterize the femoral artery, and guide the catheter from the femoral artery to the intracranial circulation. Start of thrombolytic therapy typically is delayed by 45 to 60 minutes. Urokinase was used in most early studies of intra-arterial thrombolysis but is no longer available. Prourokinase (recombinant prourokinase) was used in clinical trials, but has not been approved by the FDA. Most intra-arterial thrombolysis is now done with tPA. Doses of 20 to 50 mg have been infused over 1 to 2 hours, but no systematic dose escalation studies have been completed. Some interventionalists advocate extremely small doses of intra-arterial tPA (e.g., 0.1 to 0.2 mg), but most use higher doses. A few reports of intra-arterial therapy with reteplase (Retavase) have appeared, and small pilot studies of intra-arterial Retavase are now in progress. Other issues with intra-arterial thrombolysis include whether to use mechanical catheter manipulation in conjunction with thrombolysis, the optimal dose of heparin, and the use of boluses of thrombolytic agents beyond and within the thrombus before starting an infusion. Most protocols include a small bolus (e.g., 2 mg of tPA) beyond the thrombus followed by 2 mg within, then an infusion over 1 to 2 hours. Progress is assessed every 15 to 30 minutes with an injection of contrast material, and the catheter is repositioned if the thrombus is partially dissolved. When recanalization is achieved, infusion of the thrombolytic agent can be discontinued.

The PROACT trial was the first randomized controlled trial of intra-arterial thrombolysis. PROACT I randomized 40 patients with occlusion of the M1 or M2 segment of the middle cerebral artery to either 6 mg of intra-arterial recombinant prourokinase infused over 2 hours or direct intra-arterial injection of saline within 6 hours of stroke onset.[114] Both groups also received intravenous heparin. In this small pilot study, there was a trend toward improved outcome in the recombinant prourokinase group, but the difference did not reach statistical significance. Based on these encouraging findings, PROACT II was initiated. Over 2.5 years, 180 patients were randomized in a 2:1 ratio to 9 mg of intra-arterial recombinant prourokinase in addition to heparin or to heparin alone.[115] More than 12,000 patients were screened at 50 centers to enter these trials. The primary endpoint of modified Rankin scale 2 at 90 days was achieved by 40% of the recombinant prourokinase group and only 15% of controls ($P = .043$). At least partial recanalization at 2 hours occurred in 67% of recombinant prourokinase patients. Complete recanalization was found in 20%. Symptomatic hemorrhage occurred in 10% of patients treated with recombinant prourokinase and in 2% of controls. Although the hemorrhage rate was higher than previous intravenous thrombolytic studies, the median NIHSS score of 17 indicates that the patients in the PROACT study had more severe strokes treated at a later time interval. A higher hemorrhage rate is expected. Based on factors predicting outcome in this group of patients, the treatment and control groups can be stratified according to risk. There was no differential effect of recombinant prourokinase across risk strata, indicating that all patients, regardless of risk, benefit equally from recombinant prourokinase.[116]

The PROACT study is the only acute stroke trial to show a statistically significant improvement of outcome when given 6 hours after stroke onset. The median time to treatment was 5.5 hours, and most patients were treated after 5 hours from stroke onset.[115] The clinical benefit was apparent despite this late time to treatment, and possibly a greater benefit would have been found had patients been treated earlier.

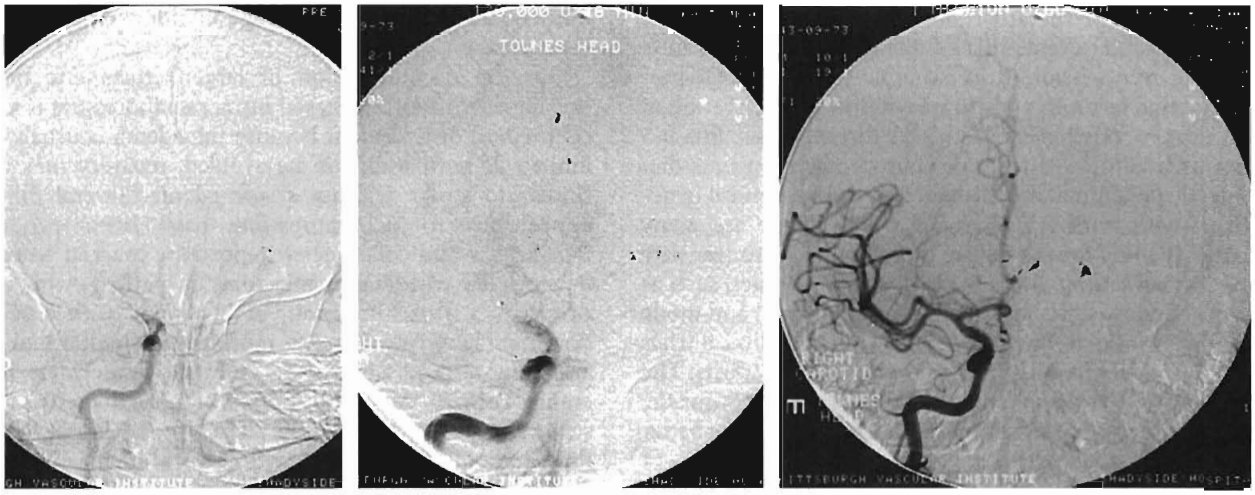


FIGURE 51–4. A, Right carotid angiogram from a patient with embolic occlusion of the right middle cerebral artery 4 hours after onset of symptoms. **B,** Angiogram from the same patient after placement of a microcatheter into the middle cerebral artery clot and infusion of 120,000 U of urokinase. There is no recanalization. **C,** Angiogram after infusion of 1 million U of urokinase directly into the clot, showing complete recanalization of the middle cerebral artery.

Several other factors may have limited the effectiveness of thrombolysis in this study. Infusion of the thrombolytic agent extended over 2 hours, and mechanical manipulation was not allowed. The thrombolytic regimen used in the PROACT study may not represent the optimal parameters, leaving considerable room for future improvement.

Basilar artery thrombosis carries a high morbidity and mortality[117] and may be particularly amenable to intra-arterial thrombolysis. Anecdotal reports indicate successful recanalization of the basilar artery is associated with good outcomes in 25% to 50% of patients,[118-120] a considerable improvement on the reported natural history. Good outcomes have been reported with intra-arterial thrombolysis of basilar thrombosis well beyond the usual 6-hour time limit.[121] Intravenous tPA also may result in improvement, but the large clot burden favors the intra-arterial approach.

Combination Therapy

The major problem with intra-arterial thrombolysis is the additional time necessary to place a catheter into the intracranial arteries; this requires 45 to 60 minutes beyond the time intravenous therapy could be given. If transport to a tertiary care center is needed, the delay may be longer. Combined therapy offers the prospect of beginning intravenous therapy, then proceeding to intra-arterial therapy if needed. If the patient presents within 3 hours of stroke onset, therapy is begun with intravenous tPA in a reduced dose of 0.6 mg/kg over 30 minutes. While the intravenous tPA is infusing, the patient is transported to angiography, and a catheter is placed in the intracranial circulation. If thrombus is present despite intravenous therapy, additional tPA is given intra-arterially in an attempt to clear the thrombus. This approach was used in a small group of patients randomized to either intravenous followed by intra-arterial tPA or placebo followed by intra-arterial tPA.[122] There was a greater recanalization rate in the combined group (partial or complete 81% combined versus 50% intra-arterial alone). Bleeding complications were slightly more common in the combined treatment group.

Mechanical Devices

Although most thrombolytic studies concentrate on time to treatment, the most important factor is probably time to recanalization. When infusion of thrombolytic agents requires 1 to 2 hours for complete thrombus dissolution, time to recanalization can be quite long. Mechanical devices offer the possibility of considerably shortening time to recanalization. In contrast to thrombolytic infusions, devices may be able to clear thrombus from large arteries within a few minutes. Thrombolytic agents may not have to be used, possibly reducing the rate of intracranial hemorrhage. Several devices are now being tested. Catheters capable of reaching the middle cerebral artery or basilar artery use lasers, ultrasound, or high-speed saline jets to agitate or emulsify thrombus. Simple snares to capture thrombotic material also are under development. These devices are now undergoing initial clinical trials but hold great promise for reducing time to recanalization and improving outcomes in acute stroke.

NEUROPROTECTIVE AGENTS

The extent of ischemic injury in the brain depends on the level of cerebral blood flow in the effected territory. Cerebral blood flows less than 10 mL/100 g/min are probably tolerated only for minutes, whereas intermediate levels of blood flow of 20 to 30 mL/100 g/min may be tolerated for several hours before irreversible changes occur.[123] During ischemia, there is insufficient energy for maintenance of normal membrane pump activity. Sodium diffuses into the cell across its gradient causing neuronal depolarization and impairing the ability of the neuron to generate an action potential. In addition, there is a tremendous outpouring of excitatory neurotransmitters, particularly glutamate.[124] Glutamate activates *N*-methyl-D-aspartate and non–*N*-methyl-D-aspartate receptors causing influx of calcium into neurons.[125] This influx results in production of toxic products, including nitric oxide, free radicals, and activation of phospholipases. The duration of this reversible ischemic state is uncertain, but animal models of focal stroke suggest it is only a few hours.[126]

Neuroprotective therapy is designed to interfere with the cascade of cellular events that results in cell death. Blocking any of the events involved in ischemic cell death may preserve function or prolong the time window for restoration of blood flow by other means, such as thrombolysis. Phase 3 randomized controlled trials of neuroprotective agents that are effective in animal models failed to show a clinical benefit in patients with stroke (Table 51-7). There are many potential reasons for the failure of animal trials to translate to the clinical setting. Aspects of the animal studies, such as the time window, dose equivalent, stroke subtype, and mode of administration, frequently were modified in clinical trials to maximize patient entry and to minimize side effects. The expected benefit from treatment often was overly optimistic, and in some cases outcomes in the control group were better than expected, making it more difficult to show a benefit from therapy. Neuroprotective agents may improve certain neurologic functions, such as cognitive activity, which is poorly measured by most commonly used stroke scales. It is also possible that what works in animals simply does not work in humans.

Despite these failures, several new neuroprotective agents are currently in phase 3 trials. NXY-059 is a nitrone spin-trap agent that has been shown to improve outcomes in rodent and primate models of acute stroke. Two randomized controlled trials are in progress to assess the efficacy of this drug for stroke within 6 hours of onset. A phase 3 trial of the serotonin agonist, repinotan, also is in progress for patients with hemispheric stroke. ONO-2506 is a neuroprotectant that modulates the uptake capacity of glutamate transporters and expression of gamma-aminobutyric acid receptors. A phase 3 trial using this agent is currently in progress. Magnesium is undergoing testing in a randomized controlled trial including patients 12 hours from stroke onset. Another study is examining hyperacute prehospital administration of magnesium. Finally, hypothermia is a promising neuroprotective therapy, and clinical trials of mild hypothermia in acute stroke are under way.

STROKECTOMY

Cerebral edema and herniation is the most frequent cause of death from stroke in the first few days.[127] Cerebral edema usually gradually increases and peaks 2 to 3 days after stroke onset. Steroids, do not effectively reduce edema due to stroke, and antiedema measures, such as mannitol or hyperventilation, are of limited benefit. Control of intracranial pressure is associated with improved outcome, but whether intracranial pressure monitoring to guide therapy is helpful is uncertain.

Surgical decompression of large hemispheric infarcts causing edema and increased intracranial pressure is a logical method of treatment because the edema is usually self-limited. If herniation can be avoided, recovery may occur similar to stroke without severe edema. Several different approaches to decompression have been proposed. Rengachary and colleagues[128] reported a marked reduction in mortality with hemicraniectomy in patients with severe edema after stroke. In a group of 32 patients with large nondominant hemisphere stroke, mortality was reduced to 40%, and long-term disability was only moderate after hemicraniectomy.[129] Kalia and Yonas[130] reported the results of strokectomy based on results of xenon CT cerebral blood flow studies in four patients with cerebral edema after stroke and impending herniation. Blood flow studies identify areas of nearly absent flow. This is a more reliable indicator than CT changes of irreversibly damaged brain and helps guide surgical removal avoiding areas of intact cortex. This procedure prevents fatal herniation, but whether long-term outcome is truly improved must be determined by randomized clinical trials. Until then, surgical decompression for hemispheric infarction should be considered for younger patients with a greater potential for recovery from massive stroke and particularly for nondominant strokes. The optimal timing of decompression is uncertain. If herniation is already in progress, irreversible brainstem damage may occur limiting the benefit of the procedure. Early edema may not progress to herniation, and surgery could be performed unnecessarily. Xenon CT findings of extensive areas of near-absent cerebral blood flow may help identify patients liable to have massive edema and herniation[131] and help select patients most likely to require surgical decompression.

Cerebellar infarction is a special case that clearly requires urgent surgical intervention.[132] Compression of the brainstem and fourth ventricle leading to hydrocephalus or severe pontomedullary compromise can be reversed by rapid surgical decompression of the infarcted cerebellum. The clinical syndrome of inferior cerebellar infarction, including vertigo and imbalance, may be mistaken for a vestibulopathy, and CT changes may be subtle or nonexistent. It is critical to suspect this diagnosis in patients at risk for cerebrovascular disease because surgical intervention may be lifesaving with little residual deficit.

TABLE 51-7. FAILED NEUROPROTECTIVE TRIALS

Study	Type	Time to Treatment (h)	Results
Lubeluzole	Phase 3	8	No benefit
Cerestat	Phase 3	6	No benefit
Selfotel	Phase 3	6	No benefit
Enlimomab	Phase 3	6	Treatment worse
Cervene	Phase 3	6	No benefit
GM1 Ganglioside	Phase 3	12	No benefit
Nimodipine	Phase 3	24	No benefit
Fosphenytoin	Phase 3	6	No benefit
Citicoline	Phase 3	24	No benefit
GV150526	Phase 3	6	No benefit

SUMMARY

The availability of effective treatment to alter outcome within the first few hours after stroke onset necessitates dramatic changes in the evaluation of stroke. Patients with symptoms suggesting cerebral ischemia must be treated emergently from the prehospital encounter to the emergency department and the treating physicians. Imaging must be performed rapidly and provide useful information for the decision-making process. Therapy for acute stroke includes much more than thrombolysis. Appropriate management of blood pressure, glucose, intravenous fluids, and temperature all contribute to the overall outcome from acute stroke. Understanding of the benefits and hazards of thrombolysis continues to evolve with greater experience and additional studies. Neuroprotection holds great promise for further improvement of outcomes and possibly enhancement of effectiveness of thrombolysis or extension of the time window for reperfusion. At present, only

a small percentage of patients with stroke arrive at an emergency department in time for acute stroke therapy.[133,134] Development of new acute stroke therapies and improvements in outcome with lower hemorrhage rates should encourage the medical system further to treat a greater number of stroke patients earlier. Rapid advancements in acute stroke therapy may necessitate a system of stroke centers similar to the trauma system to ensure that all stroke patients receive the optimal available therapy in the shortest time possible.

ANNOTATED REFERENCES

Chen ZM, Sandercock P, Pan HC, et al: Indications for early aspirin use in acute ischemic stroke: A combined analysis of 40,000 randomized patients from the Chinese Acute Stroke Trial and the International Stroke Trial. On behalf of the CAST and IST collaborative groups. Stroke 2000;31:1240-1249.

This article represents a combined analysis of two clinical trials, each with 20,000 patients, showing a significant reduction of recurrent stroke and death with aspirin treatment. There was a highly significant reduction of 7 per 1000 in recurrent ischemic stroke in patients treated with aspirin versus control, and a significant reduction of 4 per 1000 in death with aspirin treatment. The authors concluded that early aspirin treatment is of benefit for a wide range of patients and its prompt use should be widely considered for all patients with suspected acute ischemic stroke to reduce the risk of early occurrence.

Furlan A, Higashida R, Wechsler L, et al: Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: A randomized controlled trial. JAMA 1999;282:2003-2011.

Randomized controlled clinical trial of the use of intra-arterial thrombolytics in 180 patients at 50 centers showing significant improvement in outcome with treatment given up to 6 hours from stroke onset. Patients were randomized to receive 9 mg of IA r-pro UK plus heparin (n=121) or heparin only (n = 59). The primary outcome was based on the proportion of patients with slight or no neurologic disability at 90 days as defined by a modified Rankin score of 2 or less.

National Institutes of Neurological Disorders and Stroke. In Rapid Identification and Treatment of Acute Stroke. Pre-hospital Emergency Medical Care Systems, pp 17-48. NIH publication #97-4239. August 1997.

This publication provides the National Institutes of Health algorithm for the pre-hospital and emergency management of acute stroke that was developed from the experience of conducting acute stroke trials.

Rieke K, Krieger D, von Kummer R, et al: Decompressive surgery in space occupying hemispheric infarction. Crit Care Med 1995;73:1576-1587.

Clinical report of reduced mortality rate and favorable long-term outcome in 32 patients with large nondominant hemisphere stroke treated with hemicraniectomy. At follow-up in surgically treated patients, the Barthel Index showed an excellent level of daily activity in one patient, minimal assistance in 15 patients, and dependency in five patients. The Oxford Handicap Scale indicated no handicap in one patient, moderate handicaps in 15 patients, and moderately severe handicaps in five patients. In the control group, all five surviving patients needed assistance, and all but one patient demonstrated a moderately severe handicap.

The ATLANTIS, ECASS and NINDS rt-PA Study Group Investigators: Association of outcome with early stroke treatment: Pooled analysis of ATLANTIS, ECASS and NINDS rt-PA stroke trials. Lancet 2004;363:768-774.

This article represents a combined analysis of five clinical studies in 2775 patients randomly allocated to rt-PA or placebo. The study addresses the use of intravenous rt-PA and provides specific insight into its use beyond three hours of the onset of stroke. The authors concluded that the sooner that rt-PA is given to stroke patients, the greater the benefit, especially if started within 90 minutes. Their findings also suggested a potential benefit from this therapy applied beyond 3 hours, but this potential might come with some risks.

The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group: Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-1587.

A key clinical report in the field of stroke that showed, for the first time in a randomized controlled trial, a reduction in stroke morbidity with acute treatment. In June 1996, the FDA approved intravenous tPA for the treatment of stroke within 3 hours of onset.

Chapter 52

NONTRAUMATIC INTRACEREBRAL AND SUBARACHNOID HEMORRHAGE

Allyson R. Zazulia • Michael N. Diringer

KEY POINTS

INTRACEREBRAL HEMORRHAGE

1. **Intracerebral hemorrhage (ICH) injures the brain not only through direct mechanical compression** but also through secondary mechanisms such as ischemia and edema.
2. **Hematoma expansion occurs within the first few hours after symptom onset** in approximately one third of patients.
3. **In-hospital neurologic deterioration may occur in as many of two thirds of patients;** among these patients, one quarter will be found to have increased hematoma size.
4. **There appears to be no compelling reason to reduce blood pressure in the acute period after ICH.** If there are systemic concerns, modest reduction (15% to 20%) in patients with severe hypertension (mean arterial pressure >130 to 140) using short-acting agents with minimal cerebrovascular effects (e.g., labetalol, nicardipine, enalapril) appears to be safe.
5. **Randomized trials of surgical hematoma evacuation and corticosteroid treatment have failed to show a consistent benefit in the management of ICH.** The efficacy of osmotic agents has not been evaluated in a randomized trial.
6. **The most common cause of death after ICH is withdrawal of care,** followed by transtentorial herniation and medical complications of immobility.

SUBARACHNOID HEMORRHAGE

1. **Subarachnoid hemorrhage (SAH) typically presents as the sudden onset of a severe headache,** often associated with nausea, vomiting, and syncope. Focal neurologic deficits are uncommon.
2. **Rebleeding, which is often fatal, occurs most commonly within the first 24 hours** and is heralded by a sudden worsening of headache, vomiting, new neurologic deficit, or arrhythmia.
3. **Hydrocephalus may develop acutely within hours of SAH or gradually up to weeks later** and usually manifests as an insidious decline in mental status.
4. **Delayed vasospasm occurs in more than two thirds of patients, especially those with large amounts of subarachnoid blood,** and produces a new focal neurologic deficit in more than one third. Management options include nimodipine, hemodynamic augmentation, and endovascular maneuvers.
5. **Management of SAH-associated "cerebral salt wasting" often requires the administration of large volumes of fluid replacement** to prevent intravascular volume contraction and restriction of free water to treat hyponatremia.
6. **Cardiac abnormalities, including electrocardiographic changes, mildly elevated cardiac enzymes, and arrhythmias, are common after SAH** and are thought to be related to elevated catecholamine levels rather than myocardial ischemia.

INTRACEREBRAL HEMORRHAGE

Spontaneous (nontraumatic) intracerebral hemorrhage (ICH) accounts for approximately 10% of all strokes in North America and about 20% to 30% in East Asia. It is associated with greater mortality and more severe neurologic deficits than any other stroke subtype.[1-3] Nearly half of all patients die within the first 30 days; survivors often have significant residual disability.[4,5]

PATHOPHYSIOLOGY

The pathophysiologic mechanisms of brain injury due to ICH are complex. The primary injury is one of local tissue destruction as rupture of a cerebral blood vessel introduces a sudden stream of blood into the brain parenchyma. In more than one third of patients, continued bleeding or rebleeding results in hematoma enlargement and further mechanical injury within the first few hours after onset.[6] The mass of blood produces tissue shifts within the intracranial cavity.

In addition to the primary mechanical injury, further damage is believed to occur after the bleeding stops.

The mechanisms underlying this secondary injury are unknown, but ischemia and edema have been implicated. Experimental models of ICH suggest that ischemia is an important part of its pathophysiology.[7,8] Periclot and ipsilateral hemispheric hypoperfusion has been demonstrated almost uniformly in clinical studies,[9-11] but the importance of ischemia in patients with ICH has not been settled.[12,13] Positron emission tomography studies in humans performed 10 to 22 hours after symptom onset showed that both cerebral blood flow (CBF) and metabolism are reduced around the clot, suggesting that the hypoperfusion reflects the reduced metabolic demand of the damaged tissue surrounding the hematoma rather than ongoing ischemia.[13]

Cerebral edema occurs within hours of experimental ICH, variably thought to result from the toxic effects of blood-derived enzymes, from increased osmotic pressure exerted by clot-derived serum proteins, or from ischemia.[14-16] The presence, time course, and importance of edema in humans are debated. Part of the difficulty stems from the inability to unequivocally quantify edema in humans. Signal changes on radiographic studies after ICH indicate increased water content in the area surrounding the clot, but the clinical and pathophysiologic significance of this is not known.

Hemostasis after hemorrhage is initially achieved at the site of vascular injury by the formation of a platelet-fibrin plug. After several days, red blood cells within the clot begin to lyse, cellular infiltrates appear, and the process of reabsorption begins. Months later, a residual collapsed cavity is all that remains.

CAUSES AND RISK FACTORS

The leading risk factor for ICH, occurring in more than half of all cases, is chronic hypertension.[17,18] Long-term adequate treatment of chronic hypertension significantly reduces this risk.[19] Increasing age is another risk factor, with a doubling of the rate of hemorrhage with each decade of life until age 80, when the incidence plateaus at nearly 25 times that of the previous decade.[20]

Other risk factors include black race[21] and alcohol abuse.[22] The relationship of ICH to smoking[22,23] and low serum cholesterol[24,25] has not been convincingly established. Similarly, the impact of diabetes on the risk of ICH is disputed.[26,27]

Hypertensive Hemorrhage

Hypertensive ICH occurs predominantly deep in the cerebral hemispheres, most often in the putamen (Fig. 52-1).[17] Other frequently involved sites include the thalamus, lobar white matter, cerebellum, and pons. The common link among these sites is that they are all supplied by small penetrating arteries,[28] perpendicular branches directly off major arteries that are subject to high sheer stress and that have no collaterals. These features make them vulnerable to the effects of increased blood pressure. Chronic hypertension damages the tunica media, resulting in lipohyalinosis, fibrinoid necrosis, and microaneurysms (Charcot-Bouchard aneurysms). Although Charcot-Bouchard aneurysms have been demonstrated in the weakened vessel walls of patients with ICH, their pathogenetic role in vascular rupture is uncertain.[29] The occurrence of ICH in an atypical location, in multiple locations, or in association with subarachnoid hemorrhage raises the suspicion of a nonhypertensive cause, such as a cerebral vascular anomaly, blood dyscrasia, or trauma.

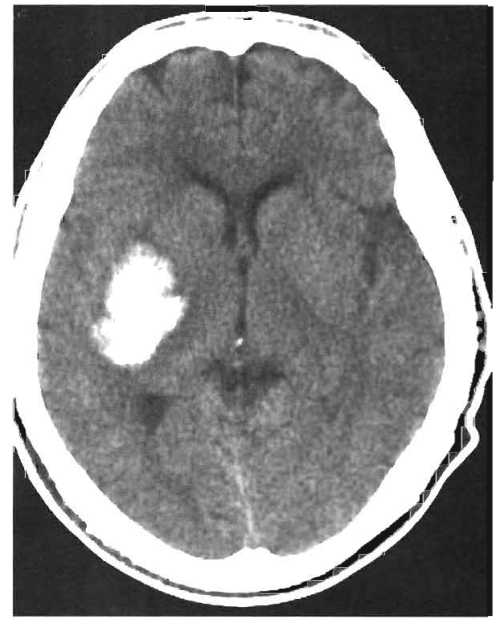


FIGURE 52–1. Typical moderate-sized putaminal hemorrhage. (From Diringer MN, Pucllicino P, Chan R: Intracerebral hemorrhage. Continuum 2003;9:170.)

Intracranial Aneurysms and Vascular Malformations

Up to one quarter of hemorrhages are due to bleeding from rupture of an intracranial aneurysm (fusiform and saccular) or vascular malformation (arteriovenous malformation [AVM] or angioma). Rupture of a saccular berry aneurysm produces ICH in 5% to 25% of cases. Although aneurysmal rupture is most commonly associated with hemorrhage in the subarachnoid space, the blood may also be directed into the substance of the brain if the aneurysm is adherent to the brain parenchyma. Rarely, aneurysms located at the middle cerebral artery bifurcation produce hemorrhages that appear identical to hypertensive hemorrhages into the basal ganglia, and anterior communicating artery aneurysms can produce flame-shaped hemorrhages in the base of the frontal lobes.

Approximately half of intracranial AVMs in adults present with hemorrhage.[30] In 60% of cases, the hemorrhage is parenchymal, involving virtually any location within the cerebrum, brainstem, or cerebellum.[31] The majority of AVMs become symptomatic by age 40; thus, hemorrhage due to AVMs occurs in a younger population than that due to aneurysms or hypertension. Multiple calcified vascular channels may be seen within the hematoma on computed tomography (CT) scans, suggesting the presence of an AVM. Magnetic resonance imaging (MRI) and four-vessel cerebral angiography are useful adjuncts in the diagnosis of these lesions.

Other Causes

Cerebral amyloid angiopathy is an important cause of predominantly lobar, often recurrent ICH in the elderly. Histopathologic studies demonstrate the deposition of β-amyloid protein in the media and adventitia of small meningeal and cortical vessels; deposition in the typical sites for hypertensive hemorrhage is rare, but it has been reported in the cerebellum.[32] The prevalence of amyloid in cerebral vessels increases dramatically with age[33,34] and may partially

account for the exponential rise in the risk of ICH with increasing age. There is an overrepresentation of the apolipoprotein E ε2 and ε4 genotypes in hemorrhages related to cerebral amyloid angiopathy, and these alleles are associated with a younger age at hemorrhage onset and a higher risk of early recurrence.[35,36] Although there is no radiographic technique for diagnosing cerebral amyloid angiopathy, the finding of recurrent lobar ICH in an elderly nonhypertensive patient strongly suggests the diagnosis.

Approximately 10% of ICHs are due to hematologic causes.[37] Coagulopathy-related ICH most often results from warfarin therapy[38] but may also be associated with the use of other antithrombotic and thrombolytic agents, as well as with systemic diseases (e.g., thrombocytopenia, leukemia, hepatic and renal failure) or congenital or acquired factor deficiencies.

Hemorrhage from an underlying neoplasm is rare; however, it occasionally occurs with malignant primary central nervous system tumors such as glioblastoma multiforme and lymphoma and with metastatic tumors such as melanoma, choriocarcinoma, renal cell carcinoma, and bronchogenic carcinoma.[39] Benign tumors are almost never associated with ICH.

ICH may also occur in association with infection (e.g., infiltration of vessel wall by fungal organisms),[40] necrotizing hemorrhagic encephalitis with herpes simplex virus,[41] vasculitis,[42] venous sinus occlusion,[43] in a delayed fashion after head trauma,[44] following reperfusion (e.g., after carotid endarterectomy or acute thrombolysis),[45] and with the use of various drugs, particularly sympathomimetics (e.g., cocaine, amphetamines, pseudoephedrine, phenylpropanolamine).[46,47] Finally, some degree of hemorrhagic transformation of acute cerebral infarcts is common,[48,49] although symptomatic ICH in this setting is rare in the absence of anticoagulation or thrombolytic therapy.[50,51]

CLINICAL FEATURES

The clinical presentation of ICH is often indistinguishable from that of ischemic stroke but more commonly includes altered level of consciousness, headache, and vomiting, reflecting the presence of increased intracranial pressure (ICP).[17] Blood pressure is elevated in the majority of patients (see later). Seizures occur in 15% to 25% of patients within the first 48 hours and are nearly always associated with lobar hemorrhages or underlying vascular or neoplastic lesions.[52,53] Symptoms are maximal at onset or develop over minutes to hours. Neurologic deterioration after hospital admission has been reported to occur in 33% to 61% of patients with ICH.[54,55] The cause for clinical worsening is not always evident, but increased hematoma size is found in more than 25% of cases.[54] The role of edema in clinical deterioration is much more elusive.

DIAGNOSTIC STUDIES

Noncontrast CT scanning remains the gold standard for the diagnosis of acute ICH. The typical CT appearance of an acute hematoma consists of a well-defined area of increased density surrounded by a rim of decreased density. Over time, the borders of both the high- and low-attenuation regions become increasingly indistinct, such that the hematoma is isodense with adjacent brain parenchyma by 2 to 6 weeks.[56,57] Peripheral contrast enhancement can often be seen at this time.[58] By 2 to 6 months, there may be no CT evidence of previous hemorrhage, or there may be an area of hypodensity or a slitlike scar.[59]

Although the ability of MRI to reliably detect acute hemorrhage is controversial,[60] MRI is better than CT for determining the approximate age of a hematoma. This is because each hemoglobin oxidation state during the evolution of the hematoma produces a predictable pattern of signal intensity.[61] In addition, gradient-echo sequences may be useful in demonstrating the iron-containing deposits of previous asymptomatic hemorrhages.[62,63]

MRI and conventional angiography can be useful in evaluating the cause of ICH if an underlying aneurysm, vascular malformation, or neoplasm is suspected, but the yield of such studies is extremely low when the patient has chronic hypertension and the hemorrhage is in one of the typical sites associated with hypertensive hemorrhage.[64]

TREATMENT

Initial Stabilization

Acute ICH is a medical emergency requiring attention to airway and respiratory management, hemodynamic status, and correction of any underlying coagulopathy. As many as half of all patients with ICH undergo mechanical ventilation.[65] Blood pressure is often elevated at presentation, sometimes markedly so. Recent evidence indicates that the majority of hematomas enlarge over the first few hours, suggesting that aggressive correction of coagulopathies might be helpful.

Airway and Respiratory Management

Airway obstruction in ICH may occur for two reasons. First, there may be diminished consciousness, resulting in relaxation of the pharyngeal musculature and tongue and suppression of the cough and gag reflexes. Second, in ICH involving the posterior fossa, there may be complete loss of pharyngeal tone and absent cough, swallow, and gag reflexes.

Initial airway management includes proper positioning, frequent suctioning, and placement of an oral or nasal airway. Frequent assessments for sonorous respiration, inability to manage oral secretions, or decreased oxygen saturation are necessary. If conservative measures are ineffective, intubation may be necessary. Intubation of patients with ICH requires adequate sedation and jaw relaxation, as well as prevention of ICP elevation. Several factors may conspire to raise ICP during intubation, including hypoxemia, hypercarbia, and direct tracheal stimulation. Intravenous lidocaine (1 to 1.5 mg/kg) has been recommended to block this response,[66] although data supporting its use are lacking.[67] Short-acting intravenous anesthetic agents (thiopental 1 to 5 mg/kg or etomidate 0.1 to 0.5 mg/kg) also block this response[68] and additionally suppress brain metabolic rate,[68a] theoretically improving tolerance of a transient fall in cerebral perfusion pressure (CPP), should it occur. Etomidate is generally preferred over thiopental because it is less likely to lower blood pressure. Paralytic agents are usually unnecessary, but if needed, short-acting agents should be used. Intubated patients are at high risk for pneumonia via colonization of the oropharynx, sinuses, trachea, and gastrointestinal tract or contamination from hospital personnel or equipment. Appropriate measures should be taken to minimize this risk.

Hemodynamics

Arterial blood pressure is elevated on admission in the majority of patients with ICH, even in the absence of a history of hypertension.[17] Mean arterial pressure (MAP) is greater than 120 mm Hg in more than two thirds of patients and greater than 140 mm Hg in more than one third.[69] Although this acute increase in blood pressure is often implicated as the cause of the hemorrhage, it may simply be a reflection of chronic hypertension, the brain's attempt to maintain CPP in response to the sudden increase in ICP, pain and anxiety, and sympathetic activation. Even without pharmacologic intervention, blood pressure tends to decline to premorbid levels during the first 7 to 10 days after hemorrhage.[70]

There is substantial controversy over whether and when to lower blood pressure after acute ICH and how aggressive any intervention should be.[71,72] Proponents of rapid treatment of acute hypertension argue that high blood pressure may predispose to hematoma enlargement and may exacerbate vasogenic edema by increasing capillary hydrostatic pressure, especially in areas with a damaged blood-brain barrier. Yet an association between hypertension and edema has never been demonstrated, and data on the effect of hypertension on hematoma enlargement are inconsistent.[6,73,74] Another potential reason to lower blood pressure is that hypertension during the acute phase of ICH has been shown to correlate with a poor prognosis in some studies.[75,76] Causality has not been established, however, so it does not necessarily follow that lowering blood pressure will improve outcome. In fact, other studies have found no relationship between admission blood pressure and mortality.[55] In one report, patients whose mean blood pressure could be lowered to less than 125 mm Hg had a better outcome,[72] but it is unknown whether lowering the blood pressure improved the outcome or whether patients who respond to antihypertensive medications have less severe injury. Perhaps the most compelling reason to consider lowering blood pressure in ICH patients with moderate to severe hypertension is the potential for end-organ damage. Such patients are at risk for systemic complications of elevated blood pressure, including myocardial ischemia, congestive heart failure, and acute renal failure. Therefore, if hypertension is not treated, monitoring for such end-organ dysfunction is necessary.

The major argument against the treatment of elevated blood pressure is that lowering blood pressure might exacerbate ischemic damage in the tissue surrounding the hematoma by impairing CBF.[71] Chronic hypertension shifts the cerebral autoregulatory curve to the right, such that a higher CPP is required to maintain adequate CBF.[77,78] Thus, lowering the blood pressure to "normal" levels in these patients could lead to inadequate CBF. Similarly, because CPP is equal to the difference between MAP and ICP, lowering blood pressure may reduce CPP below the autoregulatory limit in patients with elevated ICP due to a large space-occupying clot or hydrocephalus.

Seeking to determine whether lowering blood pressure produces cerebral ischemia in acute ICH, several studies of CBF autoregulation in patients with recent ICH and elevated blood pressure (MAP >130 to 140 mm Hg) have been carried out.[79-81] Taken together, these studies demonstrate that regional and global autoregulation is preserved after ICH, down to a lower MAP limit that averages 110 mm Hg, or about 20% of the admission MAP, but there is substantial individual variation. MAP reductions in excess of 20%, or below approximately 85 mm Hg, may reduce CBF. None of these studies provided data on ICP, and, with the exception of one in which hematoma size was not specified, all were carried out on patients with small to moderate hematomas. Although these data do not address the issue of whether early pharmacologic reduction in blood pressure is beneficial, they do challenge the assumption that such reductions are harmful and may provide useful guidelines when blood pressure treatment is deemed necessary in patients with acute ICH.

In summary, unless there are signs of systemic complications, there appears to be no compelling need to aggressively treat hypertension in the early period after ICH, especially in the setting of large hemorrhages and raised ICP. However, modest blood pressure reductions (15% to 20%) in very hypertensive patients (MAP >130 to 140 mm Hg) with small- to moderate-sized hemorrhages appear to be safe.

If the decision is made to treat hypertension in the setting of acute ICH, the most appropriate antihypertensive agent would have a short half-life and minimal cerebrovascular effects, and it would be administered in such a way as to avoid sudden large reductions in blood pressure. Vasodilators, especially those that dilate veins, can raise ICP by increasing cerebral blood volume and hence should be avoided. Sodium nitroprusside and nitroglycerin increase ICP and lower CBF in patients with reduced intracranial compliance. Ganglionic blockers may also lower CBF. Calcium channel blockers, beta blockers, and angiotensin-converting enzyme (ACE) inhibitors have minimal effects on CBF within the autoregulatory range of MAP and do not alter ICP. Therefore, popular agents in the setting of acute ICH include the combined alpha and beta blocker labetalol, the calcium channel blocker nicardipine, and the ACE inhibitor enalapril. It should be noted that large doses of labetalol may be required to counteract the sympathetic nervous system stimulation associated with ICH. Another useful agent is hydralazine.

Prevention of Hemorrhage Extension

Because hemorrhage extension is known to occur within the first few hours after symptom onset in approximately one third of patients (Fig. 52-2),[6] any coagulopathy should be corrected as rapidly as possible. Patients taking warfarin should receive intravenous vitamin K and enough fresh frozen plasma to normalize the coagulation profile. Cryoprecipitate may be a useful alternative. Care must be taken not to precipitate congestive heart failure, however, and diuretics may be required to maintain an appropriate fluid balance. Additionally, the administration of fresh frozen plasma carries the risk of transfusion-related acute lung injury, which can complicate the process considerably. Correcting coagulopathy associated with thrombolytic-induced ICH is discussed later.

Even in those patients without coagulopathy, promoting early hemostasis might limit ongoing bleeding and decrease hematoma volume. Factor VIIa is a coagulation factor that interacts with tissue factor exposed in the wall of a damaged blood vessel to drive a burst of thrombin that initiates platelet aggregation and accelerates formation of a stable fibrin clot. A recently completed international phase IIb placebo-controlled dose-ranging proof-of-concept study found that treatment with recombinant factor VIIa (rVIIa) given as a single i.v. bolus within four hours of ICH onset decreases hematoma growth and improves clinical outcome despite a small increase in thromboembolic events. The percent increase in ICH volume at 24 hours was significantly

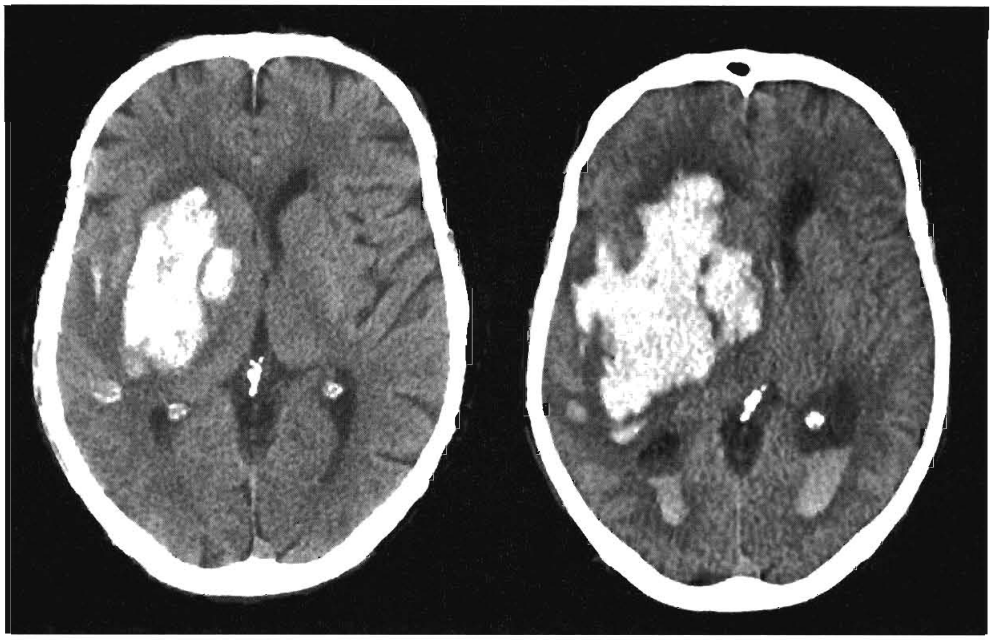


FIGURE 52–2. Hematoma enlargement with intraventricular extension. CT scan on the left was obtained 2 hours after symptom onset. CT scan on the right was obtained 2 hours later.

lower in the highest rVIIa dose group (160 μg/kg; 11%) compared with the placebo group (29%).[81a]

Intraventricular Hemorrhage and Hydrocephalus

In approximately 40% of patients with ICH, blood extends into the ventricular system (intraventricular hemorrhage).[82] Mortality in these patients is high.[83,84] Intraventricular hemorrhage may contribute to poor outcome by blocking cerebrospinal fluid pathways, with resultant hydrocephalus and increased ICP. In addition, intraventricular blood or its breakdown products may exert direct chemical irritative effects on periventricular structures.

Hydrocephalus may develop after ICH either in association with intraventricular hemorrhage or because of direct mass effect on a ventricle (e.g., on the third ventricle with a thalamic hemorrhage) (Fig. 52-3). External ventricular drainage (ventriculostomy) is frequently used to treat hydrocephalus and intraventricular hemorrhage, but its efficacy has never been established, and retrospective data suggest that it does not improve outcome.[85] Ventriculostomy in the setting of intraventricular hemorrhage is difficult to manage because the catheter frequently becomes obstructed with thrombus, interrupting drainage and raising ICP. Flushing the system helps remove thrombus from the catheter but increases the risk of ventriculitis. Recently, investigators attempted to facilitate the removal of blood from the ventricles by the direct intraventricular administration of thrombolytic agents. A preliminary study using urokinase (which is no longer available) showed no increase in complications and a trend toward reduced mortality in the group receiving the thrombolytic.[86] A multicenter randomized study is currently under way to investigate the efficacy of this promising therapy.

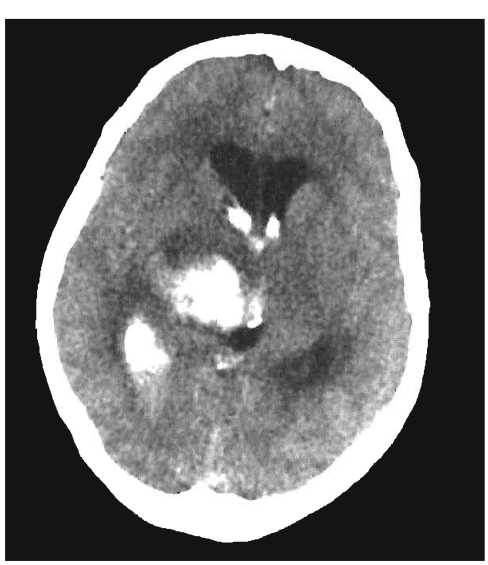


FIGURE 52–3. Small thalamic hemorrhage with blood obstructing the foramina of Monro, causing hydrocephalus.

Intracranial Hypertension

The incidence, impact, and appropriate management of intracranial hypertension in ICH are not well understood. Factors likely to contribute to elevated ICP in this population include large hematoma size, minimal degree of underlying cerebral atrophy, and hydrocephalus, but the true incidence of intracranial hypertension is unclear because routine ICP monitoring is not performed. Because the hematoma is localized and the increase in volume it produces can be partially compensated for by the reduction in the size of the ventricles and subarachnoid space, a global increase in ICP may not be seen unless the hemorrhage is massive or is associated with marked hydrocephalus. In addition, mass effect with local tissue shifts can compress the brainstem or result in herniation in the absence of a global increase in ICP.[87,88]

Invasive ICP monitoring devices can be placed in extradural, subdural, intraparenchymal, intraventricular, or intraspinal locations, but ventricular catheters have the additional capacity to manage hydrocephalus. If ICP is elevated or there are clinical signs of herniation, treatment options include hyperventilation, diuretics, osmotic agents (mannitol, hypertonic saline), and, if the ventricles are enlarged, cerebrospinal fluid drainage. A recent case series suggested that the rapid reversal of clinical transtentorial herniation

(decreased level of consciousness and dilated pupil) with hyperventilation and osmotic agents improved long-term outcome,[89] but the efficacy of these approaches in controlling ICP or altering outcome has not been evaluated in a randomized trial. Corticosteroids have no role in the management of increased ICP associated with ICH because they do not provide any benefit and increase the rate of complications.[90]

Surgical Evacuation

The rationale for surgical evacuation of a hematoma is that reducing mass effect and removing neurotoxic clot constituents should minimize injury to adjacent brain tissue and hence improve outcome. Unfortunately, several randomized, controlled trials of surgery for supratentorial ICH dating back to 1961 all failed to show a benefit.[91-94] A meta-analysis of three of these trials reported that patients undergoing surgical evacuation via open craniotomy had a higher rate of death or dependency at 6 months compared with those managed medically (83% versus 70%).[95] Criticisms of these trials are that the surgical techniques are outdated, patient selection was inadequate, and surgery was delayed too long.

Because open craniotomy is complicated by tissue damage sustained during the approach to the hematoma, a variety of new techniques for clot removal have been proposed, including an Archimedes screw, ultrasonic aspirator, modified endoscope, modified nucleotome, double-track aspirator, intraoperative CT monitoring, and instillation of thrombolytics. However, the recurrence of bleeding due to loss of the tamponade effect on adjacent tissue, which occurs in 10% of patients treated with open craniotomy, remains an issue with these techniques. In addition, because the new techniques involve limited surgical exposure, there is concern that rebleeding will be more difficult to control than with open craniotomy. One study comparing endoscopic aspiration to medical management found a better outcome in the surgical group (74% death or disability, compared with 90%), but the benefit was limited to patients with lobar hematomas.[94] Another study comparing stereotactic hematoma evacuation to conservative treatment in a select group of patients with putaminal hemorrhage found that surgery within 24 hours resulted in reduced mortality (11.8% vs. 23.5%) and greater likelihood of independent functional outcome (47.1% vs. 21.6%) in those patients who on admission had closed eyes that opened in response to strong stimuli. Of note, however, the authors provided no information regarding medical management or surgical technique.[95a] Three studies addressed the feasibility of early craniotomy for ICH. In one, 34 patients were treated within 12 hours of ICH.[96] Mortality was 18% in the surgical group and 23% in the medical group. In another study, 20 patients were randomized, with a median time to surgery of 8.5 hours from onset.[97] Good outcomes (Glasgow outcome scale score >3) were achieved in 56% of the surgical group and 36% of the medically treated group (P = NS). The third, a study of ultra-early surgery (<4 hours), found a disturbingly high rate of postoperative rebleeding.[98]

A lack of benefit of surgery in ICH was also shown in a recently completed multicenter trial in which 1033 patients were randomized within 72 hours of ICH onset to surgical hematoma evacuation (open craniotomy or stereotactic aspiration, at surgeon's discretion) or initial conservative management. Favorable outcome occurred in 26.1% in the surgery group and 23.8% in the initial conservative treatment group, a nonsignificant difference (odds ratio 0.89; 95% confidence interval 0.66 to 1.19). There was also no difference in mortality (surgery 62.6% vs. conservative treatment 63.7%). Subgroup analysis suggested a possible benefit of surgery in patients with superficial hematomas (less than 1 cm from cortical surface).[98a]

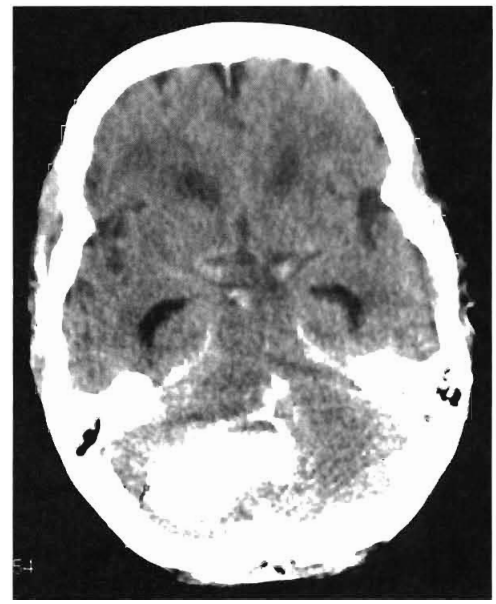


FIGURE 52–4. Typical cerebellar hemorrhage with early hydrocephalus evident by enlargement of the temporal horns of the lateral ventricles.

Whether cerebellar hemorrhage represents a unique case with regard to the role of surgery is unclear. In the pre-CT era, urgent surgery was advocated for all patients with cerebellar hemorrhage because of the perceived likelihood of severe disability or death.[99,100] With the advent of CT, however, it became evident that many patients had a benign outcome without surgery.[101-104] Proposed criteria for when to evacuate a cerebellar hematoma include diminished level of consciousness, large hematoma size (>3 cm^3), midline location, compression of basal cisterns or brainstem, and hydrocephalus (Fig. 52-4),[105-107] but whether these criteria select for patients who will benefit from surgery remains to be demonstrated in a randomized trial.

Thrombolytic-Induced Hemorrhage

Symptomatic ICH is a feared complication of thrombolytic therapy and is associated with considerable morbidity and mortality. It occurs after thrombolytic treatment of acute ischemic stroke in 3% to 20% of patients.[51,108-110] Symptomatic ICH is substantially less common after thrombolytic treatment of extracerebral thrombosis (myocardial infarction, pulmonary embolism, deep venous thrombosis, arterial and graft occlusion)[111] but results in a similarly poor outcome.[112] Factors that increase the risk of symptomatic ICH include higher dose of thrombolytic agent,[113] intra-arterial rather than intravenous route of administration,[114] elevated blood pressure before treatment,[115] and concomitant use of heparin.[116]

In the setting of thrombolytic therapy, any new neurologic deficit, especially a decline in consciousness, should be assumed to be due to hemorrhage. When ICH is suspected, the thrombolytic infusion is stopped, the patient's airway is reassessed, and an emergent CT scan is obtained. Blood studies (prothrombin time, partial thromboplastin time, thrombin and fibrinogen levels) should be performed to assess fibrinolytic state. At the first suspicion of hemorrhage, preparations should be made for giving fresh frozen

plasma, cryoprecipitate, and platelets if needed. The National Institute of Neurological Disorders and Stroke (NINDS) study of tissue plasminogen activator stipulated 6 to 8 units of cryoprecipitate or fresh frozen plasma and 6 to 8 units of platelets, but only rarely was this amount of blood product given to an individual patient during the study.[51] Although neurosurgical consultation was frequently obtained in patients with symptomatic ICH in the NINDS trial, only one patient in the study underwent surgery, and that patient died.

PROGNOSTIC FACTORS AND CAUSES OF MORTALITY

Mortality following ICH is high (25% to 50%), with more than half of the deaths occurring in the first 48 hours. Although patients who have small hemorrhages and mild deficits may recover completely, the majority of ICH survivors have significant residual disability.[4,5,117] Many clinical and radiographic prognostic indicators have been identified, but they are not consistently recognized across studies. Clinical factors reported to predict poor prognosis include older age, reduced level of consciousness on admission, elevated blood pressure on admission, and in-hospital neurologic deterioration. Radiographic features include large initial hematoma size, intraventricular spread of the hemorrhage, midline shift, hydrocephalus, and hematoma growth.[6,54,55,75,82,118-120] It has been demonstrated, however, that withdrawal of support in patients thought likely to have a poor outcome biases predictive models in ICH and negates the predictive value of all other variables.[121] Thus, the most frequent cause of death after ICH is withdrawal of care, followed by early (within 48 hours) transtentorial herniation and progression to brain death. Medical complications of immobility (pulmonary embolism, pneumonia, sepsis) account for most of the other deaths.[117] For survivors of ICH, the risk of recurrent stroke is approximately 4% per year. Recurrent ICH occurs about twice as often as ischemic stroke, especially in those with previous lobar hemorrhage.[122]

SUBARACHNOID HEMORRHAGE

Although it is the least common form of stroke, subarachnoid hemorrhage (SAH) has a great impact on its sufferers. One quarter of patients die before reaching medical attention,[123] and because of the consequences of secondary insults—rebleeding, hydrocephalus, and delayed ischemia due to vasospasm—more than half of those who reach medical attention either die or are left with neurologic deficits.

PATHOPHYSIOLOGY

In SAH, the primary site of bleeding is within the subarachnoid space, but depending on the cause, it may also involve hemorrhage into the brain parenchyma, ventricular system, or subdural space. Rupture of an intracranial saccular aneurysm is by far the most common cause of spontaneous SAH. Saccular or berry aneurysms are small, rounded protrusions of the arterial wall occurring predominantly at arterial bifurcations of the circle of Willis at the base of the brain. The most common sites of ruptured aneurysms are the internal carotid artery, including the posterior communicating artery junction (41%); anterior communicating artery–anterior cerebral artery (34%); middle cerebral artery (20%); and vertebrobasilar arteries (4%).[124] About 20% of patients have multiple aneurysms.[125]

Aneurysmal pathogenesis remains controversial, with the importance of developmental versus acquired factors in dispute. Proponents of the congenital theory suggest that aneurysms arise at sites of faulty fusion between muscular segments within the arterial wall. Supporters of the acquired-degenerative theory focus on the role of vascular damage caused by hemodynamic stress.[126] Citing the age-dependent occurrence of arterial defects and aneurysms' predilection for arterial bifurcations (sites of maximal hemodynamic stress), those favoring the importance of acquired features postulate that degenerative changes within the internal elastic lamina and media result in a local weakness that allows for aneurysm formation. The obvious third possibility is that aneurysms develop at sites harboring congenital defects with superimposed degenerative changes.

What leads to aneurysm growth and rupture is also debated. Hemodynamic stress and other factors intrinsic to the involved vessels may play a role. The time course over which aneurysms grow and subsequently rupture is unknown, although some aneurysms appear to grow rapidly, over weeks, whereas others grow slowly, over years.

The site of rupture of most aneurysms is the dome, where the wall may be as thin as 0.3 mm. Aneurysm rupture may cause local tissue damage due to the jet of blood under high pressure, as well as cause a global increase in ICP. Tension on the aneurysm wall is determined by the radius of the aneurysm and the pressure gradient across the wall (Laplace's law). The probability of rupture is related to size; aneurysms less than 7 to 10 mm in diameter have a very low rate of rupture.

CAUSES AND RISK FACTORS

Rupture of a saccular cerebral aneurysm is the cause of hemorrhage in more than three quarters of patients with nontraumatic SAH. Thus, genetic conditions that predispose to aneurysm formation, such as polycystic kidney disease, connective tissue disorders, and coarctation of the aorta, also predispose to SAH.[126] Other types of aneurysms that less commonly cause SAH include atherosclerotic, mycotic, and traumatic aneurysms. Among the causes of nonaneurysmal SAH, trauma is the most common. Arteriovenous malformations, cocaine and stimulant abuse, neoplasia, and vasculitis account for the bulk of the remainder. In a significant number of cases, no source of bleeding is identified.

The risk of SAH increases with age, peaking at 55 to 60 years. There is a slight male predominance in younger age groups and a slight female predominance among older patients.[127] Potentially reversible risk factors for SAH include cigarette smoking, oral contraceptive use, alcohol abuse, and hypertension.[128] Prospective cohort studies reported a relative risk of SAH as high as 5.7 for female and 4.7 for male smokers,[129] but no increased risk in former smokers. Oral contraceptive use, in addition to being an independent risk factor for SAH, dramatically increases the risk among smokers.[130] A dose-response relationship exists between alcohol consumption and incidence of SAH.[131,132] Finally, hypertension appears to be a risk factor[133] and may be the mechanism by which conditions such as polycystic kidney disease and stimulant drug use increase the risk for SAH.

Recently it has become clear that, in some patient populations, genetic factors play a role in aneurysm formation.[134,135] Individuals with two first-degree relatives with cerebral

aneurysms should undergo diagnostic evaluation for an aneurysm. Conventional angiography remains, at present, the appropriate test.

CLINICAL FEATURES

Presentation

The most common initial symptom of SAH, occurring in more than 90% of patients, is sudden severe headache. Less severe "sentinel" headaches[136] may precede the presenting event in as many as half of patients and are thought to represent minor leaks. In 45% of patients, transient or persistent loss of consciousness accompanies the headache.[137] The mechanism responsible for this acute loss of consciousness is that, at the moment of hemorrhage, the sudden surge in ICP approaches systemic arterial pressure, resulting in inadequate cerebral perfusion. Vomiting can be prominent in awake patients. Seizure activity may be reported.[138] In some cases, it is unclear whether this represents true epileptic seizures or reflex posturing related to the sudden rise in ICP. Focal deficits at the onset of hemorrhage occur in less than 10% of cases but, when present, may point to the location of a thick extra-axial or intraparenchymal blood clot. After a few hours, a stiff neck can develop, reflecting the sterile meningeal inflammation induced by the presence of blood in the subarachnoid space.

Complications

A worsening neurologic status following stabilization or improvement of symptoms often indicates one of the three major complications of SAH: rebleeding, hydrocephalus, or vasospasm. An understanding of the timing and nature of the deterioration facilitates rapid diagnosis and treatment. It must be emphasized that systemic perturbations, such as infection, disturbance in serum sodium levels, fever, hypoxemia, and hypotension, may produce similar symptoms and should be sought and corrected as part of the evaluation process.

Early Complications

Rebleeding. Rebleeding is heralded by a sudden worsening of headache, vomiting, development of a new neurologic deficit, or arrhythmia. It occurs in up to one third of patients and is often fatal. The risk of rebleeding is greatest during the first 24 hours and declines rapidly over the next 2 weeks.[139] Rates of rebleeding are highest in women, those with a poor clinical grade, those in poor medical condition, and those with elevated systolic blood pressure.

Hydrocephalus. Hydrocephalus occurs after SAH because of disturbances in cerebrospinal fluid flow or reabsorption; subarachnoid blood may impair cerebrospinal fluid reabsorption at the arachnoid granulations, and ventricular blood may obstruct its flow. Acute hydrocephalus can develop within hours of SAH,[140] often in the absence of intraventricular blood. Hydrocephalus may also develop gradually at any time, even weeks later. It usually manifests as an insidious decline in level of responsiveness and must be distinguished from metabolic derangements, infection, and vasospasm. CT scan is essential in making the diagnosis. The natural history of untreated acute hydrocephalus is that about one third of patients progress, one third spontaneously improve, and one third remain static.[141]

Cardiac Abnormalities. Cardiac abnormalities are common in the first 48 hours after SAH. Electrocardiographic changes (Fig. 52-5), including tall peaked T waves ("cerebral T waves"), ST segment depression, and prolonged QT segments,[142] are frequent and have been linked to elevated levels of circulating catecholamines. It appears that these changes do not represent true myocardial ischemia; the myocardial lesions reported are pathologically distinct from ischemia. Cardiac enzymes may be mildly elevated.[143] Arrhythmias are typically benign but can be severe or fatal. In rare cases, "stunned myocardium" may occur, with impairment of myocardial contractility leading to a fall in cardiac output, hypotension, and pulmonary edema.[144] This phenomenon is transient, usually lasting 2 to 3 days, after which cardiac function returns to baseline.[145]

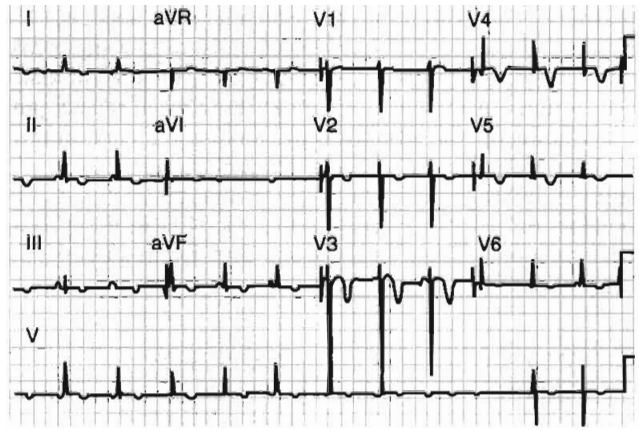


FIGURE 52-5. Electrocardiographic abnormalities following subarachnoid hemorrhage. (From Diringer MN: Subarachnoid hemorrhage. Continuum 2003;9:188.)

Delayed Complications

Vasospasm. Defined as segmental or diffuse narrowing of intracerebral arteries, vasospasm is a leading cause of morbidity and mortality following SAH. It can be detected angiographically (Fig. 52-6) in up to 70% of patients,[146] almost half of whom become symptomatic. The pathogenesis of vasospasm is complex and is not fully understood, but sustained exposure of vessels to extraluminal blood constituents and catecholamines is thought to play a role. It involves structural changes in the vessel walls and in adrenergic nerve fibers. The onset of vasospasm is delayed, most commonly developing in the latter half of the first week after the initial hemorrhage, and it may persist for up to 3 weeks. The strongest predictor of vasospasm is the amount and distribution of subarachnoid blood on the initial CT scan, with the greatest risk occurring in those having subarachnoid clots larger than 5 by 3 mm in the basal cisterns or layers of blood 1 mm thick or greater in the cerebral fissures (Fisher grade 3).[147] Focal neurologic deficits resulting from vasospasm reflect the territory of the involved arteries. They may appear abruptly or gradually and may fluctuate, exacerbated by hypovolemia or hypotension. Infarction may occur.

Serial transcranial Doppler studies have been used to screen for vasospasm. Criteria for vasospasm use an absolute linear blood flow velocity to define mild (>120 cm/sec), moderate (>160 cm/sec), or severe (>200 cm/sec) vasospasm.[148-150] Alternatively, the rate of rise in the linear blood flow velocity is used to define the onset of vasospasm. The sensitivity of transcranial Doppler in detecting vasospasm is about 80% when compared with angiography, at

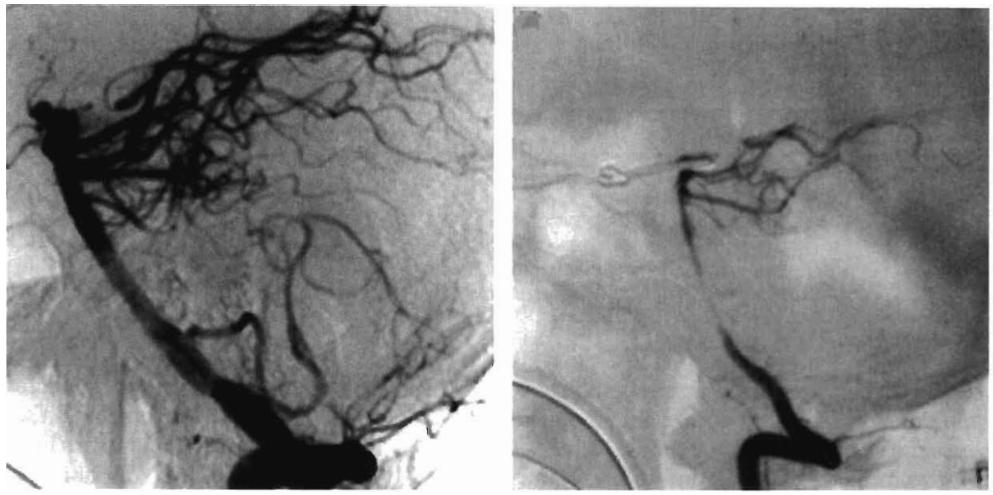


FIGURE 52–6. Baseline angiogram after subarachnoid hemorrhage (left) showing normal basilar artery caliber and distal flow, and repeat angiogram after 1 week (right) showing severe vasospasm of the basilar artery, with reduced distal flow. (From Diringer MN: Subarachnoid hemorrhage. Continuum 2003;9:191.)

least partly due to the fact that it samples only a small segment of the vasculature.[151]

Medical Complications

Blood pressure is often elevated after SAH and is associated with a greater risk of rebleeding and vasospasm, as well as higher mortality. Multiple factors may underlie the rise in blood pressure, including increased catecholamine production induced by hypothalamic dysfunction, agitation, and pain. Early on, the management of blood pressure focuses on preventing rerupture of the aneurysm. Following surgical or endovascular repair, the risk of rebleeding is virtually eliminated, and spontaneous elevations in blood pressure should be allowed to occur without intervention, because the risk of exacerbating vasospasm with hypotension is now the predominant concern.

Disturbances in sodium and water balance occur in approximately one third of patients, and hyponatremia and volume depletion after SAH are correlated with an increased risk of symptomatic vasospasm and poor outcome.[152,153] Although hyponatremia was once attributed to inappropriate secretion of antidiuretic hormone and was therefore treated with fluid restriction, later evidence suggested that both sodium and water are lost. In fact, when administered in normal "maintenance" volumes of fluid (2 to 3 L/day), as many as half of patients develop intravascular volume contraction.[154-158] The mechanisms underlying the volume contraction and the inability to conserve sodium ("cerebral salt wasting") are unknown.

Cardiac rhythm disturbances occur in about 30% to 40% of patients, although life-threatening cardiac arrhythmias occur in only about 5%.[159,160] Cardiac arrhythmias are most common on the day of hemorrhage and in the perioperative period. Although pulmonary edema has been reported in up to one quarter of patients,[161,162] its incidence is lower with careful monitoring of hemodynamic treatment for vasospasm.[163]

In a review of more than 450 patients with SAH, Solenski and colleagues reported some degree of hepatic dysfunction in 24%.[161] The majority had only mild abnormalities of hepatic enzymes, but severe hepatic dysfunction occurred in 4%. Thrombocytopenia was found in 4% of patients, usually in the setting of sepsis. Renal dysfunction occurred in 7% of patients and was considered life threatening in about 15% of those.

DIAGNOSTIC STUDIES

CT is the imaging modality of choice in screening for SAH, having a sensitivity of greater than 90%.[164] Blood appears as high attenuation within the perimesencephalic and interpeduncular cisterns surrounding the brainstem, basal cisterns, sylvian fissure, and sulci (Fig. 52-7). Certain bleeding patterns are associated with specific aneurysm locations; for example, blood in the anterior interhemispheric fissure commonly occurs with anterior communicating artery aneurysms. When blood is spread diffusely throughout the cerebrospinal fluid spaces, its site of origin may be difficult to detect.

The amount of subarachnoid blood on CT is graded using the Fisher scale (Table 52-1).[147] The risk of vasospasm is proportional to the Fisher grade. Early hydrocephalus is suggested by enlargement of the third ventricle and of the temporal horns of the lateral ventricles.

CT may fail to demonstrate SAH if the volume of blood is small, if the hemorrhage occurred several days before the CT scan, or if the hematocrit is extremely low.[164] If CT is negative and clinical suspicion is high, lumbar puncture is indicated for cerebrospinal fluid analysis. Following SAH,

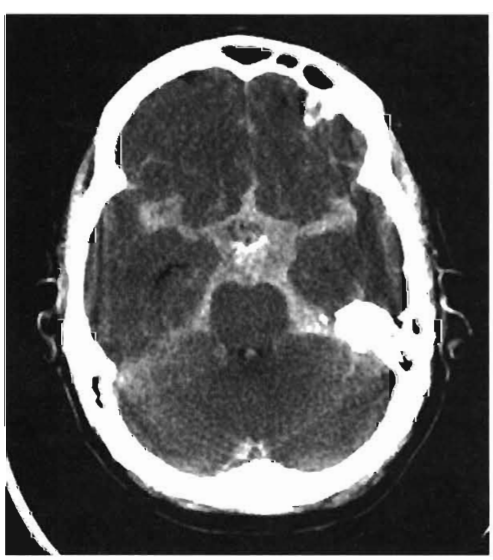


FIGURE 52–7. Subarachnoid hemorrhage with a thick layer of hyperdense blood filling the basal cisterns.

TABLE 52–1. FISHER GRADE OF SUBARACHNOID HEMORRHAGE ON INITIAL COMPUTED TOMOGRAPHY SCAN

Grade	Description
1	No blood detected
2	Diffuse or vertical layers <1 mm thick
3	Localized subarachnoid clot and/or vertical layers ≥1 mm thick
4	Intraparenchymal or intraventricular clot with diffuse or no subarachnoid hemorrhage

TABLE 52–2. HUNT AND HESS CLINICAL CLASSIFICATION OF SUBARACHNOID HEMORRHAGE

Grade	Description
I	Asymptomatic or mild headache and neck stiffness
II	Moderate to severe headache and neck stiffness ± cranial nerve palsy
III	Mild focal deficit, lethargy or confusion
IV	Stupor, moderate to severe hemiparesis
V	Deep coma, extensor posturing

cerebrospinal fluid contains red blood cells indicative of the hemorrhage, as well as a few white blood cells reflecting the secondary inflammatory response. A yellow pigment (xanthochromia), resulting from red cell breakdown, can be detected in the centrifuged fluid 2 to 6 hours after hemorrhage, allowing differentiation from a traumatic spinal puncture.[165] The common technique of comparing cell counts in the first and last tubes collected is not reliable in making this distinction. Xanthochromia persists for 1 to 4 weeks after SAH.

Once SAH has been diagnosed, cerebral angiography is performed to identify the responsible vascular lesion, search for other lesions (multiple aneurysms are found in 20% to 30% of patients with aneurysmal SAH), and assist in operative management. Angiography is negative in 10% to 15% of patients with nontraumatic SAH. In some cases, this may be due to vasospasm or inadequate views to detect a subtle aneurysm, especially in the region of the anterior communicating artery or in the posterior circulation. Repeat angiography in 1 to 2 weeks is therefore often recommended.[166] If the blood on CT is localized to the perimesencephalic cisterns and angiography is negative, the prognosis is excellent, and repeat angiography is almost always negative.[167]

MRI is not as sensitive as CT for the detection of SAH, and magnetic resonance angiography and CT angiography are not sufficiently sensitive to replace conventional angiography, because they tend to miss smaller aneurysms. Magnetic resonance angiography and CT angiography may be of assistance in planning surgical or endovascular approaches to aneurysm treatment, however.

TREATMENT

Initial Stabilization

The initial steps in the evaluation of a patient with suspected SAH should include assessment of ability to protect the airway and level of neurologic function. The Hunt and Hess scale[168] and the more recently developed World Federation of Neurological Surgeons scale[169] provide standardized measures of the patient's clinical condition (Tables 52-2 and 52-3).

As in ICH, some patients with SAH may not be able to protect the airway because of diminished consciousness. If the patient is lethargic or agitated, elective intubation should be considered before angiography. Sedation is often necessary for angiography, and in lethargic patients or those with mild early hydrocephalus, this can lead to airway obstruction.

Routine Care and Monitoring

The routine monitoring of all patients with acute SAH should include serial neurologic examinations, continuous electrocardiogram monitoring, and frequent determinations of blood pressure, electrolytes, body weight, and fluid balance.

Because seizures can increase the risk of rebleeding, anticonvulsants are indicated if seizures occur. The value of prophylactic anticonvulsants in patients who have not had a seizure is unknown. Dexamethasone is widely used to reduce meningeal irritation and intra- and postoperative edema, but there is no convincing evidence documenting its efficacy.

Fluid Management

A stable intravascular volume should be maintained by the use of hydration with isotonic saline and daily monitoring of fluid balance, body weight, and hematocrit. In some patients with severe cerebral salt wasting, large volumes of fluid are required to prevent intravascular volume contraction.[152] Hyponatremia can often be managed with the restriction of all *free* water by administering only isotonic intravenous fluids, minimizing oral liquids, and using concentrated enteral feedings. It is important to adjust the *tonicity*, not the *volume*, of fluids administered.[153] Fludrocortisone is of marginal benefit in treating salt wasting.[154,170] Persistent hyponatremia can be treated by using mildly hypertonic solutions (1.25% to 2% saline) as the sole intravenous fluid.

Hypertension

Initial attempts to treat hypertension should consist of analgesics and nimodipine; other antihypertensive agents should follow if needed. Useful medications include beta blockers (often in higher-than-usual doses to block the high level of sympathetic nervous system activity), hydralazine, nicardipine, and nitroprusside. When significant hydrocephalus is present, hypertension should not be treated until after the hydrocephalus is addressed. This is because the hypertension may be acting to maintain adequate cerebral perfusion in the face of elevated ICP.

Surgical and Endovascular Treatment

In aneurysmal SAH, the definitive way to prevent rebleeding is to obliterate the aneurysm by surgically clipping its neck. The optimal timing of surgery is controversial, but in patients

TABLE 52–3. WORLD FEDERATION OF NEUROLOGICAL SURGEONS CLINICAL CLASSIFICATION OF SUBARACHNOID HEMORRHAGE

Grade	Glasgow Coma Scale Score	Motor Deficits
I	15	Absent
II	13-14	Absent
III	13-14	Present
IV	7-12	Present or absent
V	3-6	Present or absent

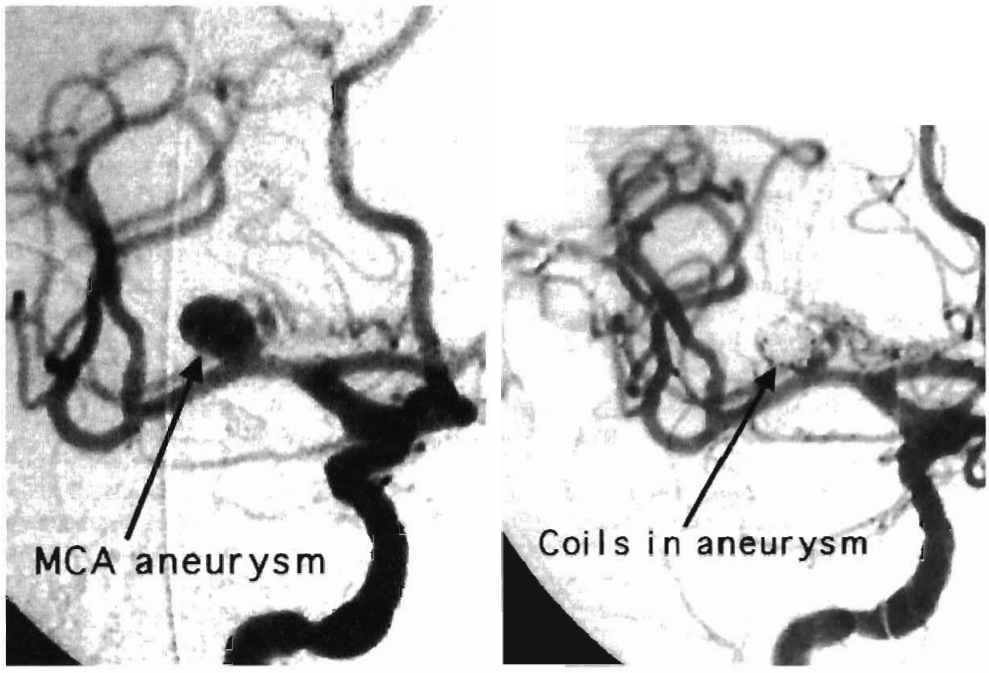


FIGURE 52-8. Angiography of middle cerebral artery (MCA) aneurysm before (*A*) and after (*B*) placement of detachable coils thrombosing the aneurysm. (From Diringer MN: Subarachnoid hemorrhage. Continuum 2003;9:190.)

with a good clinical grade (Hunt-Hess grades I to III), favorable neurologic outcome is more common when surgery is performed early (within 72 hours).[171] Clipping of aneurysms has the additional advantage of permitting a safe elevation of blood pressure to treat vasospasm.

Endovascular techniques, using either detachable balloons that trap the aneurysm or electrolytically detachable coils that thrombose the aneurysm,[172] have been used to repair acutely ruptured aneurysms (Fig. 52-8). Initial experience was limited to patients who were considered poor surgical candidates owing to aneurysm configuration or poor medical condition.[173] Subsequent reports in which surgical considerations did not heavily influence the selection of patients for endovascular procedures suggest a similar outcome for the two treatments. A recent, somewhat controversial study suggested that for acutely ruptured aneurysms that were deemed equally amenable to surgical or endovascular repair, morbidity and mortality were lower with coiling.[174]

Management of Secondary Complications

Rebleeding

Multiple clinical trials have demonstrated that antifibrinolytic agents such as ε-aminocaproic acid and tranexamic acid reduce the risk of rebleeding, but this benefit is offset by an increased incidence of vasospasm and hydrocephalus.[175,176] With the advent of early surgery and endovascular treatment, the use of these agents has declined dramatically. A shorter course of antifibrinolytic therapy while awaiting surgery or endovascular treatment (before the risk period for vasospasm begins) has been suggested, but it appears that the negative effects persist.[177]

Initial management directed at the prevention of rebleeding includes avoiding situations that produce sudden changes in the transmural pressure across the wall of the aneurysm (i.e., sudden increases in arterial or venous pressure or decreases in ICP). Patients are placed on bed rest with minimal stimulation. In an agitated patient, sedation is indicated, though care must be taken to preserve the ability to assess the patient's responsiveness to stimulation. Opiates are a good choice for sedation because they also provide analgesia for headache. Because of the risk of impairing the ability to evaluate for clinical deterioration, long-acting sedative agents such as phenobarbital should be avoided. Measures should be taken to minimize cough and Valsalva's maneuvers. In intubated patients, repositioning of the endotracheal tube, suctioning, and antitussive agents (codeine, lidocaine) may be needed. Stool softeners are administered to avoid straining. If lumbar puncture or ventriculostomy is performed, rapid drainage of a large volume of cerebrospinal fluid should be avoided so as not to induce sudden changes in the transmural pressure.

Definitive prevention of rebleeding is accomplished by obliteration of the aneurysm, as described earlier. This should be performed as soon as possible.

Hydrocephalus

The decision to treat hydrocephalus is usually based on the CT appearance of enlarging ventricles in a patient whose level of consciousness is deteriorating to the point of obtundation. Upon placement of a ventriculostomy, the cerebrospinal fluid pressure is reduced slowly to lessen the risk of aneurysm rerupture. Cerebrospinal fluid drainage via ventriculostomy may be needed for many days to clear intraventricular blood before it can be determined whether a permanent shunt is required.

Vasospasm

Prevention. Routine measures to prevent or ameliorate the effects of vasospasm include mechanical removal of subarachnoid blood at the time of aneurysm surgery, administration of the centrally acting calcium channel antagonist nimodipine, and avoidance of intravascular volume contraction (see earlier) and hypotension. Nimodipine treatment (60 mg orally every 4 hours) for 3 weeks after SAH reduces the impact of symptomatic vasospasm and improves outcome.[178-181] It is not clear whether this beneficial effect is due to action on the cerebral vessels or prevention of calcium influx into ischemic

neurons. Hypotension that develops with nimodipine administration can usually be managed with fluids or by adjusting the dosage schedule to 30 mg every 2 hours. In patients receiving hemodynamic augmentation for symptomatic vasospasm, it may be difficult to maintain blood pressure goals following nimodipine administration.

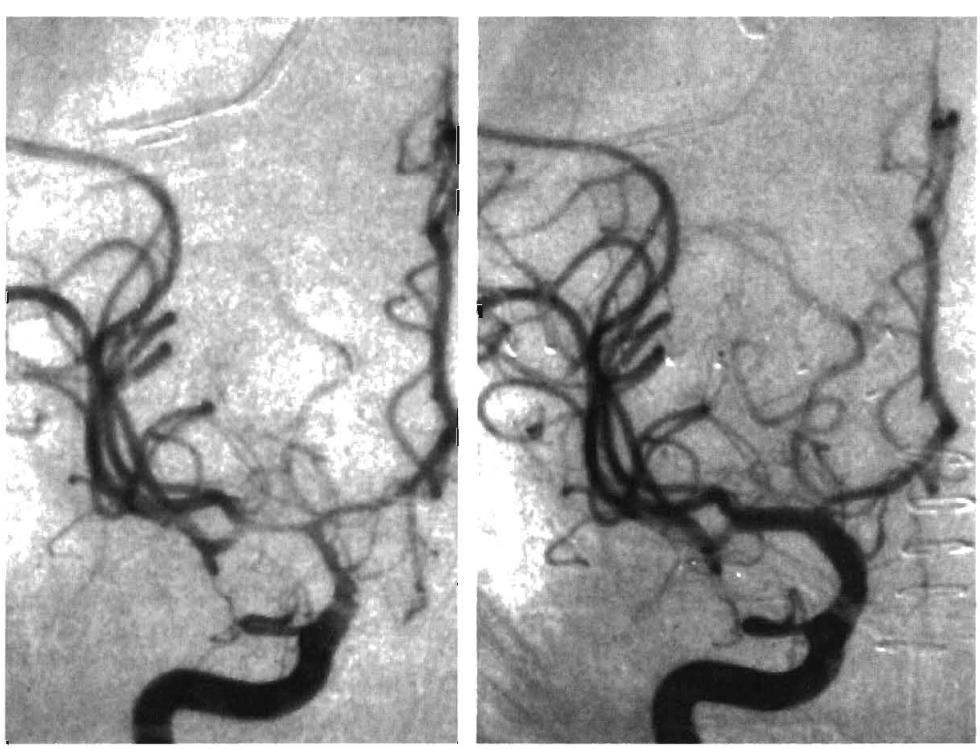
Treatment of Delayed Ischemic Deficits. Because of the disparity in the incidence of vasospasm detected angiographically, by transcranial Doppler, and clinically, there is disagreement about the management of vasospasm when it is detected. Although the aggressive management of clinical vasospasm with hemodynamic augmentation and endovascular maneuvers to open constricted vessels is widely accepted, there is dispute over how aggressive to be in an asymptomatic patient with vasospasm detected by transcranial Doppler or angiography.

Hemodynamic Augmentation. Treatment of symptomatic vasospasm in patients with surgically clipped aneurysms begins with hemodynamic augmentation, in which blood volume and cardiac output are optimized with fluids, and blood pressure is increased by the administration of vasoactive agents to enhance CBF and prevent cerebral infarction.[182,183] The initial step is to rapidly correct hypovolemia with isotonic crystalloid or colloid. No data exist to indicate that hypervolemia is more beneficial than euvolemia,[184-186] but the potential complications of hypovolemia are clear. Some degree of volume expansion may be helpful in improving cardiac output, but this effect may plateau at pulmonary capillary wedge pressures greater than 14 mm Hg.[187] If there is no immediate response to fluid administration, vasoactive agents are required—either inotropes (dobutamine, dopamine) to improve cardiac output or vasopressors (phenylephrine, norepinephrine) to raise MAP.

It is unclear whether augmenting volume, cardiac output, or MAP is the most efficacious intervention.[185] One approach is to measure pulmonary capillary wedge pressure, cardiac output, and systemic vascular resistance with a Swan-Ganz catheter to titrate hemodynamic management. Use of a Swan-Ganz catheter is also beneficial in patients with cardiac disease to help guide therapy and prevent the congestive heart failure and myocardial ischemia that may complicate hemodynamic augmentation.

Goals for intravascular volume and blood pressure should be defined as a percent change from baseline (beginning with about a 15% change), rather than prespecified levels. Although defining such goals is useful to guide therapy, the degree of hemodynamic augmentation should be titrated continuously to the patient's neurologic status; thus, if a goal is reached but there is no neurologic improvement, the goal should be reassessed. Hemodynamic augmentation is weaned gradually over several days, guided by neurologic status.

Endovascular Treatment. The second strategy involves endovascular treatment of constricted vessels with either balloon angioplasty or intra-arterial infusion of vasodilating agents such as papaverine or nicardipine. Angioplasty on the proximal segments of vasospastic cerebral vessels yields impressive angiographic changes (Fig. 52-9) that appear to be long lasting,[188-191] but clear clinical efficacy has been difficult to establish because the procedure is typically used in conjunction with hemodynamic augmentation. One study suggested that "prophylactic" angioplasty in high-risk patients might reduce the incidence of symptomatic vasospasm.[192] The direct infusion of papaverine and nicardipine into vasospastic vessels has also been used to treat vasospasm. Papaverine produces clear vasodilatation and improvement in global blood flow, but the response is often transient, with



A B

FIGURE 52–9. Severe distal internal carotid and proximal middle cerebral artery vasospasm before *(A)* and after *(B)* angioplasty.

vasospasm returning after 24 to 48 hours.[193-195] Multiple treatments are frequently necessary to yield a sustained angiographic effect.

The timing of when to initiate endovascular therapy is debated. It is generally used if, after a few hours, the response to hemodynamic augmentation is inadequate, but it may be the initial therapy in patients with poor cardiac function who are at high risk of complications of hemodynamic augmentation. Potential complications of endovascular treatments include arterial perforation, cerebral infarction, and rebleeding of unprotected aneurysms.

PROGNOSTIC FACTORS AND CAUSES OF MORTALITY

Aneurysmal SAH carries a poor prognosis, with death occurring in 20% to 40% of those who reach medical care. Causes of death are about equally distributed among direct effects of the initial hemorrhage, rebleeding, vasospasm, and medical complications.[161] Overall, less than one third of patients achieve good neurologic recovery. Predictors of poor prognosis include loss of consciousness or poor neurologic condition (i.e., high Hunt-Hess grade) on admission, older age, hypertension, preexisting medical illness, subarachnoid blood 1 mm thick or greater on CT scan (Fisher grade 3), seizures, cerebral edema, aneurysm in the basilar artery, and symptomatic vasospasm.[196-200]

ACKNOWLEDGMENTS

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This prospective, multicenter, randomized trial demonstrated that administration of the calcium channel blocker nimodipine within 96 hours of SAH was well tolerated and reduced the severity of ischemic neurologic deficits associated with vasospasm.

Brott T, Broderick J, Kothari R, et al: Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke 1997;28:1-5.

This prospective observational study demonstrated that hematoma growth occurs in more than one third of patients with ICH within the first few hours of symptom onset and is associated with clinical deterioration.

Hankey GJ, Hon C: Surgery for primary intracerebral hemorrhage: Is it safe and effective? A systematic review of case series and randomized trials. Stroke 1997;28:2126-2132.

This meta-analysis of randomized controlled trials of surgical hematoma evacuation in primary ICH found a nonsignificant increase in the odds of death or dependency in patients treated surgically relative to those managed medically.

Kassell NF, Sasaki T, Colohan AR, Nazar G: Cerebral vasospasm following aneurysmal subarachnoid hemorrhage. Stroke 1985;16:562-572.

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Molyneux A, Kerr R, Stratton I, et al: International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: A randomised trial. Lancet 2002;360:1267-1274.

This prospective, multicenter, randomized trial evaluated the efficacy of surgical aneurysm clipping versus endovascular treatment by detachable platinum coils in patients with acutely ruptured intracranial aneurysms deemed equally amenable to either treatment. In this carefully selected population, with follow-up limited to 1 year, treatment with coils resulted in better outcome.

Chapter 53
SEIZURES IN THE CRITICALLY ILL

Sarice L. Bassin • Thomas P. Bleck

KEY POINTS

1. Although conventional definitions of status epilepticus have used a cutoff of 30 or 60 minutes of sustained seizure duration, or discrete seizures without recovery, clinicians should recognize that most seizures will terminate spontaneously within a few minutes. Therefore, seizures that persist longer than 5 to 7 minutes should probably be treated as status epilepticus.
2. Patients begin to awaken within 15 to 20 minutes after the successful termination of status epilepticus; many regain consciousness much faster. Patients who do not start to awaken after 20 minutes should be assumed to have entered nonconvulsive status epilepticus. Nonconvulsive status epilepticus demands emergency treatment guided by electroencephalographic monitoring to prevent further cerebral damage, since there are no clinical criteria to indicate whether therapy is effective.
3. Observation is the most important activity to perform when a patient has a single seizure. This is the time to collect evidence of a partial onset to implicate structural brain disease. The postictal examination is similarly valuable; language, motor, sensory, or reflex abnormalities after an apparently generalized seizure are evidence of focal pathology.
4. In contrast to the patient with a single or a few seizures, the status epilepticus patient requires concomitant diagnostic and therapeutic efforts. Although 30 minutes of continuous or recurrent seizure activity usually define status epilepticus, one should not stand by waiting for this period to pass to start treatment. Since most seizures in critically ill patients stop within 2 to 3 minutes, it is reasonable to start treatment after 5 minutes of continuous seizure activity or after the second or third seizure occurs without recovery between the spells.
5. Electroencephalographic monitoring after control of convulsive status epilepticus can be essential in directing the course of treatment.
6. The intensive care unit patient with central nervous system disease who has even one seizure should usually be given chronic anticonvulsant therapy, and this approach should be reviewed before the patient is discharged. Initiating this treatment after the first *unprovoked* seizure may help prevent subsequent epilepsy. In the intensive care unit setting, phenytoin is frequently selected because of its ease of administration and lack of sedative effects.
7. The conventional agents used in the first-line of treatment of status epilepticus are the benzodiazepines (especially lorazepam, diazepam, and midazolam), phenytoin, and phenobarbital. Status epilepticus that is refractory to the traditional agents is treated with continuous infusions of the short-acting barbiturates, midazolam, or propofol.

Seizures complicate the course of about 3% of adult intensive care unit (ICU) patients admitted for non-neurologic conditions. The medical and economic impact of these seizures confers importance on them out of proportion to their incidence. A seizure is often the first indication of a central nervous system (CNS) complication, and delay in recognition and treatment of seizure is associated with an increased risk of mortality[2]; thus, the rapid diagnosis of this disorder is mandatory. In addition, since epilepsy affects 2% of the population, patients with preexisting seizures occasionally enter the ICU for treatment of other problems. Since the initial treatment of these patients is the province of the intensivist, he or she must be familiar with seizure management as it affects the critically ill patient. Patients developing status epilepticus often require a critical care specialist in addition to a neurologist.

Seizures have been recognized at least since Hippocratic times, but their relatively high rate of occurrence in critically ill patients has only recently been appreciated. Seizures complicating critical care treatments (e.g., lidocaine use) are also a recent phenomenon. Early attempts at treatment included bromides[3] and morphine[4] as well as ice applications. Barbiturates were first employed in 1912, and phenytoin in 1937.[5] Paraldehyde was popular in the next two decades.[6] More recently, emphasis has shifted to the benzodiazepines, which were pioneered in the 1960s.[7] Newer agents for treatment of seizures in critically ill patients include the phenytoin prodrug fosphenytoin, the anesthetic agent propofol, and the water-soluble benzodiazepine midazolam.

Status epilepticus refers to prolonged seizure episodes. Status epilepticus may be the primary indication for admission to the ICU or it may occur in any ICU patient with CNS disease. The definitions employed in studies of status epilepticus have varied substantially. Although conventional definitions of status epilepticus have used a cutoff of 30 or

60 minutes of sustained seizure duration, or discrete seizures without recovery, clinicians should recognize that most seizures terminate spontaneously within a few minutes. Recent data suggest that in only half of patients with seizure episodes lasting 10 to 29 minutes will the seizure self-terminate.[8] Therefore, seizures that persist longer than 5 to 7 minutes should probably be treated as status epilepticus.[9]

EPIDEMIOLOGY

Limited data are available on the epidemiology of seizures in the ICU. A 10-year retrospective study of all ICU patients with seizures at the Mayo Clinic revealed that 7 patients had seizures per 1000 ICU admissions.[10] Our 2-year prospective study of medical ICU patients identified 35 with seizures per 1000 admissions.[11] These two studies are not exactly comparable, as the patient populations and methods of detection differed. A recent series found 8% of comatose patients without clinical signs of seizure activity to be in electrographic status epilepticus.[12]

Up to 34% of hospital in-patients experiencing a seizure die during their hospitalization.[10] Our prospective study of neurologic complications in medical ICU patients showed that having even one seizure while in the ICU for a non-neurologic reason doubled in-hospital mortality.[12] Incidence estimates for generalized convulsive status epilepticus in the United States vary from 50,000 cases per year[13] to 195,000 cases per year.[14] Some portion of this difference can be accounted for by different definitions; however, the latter estimate represents the only population-based data available and may be more accurate. Mortality estimates similarly vary from 1% to 2% in the former study to 22% in the latter. This disagreement follows from a conceptual discordance: the smaller number describes mortality that the authors directly attribute to status epilepticus, whereas the larger figure estimates the overall mortality rate, even though death was frequently caused by the underlying disease rather than by status epilepticus itself. The elderly have an incidence of status epilepticus almost twice that of the general population and the highest associated mortality rate of any age group at 38%.[15]

Table 53-1 summarizes the most common causes of status epilepticus in adults in the community. Almost 50% of the cases were attributed to cerebral vascular disease.[13] Garzon and colleagues[16] found anti-epileptic drug noncompliance as the main cause of status epilepticus in patients with a prior history of epilepsy, and CNS infection, stroke, and metabolic disturbances predominated in the group without previous seizures.

Three major factors determine outcome in patients with status epilepticus: the type of status epilepticus, its cause, and its duration. Generalized convulsive status epilepticus has the worst prognosis for neurologic recovery; myoclonic status epilepticus following an anoxic episode carries a very poor prognosis for survival. Complex partial status epilepticus can produce limbic system damage, usually manifested as a memory disturbance. Causes associated with increased mortality included anoxia, intracranial hemorrhages, tumors, infections, and trauma. The mortality of patients with nonconvulsive status epilepticus has been reported as high as 33%[17] and correlates with the underlying cause, severe impairment of mental status, and the development of acute complications, especially respiratory failure and infection.[18] Data strongly suggest that prolonged seizure duration is a negative prognostic factor. A study of 253 adult status epilepticus patients demonstrated a 30-day mortality rate of 2.7% in patients with seizures lasting 30 to 59 minutes, compared with 32% in those with seizures of 60 minutes or longer.[19]

Limited data are available concerning the functional abilities of generalized convulsive status epilepticus survivors, and no data reliably permit a distinction between the effects of status epilepticus and effects of its causes. One review concluded that intellectual ability declined as a consequence of status epilepticus.[20] Survivors of status epilepticus frequently seem to have memory and behavioral disorders out of proportion to the structural damage produced by the cause of their seizures. Case reports of severe memory deficits following prolonged complex partial status epilepticus have been published.[21] Conversely, one prospective study of 180 children with febrile status epilepticus demonstrated no deaths and no cases of new cognitive or motor handicap.[22] Experimental animal[23] and human epidemiologic[24] studies suggest that status epilepticus may be a risk factor in the development of future seizures. Whether treatment of prolonged seizures reduces the risk of subsequent epilepsy remains uncertain.

TABLE 53–1. CAUSES OF STATUS EPILEPTICUS IN ADULTS PRESENTING FROM THE COMMUNITY

Prior Seizures	No Prior Seizures
Common	
Subtherapeutic anticonvulsant	Ethanol-related
Ethanol-related	Drug toxicity
Intractable epilepsy	CNS infection
	Head trauma
	CNS tumor
Less Common	
CNS infection	Metabolic aberration
Metabolic aberration	Stroke
Drug toxicity	
Stroke	
CNS tumor	
Head trauma	

CNS, central nervous system.

CLASSIFICATION

The most frequently used classification scheme is that of the International League Against Epilepsy (Table 53-2).[25] This scheme allows classification on clinical criteria without inferring cause. *Simple partial seizures* start focally in the cerebral cortex, without invading other structures. The patient is aware throughout the episode and appears otherwise unchanged. Bilateral limbic dysfunction produces a *complex partial seizure*; awareness and ability to interact are diminished (but may not be completely abolished). *Automatisms* (movements that a patient makes without awareness) may occur. *Secondary generalization* results from invasion by epileptic electrical activity of the other hemisphere or subcortical structures.

Primary generalized seizures arise from the cerebral cortex and diencephalon at the same time; no focal phenomena are visible, and consciousness is lost at the onset. *Absence seizures* are frequently confined to childhood; they consist of the abrupt onset of a blank stare that usually lasts 5 to 15 seconds, after which the patient abruptly returns to normal. *Atypical absence seizures* occur in children with the Lennox-Gastaut

TABLE 53–2. INTERNATIONAL CLASSIFICATION OF EPILEPTIC SEIZURES

I. Partial seizures (seizures beginning locally)
  A. Simple partial seizures (consciousness not impaired; simple partial seizures)
    1. with motor symptoms
    2. with somatosensory or special sensory symptoms
    3. with autonomic symptoms
    4. with psychic symptoms
  B. Complex partial seizures (with impairment of consciousness; complex partial seizures)
    1. beginning as simple partial seizures and progressing to impairment of consciousness
      a. without automatisms
      b. with automatisms
    2. with impairment of consciousness at onset
      a. with no other features
      b. with features of simple partial seizures
      c. with automatisms
  C. Partial seizures (simple or complex), secondarily generalized
II. Primary generalized seizures (bilaterally symmetric, without localized onset)
  A. Absence seizures
    1. true absence ("petit mal")
    2. atypical absence
  B. Myoclonic seizures
  C. Clonic seizures
  D. Tonic seizures
  E. Tonic-clonic seizures ("grand mal")
  F. Atonic seizures
III. Unclassified seizures

Adapted from Bleck TP: Status epilepticus. In Klawans HL, Goetz CG, Tanner CM (eds): Textbook of Clinical Neuropharmacology, 2nd ed. New York, Raven Press, 1992, pp 65-73.

TABLE 53–3. CLINICAL CLASSIFICATION OF STATUS EPILEPTICUS

I. Generalized seizures
  A. Generalized convulsive status epilepticus
    1. Primary generalized status epilepticus
      a. tonic-clonic status epilepticus
      b. myoclonic status epilepticus
      c. clonic-tonic-clonic status epilepticus
    2. Secondarily generalized status epilepticus
      a. partial seizure with secondary generalization
      b. tonic status epilepticus
  B. Nonconvulsive status epilepticus
    1. absence status epilepticus (petit mal status)
    2. atypical absence status epilepticus (e.g., in the Lennox-Gastaut syndrome)
    3. atonic status epilepticus
    4. nonconvulsive status epilepticus as a sequel of partially treated generalized convulsive status epilepticus
II. Partial status epilepticus
  A. Simple partial status epilepticus
    1. typical
    2. epilepsia partialis continua
  B. Complex partial status epilepticus
III. Neonatal status epilepticus

Adapted from Lothman EW: The biochemical basis and pathophysiology of status epilepticus. Neurology 1990;40(Suppl 2):13-23.

syndrome. *Myoclonic seizures* start with brief synchronous jerks, without alteration of consciousness initially followed by a generalized convulsion. They frequently occur in patients with genetic epilepsy; in the ICU, they commonly follow anoxia or metabolic disturbances.[26] *Tonic-clonic seizures* start with tonic extension, evolve to bilaterally synchronous clonus, and conclude with a postictal phase. Clinical judgment is required to apply this system in the ICU. In patients in whom consciousness has already been altered by drugs, hypotension, sepsis, or intracranial pathologic lesion, the nature of partial seizures may be difficult to classify.

Status epilepticus is classified by a similar system that has been altered to match observable clinical phenomena (Table 53-3).[27] Generalized convulsive status epilepticus is the most common type encountered in the ICU and poses the greatest risk to the patient. It may either be primarily generalized, as in the drug-intoxicated patient, or secondarily generalized, as in the brain abscess patient who develops generalized convulsive status epilepticus. *Nonconvulsive status epilepticus* in the ICU frequently follows partially treated generalized convulsive status epilepticus. Some practitioners use the term for all cases of status epilepticus that involve altered consciousness without convulsive movements; this blurs the distinctions among absence status epilepticus, partially treated generalized convulsive status epilepticus, and complex partial status epilepticus, which have different causes and treatments. *Epilepsia partialis continua* (a special form of partial status epilepticus in which repetitive movements affect a small area of the body) sometimes continues for months or years.

The International League Against Epilepsy continues to work toward revising and updating the current classification system. The goal is a multi-axis diagnostic scheme that incorporates anatomic, etiologic, therapeutic, and prognostic implications. For the most recent information regarding this ongoing project, refer to *www.epilepsy.org*.[28]

PATHOGENESIS AND PATHOPHYSIOLOGY

The causes and effects of status epilepticus at the cellular, brain, and systemic levels are interrelated, but their individual analysis is useful for understanding them and their therapeutic implications. The ionic events of a seizure follow the opening of ion channels coupled to excitatory amino acid receptors. From the standpoint of the intensivist, three channels are particularly important because their activation may raise intracellular free calcium to toxic concentrations: alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), *N*-methyl-D-aspartate (NMDA), and metabotropic channels. These excitatory amino acid systems are crucial for learning and memory. Many drugs that block these systems are available but are too toxic for chronic use. Counter-regulatory ionic events are triggered by the epileptiform discharge as well, such as the activation of inhibitory interneurons, which suppress excited neurons via $GABA_A$ synapses.

The cellular effects of excessive excitatory amino acid channel activity include (1) the generation of toxic concentrations of intracellular free calcium; (2) activation of autolytic enzyme systems; (3) production of oxygen free radicals; (4) generation of nitric oxide, which both enhances subsequent excitation and serves as a toxin; (5) phosphorylation of enzyme and receptor systems, making seizures more likely; and (6) an increase in intracellular osmolality, which produces neuronal swelling. If adenosine triphosphate production fails, then membrane ion-exchange ceases and neurons swell further. These events produce the neuronal damage associated with status epilepticus. Longer status epilepticus duration produces more profound alterations and an increasing likelihood of permanence and of becoming refractory to treatment.[29] The processes involved in a single

seizure and the transition to status epilepticus have been reviewed.[30]

Many other biophysical and biochemical alterations occur during and after status epilepticus. The intense neuronal activity activates immediate-early genes and produces heat shock proteins, providing indications of the deleterious effects of status epilepticus and insight into the mechanisms of neuronal protection.[31] The mechanisms by which status epilepticus damages the nervous system have been reviewed.[32] Absence status epilepticus is an exception among these conditions; it consists of rhythmically increased inhibition and does not produce clinical or pathologic abnormalities.

The electrical phenomena of status epilepticus at the whole brain level, as seen in the scalp electroencephalogram (EEG), reflect the seizure type that initiates status epilepticus (e.g., absence status epilepticus begins with a 3-Hz wave-and-spike pattern). During status epilepticus, this rhythm slows, but the wave-and-spike characteristic remains. Generalized convulsive status epilepticus goes through a sequence of electrographic changes (Table 53-4).[33] The initial discharge becomes less well formed, implying that neuronal firing loses synchrony. The sustained depolarizations that characterize status epilepticus alter the extracellular milieu, most importantly by raising extracellular potassium. The excess potassium ejected during status epilepticus exceeds the buffering ability of astrocytes.

The increased cellular activity of status epilepticus elevates demand for oxygen and glucose, and cerebral blood flow initially increases. After approximately 20 minutes, however, energy supplies are exhausted, causing local catabolism to support ion pumps (in an attempt to restore the internal milieu); this is a major cause of epileptic brain damage. In addition to damaging the CNS, generalized convulsive status epilepticus produces life-threatening systemic effects.[34] Excess secretion of epinephrine and cortisol cause systemic and pulmonary arterial pressures to rise dramatically at seizure onset and also produce hyperglycemia. Muscular work raises blood lactate levels. Both airway obstruction and abnormal diaphragmatic contractions impair respiration. Carbon dioxide excretion falls while its production increases markedly. Muscular work accelerates heat production, raising core body temperature.

The combined respiratory and metabolic acidoses frequently reduce the arterial blood pH to 6.9 or lower. The acidemia may produce hyperkalemia; in addition to its deleterious effects on cardiac electrophysiology, the elevated extracellular potassium level helps propagate seizure activity. Coupled with hypoxemia and the elevation of circulating catecholamine concentrations, these conditions rarely can produce cardiac arrest. This sequence probably accounts for some cases of epileptic sudden death; neurogenic pulmonary edema is the likely cause of many others. The severity of the acidosis may prompt consideration of bicarbonate administration. When this is attempted, however, the likelihood of the occurrence of pulmonary edema is inordinately high. Rapid termination of seizure activity is the most appropriate treatment; the restitution of ventilation and the metabolism of lactate quickly restore a normal pH.

After approximately 30 minutes of continuous convulsions, motor activity may diminish while electrographic seizures persist. Hypotension and hyperthermia ensue, and gluconeogenesis can fail, resulting in hypoglycemia. Generalized convulsive status epilepticus patients often aspirate oral or gastric contents, producing chemical pneumonitis or bacterial pneumonia. Rhabdomyolysis is common and may lead to renal failure. Compression fractures, joint dislocations, and tendon avulsions are other serious sequelae.

The mechanisms that terminate seizure activity are poorly understood. The leading candidates are inhibitory mechanisms, primarily GABA-ergic interneurons and inhibitory thalamic neurons.

CLINICAL MANIFESTATIONS

Three problems complicate seizure recognition: (1) the occurrence of complex partial seizures in the setting of impaired awareness, (2) the occurrence of seizures in patients receiving pharmacologically induced paralysis and/or sedation, and (3) misinterpretation of other abnormal movements as seizures. ICU patients often have depressed consciousness in the absence of seizures owing to their disease, its complications (such as hepatic[35] or septic[36] encephalopathy), or drug administration. A further decline in alertness may reflect a seizure; an EEG is required to confirm that one has occurred.

Patients receiving neuromuscular junction blocking agents do not manifest the usual signs of seizures. Patients with increased intracranial pressure (ICP) from primary brain injury, hepatic encephalopathy, or other critical illnesses may be both paralyzed and sedated, making identification of seizures particularly challenging. Tachycardia, tachypnea, and hypertension are signs of seizure that can be misinterpreted as evidence of inadequate sedation. Continuous EEG monitoring is warranted in this population if seizures are suspected.

Patients with metabolic disturbances, anoxia, and other types of nervous system injury may demonstrate abnormal movements that can be confused with seizure. Asterixis is a brief asynchronous loss of tone at the wrist or hip joints that

TABLE 53–4. ELECTROGRAPHIC-CLINICAL CORRELATIONS IN GENERALIZED CONVULSIVE STATUS EPILEPTICUS

Stage	Typical Clinical Manifestations*	Electroencephalographic Features
1	Tonic-clonic convulsions; hypertension and hyperglycemia common	Discrete seizures with interictal slowing
2	Low or medium amplitude clonic activity, with rare convulsions	Waxing and waning of ictal discharges
3	Slight but frequent clonic activity, often confined to the eyes, face, or hands	Continuous ictal discharges
4	Rare episodes of slight clonic activity; hypotension and hypoglycemia become manifest	Continuous ictal discharges punctuated by flat periods
5	Coma without other manifestations of seizure activity	Periodic epileptiform discharges on a flat background

*The clinical manifestations may vary considerably, depending on the underlying neuropathophysiologic process (and its anatomy), systemic diseases, and medications. In particular, stages of the electrographic progression may be sufficiently brief to be overlooked. Partially treating status epilepticus may dissociate the clinical and electrographic features.

Data from Treiman DM: Generalized convulsive status epilepticus in the adult. Epilepsia 1993;34(Suppl 1):S2-S11.

can appear in the setting of hepatic dysfunction. Stimulus-sensitive massive myoclonus after anoxia can be dramatic but usually self-abates in a few days. Controversy exists as to the epileptic origin of this disorder, and post-anoxic myoclonus has been reported in the presence of almost total cortical suppression.[37] Brain-injured patients may manifest paroxysmal episodes of sympathetic hyperactivity and associated rigidity or decerebrate posturing. These "hypothalamic seizures" can sometimes be distinguished from epileptic seizures with observation. Patients with tetanus are awake during their spasms and flex rather than extend their arms as seizure patients do. Psychiatric disturbances in the ICU occasionally resemble complex partial seizures. If doubt about the nature of abnormal movements persists, an EEG should be obtained.

The manifestations of status epilepticus depend on the type and, for partial status epilepticus, the cortical area of abnormality. Table 53-3 presents the types of status epilepticus encountered and focuses on those seen most frequently in the ICU.

Primary generalized convulsive status epilepticus begins as tonic extension of the trunk and extremities without preceding focal activity. No aura is reported and consciousness is immediately lost. After several seconds of tonic extension, the extremities start to vibrate; clonic (rhythmic) extension of the extremities quickly follows. This phase wanes in intensity over a few minutes. The patient may then repeat the cycle of tonus followed by clonic movements, or continue to have intermittent bursts of clonic activity without recovery. *Myoclonic status epilepticus* (bursts of myoclonic jerks that increase in intensity and lead to a generalized convulsion) is a less common form of generalized convulsive status epilepticus that is usually associated with anoxic coma.

Secondarily generalized status epilepticus begins with a partial seizure and progresses to a convulsive activity. The initial focal clinical activity may be overlooked. This seizure type implies a structural lesion, so care must be taken to elicit evidence of lateralized movements.

Of the several forms of generalized nonconvulsive status epilepticus, the one of greatest importance to intensivists is nonconvulsive status epilepticus as a sequela of inadequately treated generalized convulsive status epilepticus. When a patient with generalized convulsive status epilepticus is treated with anticonvulsants in inadequate doses, visible convulsive activity may stop, but the electrochemical seizure continues. Patients begin to awaken within 15 to 20 minutes after the successful termination of status epilepticus; many regain consciousness much faster. Patients who do not start to awaken after 20 minutes should be assumed to have entered nonconvulsive status epilepticus. Careful observation may disclose slight clonic activity. Nonconvulsive status epilepticus is an extremely dangerous problem because the destructive effects of status epilepticus continue even without obvious motor activity. Nonconvulsive status epilepticus demands emergency treatment guided by EEG monitoring to prevent further cerebral damage since there are no clinical criteria to indicate whether therapy is effective.

Failure to recognize nonconvulsive status epilepticus is common in patients presenting with nonspecific neurobehavioral abnormalities, such as delirium, lethargy, bizarre behavior, cataplexy, or mutism.[38] Patients may present in nonconvulsive status epilepticus without an inciting episode of generalized convulsive status epilepticus. A high suspicion for this disorder should be maintained in patients with unexplained alteration in level of consciousness or cognition admitted to the ICU.

Partial status epilepticus in ICU patients often follows a stroke or occurs with the rapid expansion of brain masses. Clonic motor activity is most easily recognized, but the seizure takes on the characteristics of adjacent functional tissue. Therefore, somatosensory or special sensory manifestations occur, and the ICU patient may be unable to report such symptoms. *Aphasic status epilepticus* occurs when a seizure begins in a language area and may resemble a stroke. *Epilepsia partialis continua* involves repetitive movements confined to a small region of the body. It may be seen with nonketotic hyperglycemia[39] or with focal brain disease; anticonvulsant treatment is seldom useful. *Complex partial status epilepticus* manifests with diminished awareness. The diagnosis often comes as a surprise when an EEG is obtained.

DIAGNOSTIC APPROACH

When an ICU patient has a seizure, one has a natural tendency to try to stop the event. This leads to both diagnostic obscuration and iatrogenic complications. Beyond protecting the patient from harm, very little can be done rapidly to influence the course of the seizure. Padded tongue blades, or similar items, should not be placed in the mouth; they are more likely to obstruct the airway than to preserve it. The seizures of most patients stop before any medication can reach the brain in an effective concentration.

Observation is the most important activity to perform when a patient has a single seizure. This is the time to collect evidence of a partial onset to implicate structural brain disease. The postictal examination is similarly valuable; language, motor, sensory, or reflex abnormalities after an apparently generalized seizure are evidence of focal pathology.

Seizures in ICU patients have several potential causes that must be investigated. Drugs are a major cause of ICU seizures, especially in the setting of diminished renal or hepatic function or when the blood-brain barrier is breached. Theophylline frequently produces seizures or status epilepticus if it has been rapidly loaded or if high concentrations of the drug occur; occasionally, however, these complications arise at "therapeutic" levels. Imipenem-cilastatin[40] and fluoroquinolones[41] have substantial potential to lower the seizure threshold, especially in patients with renal dysfunction. They should be avoided if possible in patients already at risk for seizure. Other antibiotics, especially beta-lactams, are occasionally implicated.[42] Sevoflurane, a volatile anesthetic agent, is dose-dependently epileptogenic in patients with no predisposition to seizures.[43]

Recreational drugs are frequently overlooked offenders in patients presenting to the ICU. Acute cocaine or methamphetamine intoxication is characterized by a state of hypersympathetic activity followed by seizures.[44] Although ethanol withdrawal is a common cause of seizures, discontinuing any hypnosedative agent may prompt convulsions 1 to 3 days later. One report suggests that narcotic withdrawal may produce seizures in the critically ill.[10] In the absence of other clear causes for seizure, complete toxicologic screening should be performed.

Serum glucose, electrolyte concentrations, and serum osmolality should also be measured. Nonketotic hyperglycemia[45,46] and hyponatremia can precipitate both focal and generalized seizures. Seizure activity may infrequently

be the first presenting sign of diabetes mellitus. However, hypocalcemia rarely causes seizures beyond the neonatal period; its identification on analysis must *not* signal the end of the diagnostic work-up. Hypomagnesemia has an equally unwarranted reputation as the cause of seizures in malnourished alcoholic patients.

The physical examination should emphasize assessment for both global and focal abnormalities of the CNS. Evidence of cardiovascular disease or systemic infection should be sought and the skin and fundi examined closely.

The need for imaging studies in these patients has been an area of uncertainty. A prospective study of neurologic complications in medical ICU patients determined that 38 of 61 patients (62%) had a vascular, infectious, or neoplastic explanation for their seizures.[11] Hence, head computed tomography or magnetic resonance imaging should be performed on ICU patients with new seizures. With current technology, there are almost no patients who cannot undergo computed tomography scanning. Magnetic resonance imaging is particularly helpful in detecting evidence of acute ischemic stroke and encephalitis. Magnetic resonance imaging cannot be performed on patients with pacemakers. Many ICP monitor catheters are compatible with magnetic resonance imaging, provided the device is not coiled when it is secured to the scalp. Patients who need cerebrospinal fluid analysis always require imaging of the brain first. When CNS infection is suspected, empirical antibiotic treatment should be started while these studies are being performed.

Electroencephalography is a vital diagnostic tool for evaluating the seizure patient. Partial seizures usually show EEG

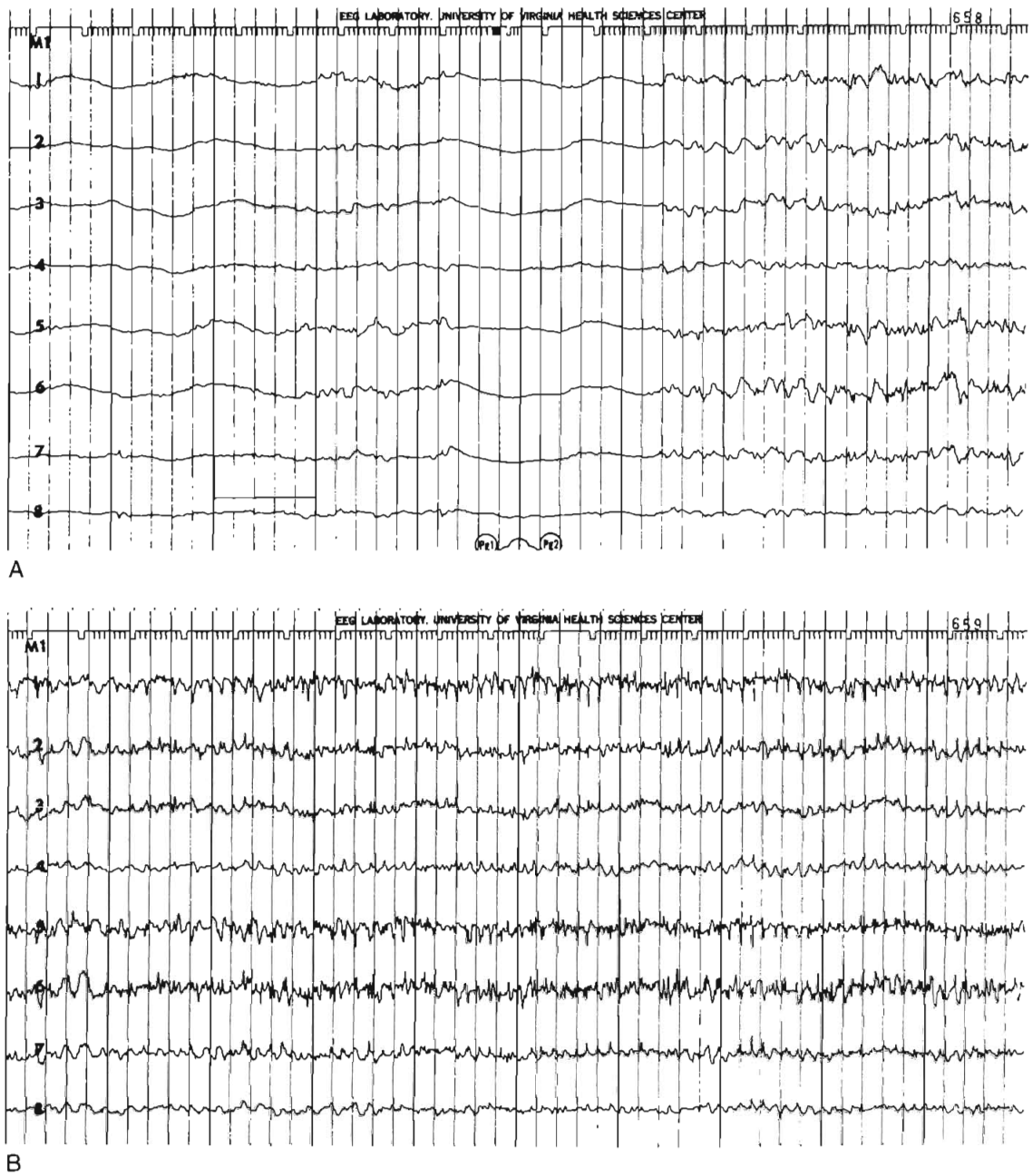
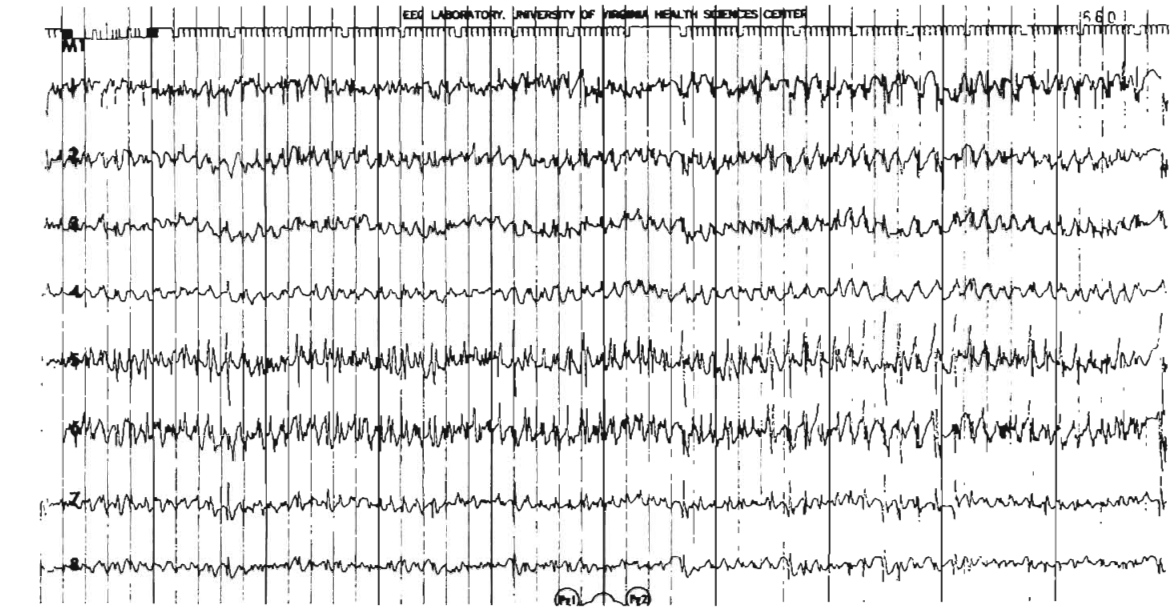


FIGURE 53–1. Electroencephalographic recording during status epilepticus. The first panel illustrates the onset of the seizure; the subsequent panels show its evolution. Montage: longitudinal bipolar; channels 1-4, left temporal, and channels 5-8, left parasagittal. Calibration: vertical, 50 μv; horizontal, 1 sec.



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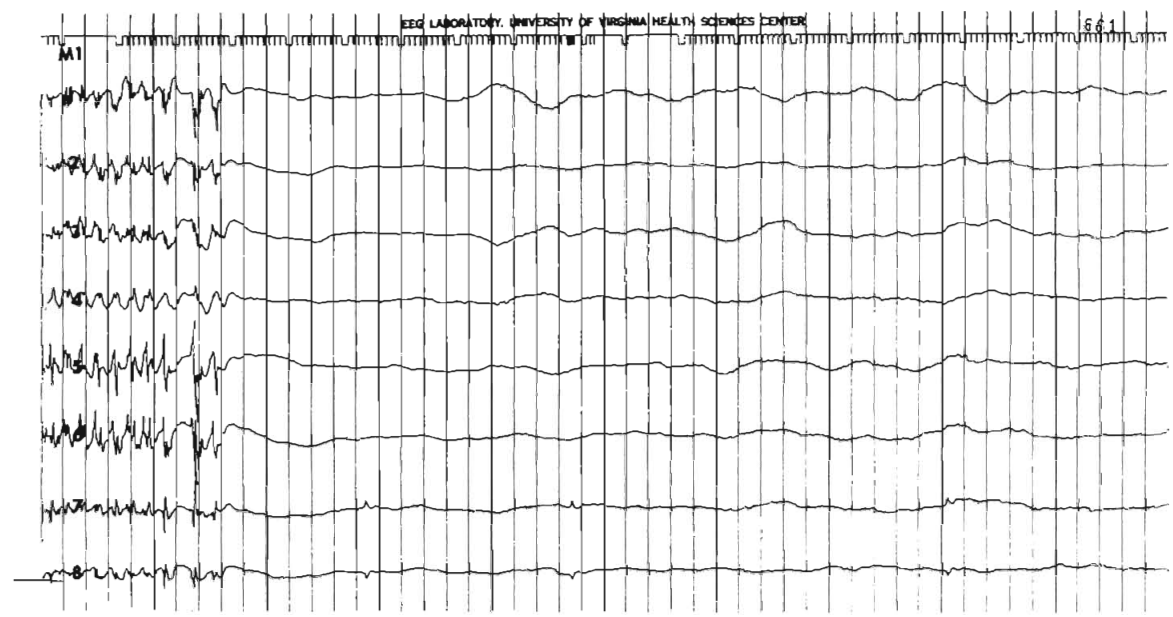

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FIGURE 53-1.—cont'd

abnormalities that begin in the area of cortex that produces seizures. Primary generalized seizures appear to start over the entire cortex simultaneously. Postictal slowing or depressed amplitude provides clues as to the focal cause of the seizures, and epileptiform activity helps to classify the type of seizure and to guide treatment. An emergency EEG is necessary to exclude nonconvulsive status epilepticus in those patients who do not begin to awaken soon after seizures have apparently been controlled (Fig. 53-1).

In contrast to the patient with a single or a few seizures, the status epilepticus patient requires concomitant diagnostic and therapeutic efforts. Although 30 minutes of continuous or recurrent seizure activity usually define status epilepticus, one should not stand by waiting for this period to pass to start treatment. Since most seizures in critically ill patients stop within 2 to 3 minutes, it is reasonable to start treatment after 5 minutes of continuous seizure activity or after the second or third seizure occurs without recovery between the spells.

Treatment for status epilepticus should not be delayed to obtain an EEG. However, a prospective evaluation of 164 patients demonstrated that nearly half manifested persistent electrographic seizures in the 24 hours after clinical control of convulsive status epilepticus.[47] These data suggest that EEG monitoring after control of convulsive status epilepticus can be essential in directing the course of treatment. A variety of findings may be present on the EEG, depending on the type of status epilepticus and its duration (see Table 53-4). Complex partial status epilepticus patients are often without such organized discharges of generalized convulsive status epilepticus; instead, they have waxing and waning rhythmic activity in one or several brain regions. A diagnostic trial of

intravenous benzodiazepine therapy is often necessary to diagnose complex partial status epilepticus. Patients developing refractory status epilepticus or having seizures during neuromuscular junction blockade require continuous EEG monitoring.

The availability of continuous paperless EEG monitoring allows for detection of seizure activity over a long period. Subclinical seizures have been observed to occur in patients receiving aggressive treatment for status epilepticus and even in patients treated with barbiturates to a burst-suppression EEG pattern. The clinical significance of these subclinical seizures, and their effect on prognosis, remains uncertain.

MANAGEMENT APPROACH

TREATING ISOLATED SEIZURES

Making the decision to administer anticonvulsants to an ICU patient who experiences one or a few seizures requires consideration of a provisional cause, estimation of the likelihood of recurrence, and recognition of the utility and limitations of anticonvulsants. For example, the occurrence of seizures during ethanol withdrawal does not indicate the need for chronic treatment, and giving phenytoin does not prevent further withdrawal convulsions. The patient may need prophylaxis against delirium tremens, but the few seizures themselves seldom require treatment. Patients with convulsions during barbiturate or benzodiazepine withdrawal, in contrast, should usually receive short-term treatment with lorazepam to prevent status epilepticus. Prolonged or frequent seizures caused by metabolic disturbances can be treated temporarily with benzodiazepines while the abnormality is being corrected. Seizures in these settings are notoriously resistant to treatment with phenytoin. In particular, treatment of patients with partial seizures related to nonketotic hyperglycemia should be directed at correction of the hyperglycemia and hypovolemia rather than anticonvulsant therapy.[46]

The ICU patient with CNS disease who has even one seizure should be given chronic anticonvulsant therapy, and this approach should be reviewed before the patient is discharged. Initiating this treatment after the first *unprovoked* seizure may help prevent subsequent epilepsy,[48] although there is considerable difference of opinion regarding this concept.[49] Starting therapy after the first seizure in a critically ill patient at risk for seizure recurrence may be even more important, especially if the patient's condition would be seriously complicated by a convulsion.

In the ICU setting, phenytoin is frequently selected owing to its ease of administration and lack of sedative effects. Hypotension and arrhythmias may complicate intravenous administration and can usually be prevented by slowing the infusion to less than 25 mg/min. Because of the rare occurrence of third-degree atrioventricular block, an external cardiac pacemaker should be available when patients with conduction abnormalities receive intravenous phenytoin. Propylene glycol in the parenteral formulation of phenytoin is the probable cause of these effects. Additionally, the parenteral formulation of phenytoin is alkaline, and this is thought to contribute to pain, burning, and redness at the injection site.

The phenytoin prodrug fosphenytoin is water soluble and its vehicle does not contain propylene glycol; adverse effects are less common with fosphenytoin than with intravenous administration of phenytoin.[50,51] Fosphenytoin is dosed by phenytoin equivalent units; therefore, no dosage adjustments are needed when converting patients from phenytoin to fosphenytoin. Fosphenytoin can be administered by intramuscular injection or by intravenous infusion at a rate of up to 150 mg phenytoin equivalents/min. Fosphenytoin is rapidly converted to phenytoin in vivo, and free phenytoin levels after fosphenytoin administration are not markedly different compared with phenytoin.

Whether phenytoin or fosphenytoin is used, the serum phenytoin concentration should be kept in the "therapeutic" range of 10 to 20 μg/mL (corresponding to an unbound or "free" concentration of 1 to 2 μg/mL), unless further seizures occur; the level can then be increased until signs of toxicity occur. Failure to prevent seizures at a concentration of 25 μg/mL is usually an indication to add phenobarbital to the regimen. When fosphenytoin is administered, phenytoin concentrations should not be measured until the biologic conversion to phenytoin is complete: 2 hours after an intravenous infusion or 4 hours after an intramuscular injection of fosphenytoin.

Phenytoin is approximately 90% protein bound in normal hosts. Patients with renal dysfunction have lower total phenytoin levels at a given dose because the drug is displaced from binding sites, but the unbound level is not affected. Thus, renal failure patients, and perhaps others who are receiving highly protein-bound drugs (which compete for binding), may benefit from determination of free phenytoin level. Only the free fraction is metabolized, so the dose is not altered with changes in renal function. The clearance half-time with normal liver function varies from about 12 to 20 hours (intravenous form) to more than 24 hours (extended-release capsules), so that a new steady-state serum concentration occurs in 3 to 6 days. Phenytoin need not be given more frequently than every 12 hours. Hepatic dysfunction mandates a decrease in the maintenance dose. Hypersensitivity is the major adverse effect of concern to the intensivist. This may manifest itself solely as fever but commonly includes rash and eosinophilia. Adverse reactions to phenytoin and other anticonvulsants have been reviewed elsewhere.[52]

Phenobarbital remains a useful anticonvulsant for patients who are intolerant to phenytoin or who have persistent seizures after adequate phenytoin administration. The target for phenobarbital in the ICU should be a serum concentration of 20 to 40 μg/mL. Hepatic and renal dysfunction alter phenobarbital metabolism. Since its usual clearance half-time is about 96 hours, maintenance doses of this agent should be given once a day. A steady-state level takes about 3 weeks to become established. Sedation is the major adverse effect; allergy to the drug occurs rarely.

Carbamazepine therapy is seldom started in the ICU because its insolubility precludes parenteral formulation. Oral loading in conscious patients may produce coma that lasts several days. This drug also causes hyponatremia in patients who receive it chronically.

TREATING STATUS EPILEPTICUS

Generalized convulsive status epilepticus obviously constitutes a medical emergency; however, nonconvulsive status epilepticus and complex partial status epilepticus are also emergencies but are more difficult to recognize. In each circumstance, one must act quickly to prevent additional cerebral damage.

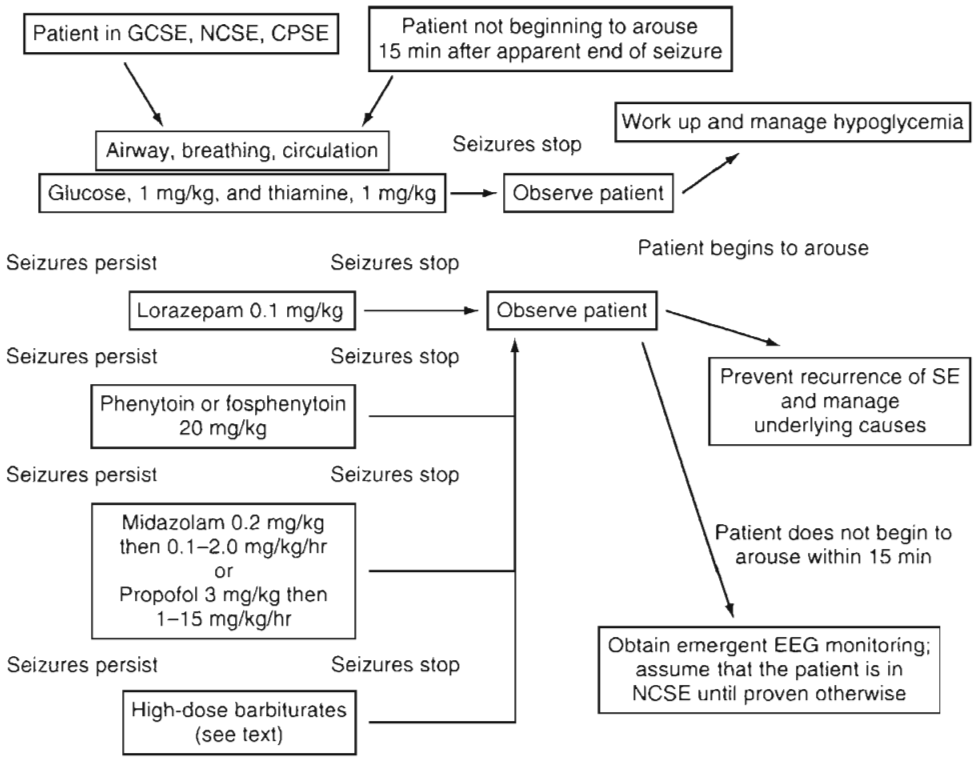

FIGURE 53–2. Management algorithm for status epilepticus. CPSE, complex partial status epilepticus; GSCE, generalized convulsive status epilepticus; NCSE, nonconvulsive status epilepticus; SE, status epilepticus.

Figure 53-2 shows a management algorithm for status epilepticus and Table 53-5 presents a sample management protocol for drug administration.[53] Patients with simple partial status epilepticus or epilepsia partialis continua are at less risk for the development of widespread cerebral damage and are also less likely to respond to the aggressive approach outlined in Table 53-5. In these patients, correcting underlying problems, such as nonketotic hyperosmolar hyperglycemia, is crucial. Errors in terminating status epilepticus include inadequate dosing of effective drugs and continued use of drugs that are ineffective in the patient being treated.

The conventional agents used in the first line of treatment of status epilepticus are the benzodiazepines (especially lorazepam, diazepam, and midazolam), phenytoin, and phenobarbital. Status epilepticus that is refractory to the traditional agents is treated with continuous infusions of the short-acting barbiturates, midazolam, or propofol. A recent multicenter clinical trial comparing lorazepam alone, phenytoin alone, diazepam followed by phenytoin, and phenobarbital alone as the initial drug treatment for generalized convulsive status epilepticus has been reported.[54] In this study, the highest rate of successful treatment of "overt" generalized convulsive status epilepticus was achieved with lorazepam. There was no demonstrable difference among these four drug regimens in the initial treatment of "subtle" generalized convulsive status epilepticus. Lorazepam has been our agent of first choice for terminating status epilepticus for many years and remains so with support from this study.

Advantages of lorazepam over diazepam are its duration of action against status epilepticus (4 to 14 hours as opposed to 20 minutes) and its higher initial response rate. European practitioners often use midazolam or clonazepam initially. In patients in whom intravenous access is difficult to attain, 0.2 mg/kg of midazolam administered intramuscularly will be rapidly and reliably absorbed. The use of midazolam in refractory status will be discussed later. Respiratory depression is the major adverse effect of the benzodiazepines, especially when they are given together with barbiturates or paraldehyde.

Phenytoin is an effective agent in the treatment of status epilepticus; however, the constraint on the rate of intravenous administration is of concern. Phenytoin has a long duration of action when an adequate dose is given (a 20 mg/kg dose produces a serum level above 20 μg/mL for 24 hours). Adding 5 mg/kg if the first 20 mg/kg load fails to stop status epilepticus may be useful. Fosphenytoin can be administered by a more rapid intravenous infusion and has fewer cardiovascular side- effects than phenytoin. Free phenytoin levels reach a therapeutic range 10 to 20 minutes after an infusion of fosphenytoin is started.[55,56] Intramuscular injection of fosphenytoin in patients with status epilepticus may be supported by the known pharmacokinetics of this route, but it should not be considered to be acceptable therapy for status epilepticus and should be reserved for only those rare circumstances in which intravenous access cannot be obtained.

Some practitioners advocate the use of phenobarbital as a first-line drug,[57] but it has typically been used as a third-line agent, after administration of a benzodiazepine and phenytoin.[58] Although this approach has been widely accepted by the neurologic community, we rarely use phenobarbital for two reasons. First, only a small percentage of patients who have failed treatment with two anticonvulsant drugs respond to a third conventional agent[59]; second, at least an additional 20 minutes are required to obtain control in the few patients who do respond. Phenobarbital remains an important drug in the management of simple partial status epilepticus and for those patients who are being weaned from high-dose midazolam or anesthetic barbiturates.

Pentobarbital and thiopental infusions are usually reserved for refractory status epilepticus.[55] Although these drugs are effective in sufficiently large doses, their side effects

TABLE 53–5. SUGGESTED PROTOCOL FOR TREATING STATUS EPILEPTICUS

I. Establish an airway, provide oxygen, and ensure ventilation. If neuromuscular junction blockade is required for intubation, use a short-acting agent (e.g., succinylcholine or vecuronium).

II. Determine blood pressure. If the patient is hypotensive, begin volume replacement or administration of vasoactive agents (or both), as indicated. Generalized convulsive status epilepticus patients who present with hypotension will usually require admission to a critical care unit. Hypertension should not be treated until status epilepticus is controlled, since terminating status epilepticus usually substantially corrects it, and many of the agents used to terminate status epilepticus can produce hypotension.

III. Unless the patient is known to be normo- or hyperglycemic, administer dextrose (1 g/kg) and thiamine (1 mg/kg).

IV. Terminate status epilepticus. The following sequence is recommended (see text for details); be cognizant of the potential of these drugs to eliminate the visible convulsive movements of generalized convulsive status epilepticus when leaving the patient in nonconvulsive status epilepticus. Patients who do not begin to respond to external stimuli 15 minutes after the apparent termination of generalized convulsive status epilepticus should be considered at risk for nonconvulsive status epilepticus and should undergo emergent EEG monitoring.

A. Give lorazepam, 0.1 mg/kg at a rate of 0.04 mg/kg per min. This drug should be diluted in an equal volume of the solution being used for intravenous infusion, as it is quite viscous. Most adult patients who respond do so by a total administered dose of 8 mg. The latency of effect is debated, but lack of response after 5 minutes should indicate failure.

B. If status epilepticus persists after lorazepam administration, consider phenytoin at up to 50 mg/min or fosphenytoin 20 mg/kg at up to 150 mg/min (dosed by phenytoin equivalent). Many investigators believe that an additional 5 mg/kg dose of phenytoin equivalent should be administered before the next line of therapy is attempted. However, this step may have more value for the prevention of status epilepticus recurrence than for its initial control.

C. If status epilepticus persists, administer midazolam 0.2 mg/kg as a bolus, followed by an infusion of 0.1-2.0 mg/kg per hour to achieve seizure control (as determined by EEG monitoring). Intubate the patient at this stage if this has not already been accomplished. A patient reaching this stage should be treated in a critical care unit.

E. Should the patient's condition not be controlled with midazolam, administer propofol or pentobarbital. Propofol is given as a continuous infusion at a rate of 1-15 mg/kg per hour to achieve seizure control (as determined by EEG monitoring). A bolus dose of propofol (3.0 mg/kg) is often given but may increase the occurrence of hypotension. Pentobarbital is given as a bolus dose of 12 mg/kg at a rate of 0.2-0.4 mg/kg per minute as tolerated, followed by an infusion of 0.25-2.0 mg/kg per hour, as determined by EEG monitoring (with an initial goal of burst-suppression; in some cases, an isoelectric electroencephalogram may be required to eliminate all electrical seizures). Most patients require systemic and pulmonary arterial catheterization, with fluid and vasoactive drug therapy as indicated to maintain blood pressure. Other complications of this treatment are discussed in the text.

V. Prevent recurrence of status epilepticus. The choice of drugs depends greatly on the cause of status epilepticus and the patient's medical and social situation. In general, patients not previously receiving anticonvulsants whose status epilepticus is easily controlled often respond well to chronic treatment with phenytoin or carbamazepine. In contrast, others (e.g., patients with acute encephalitis) will require two or three anticonvulsants at 'toxic' levels (e.g., phenobarbital at greater than 100 μg/mL) to be weaned from midazolam or pentobarbital and may still have occasional seizures.

VI. Treat complications.

A. Rhabdomyolysis should be treated with a vigorous saline diuresis to prevent acute renal failure; urinary alkalinization may be a useful adjunct. If definitive treatment of generalized convulsive status epilepticus takes longer than expected because of hypotension or arrhythmias, neuromuscular junction blockade under EEG monitoring might be considered.

B. Hyperthermia usually remits rapidly after termination of status epilepticus. External cooling usually suffices if the core temperature remains elevated. In rare instances, cool peritoneal lavage or extracorporeal blood cooling may be required. High-dose pentobarbital generally produces poikilothermia.

C. The treatment of cerebral edema occurring secondary to status epilepticus has not been well studied. When substantial edema is present, one should suspect that status epilepticus and cerebral edema are both manifestations of the same underlying condition. Mannitol and mild hyperventilation may be valuable if edema is life threatening. If substantial cerebral edema is present, ICP monitoring should be strongly considered. Edema due to status epilepticus is vasogenic in origin; thus, steroids may be useful as well, but they have not been studied in this setting.

can limit their use and may be fatal.[60] However, they are important when other modalities have failed (see Table 53-5). Endotracheal intubation and mechanical ventilation are mandatory when high-dose barbiturates are used, and both continuous EEG and invasive hemodynamic monitoring are highly recommended. Severe hypotension is the most frequent side effect of pentobarbital therapy, and its occurrence is associated with increased mortality.[61] An increased occurrence of nosocomial respiratory tract infection has been reported in patients treated with pentobarbital infusion.[62] An inhibitory effect on leukocyte chemotaxis and paralysis of respiratory cilia by the barbiturates have been postulated. Despite these side-effects, barbiturate anesthesia should not be rapidly discontinued if it is successful in terminating refractory status epilepticus; rather, continuing therapy for at least 48 hours, gradual tapering of the infusion dose, and the administration of phenobarbital during the drug taper are recommended.[63]

Midazolam is a water soluble benzodiazepine that has demonstrated high efficacy in refractory status in adults and children.[64,65] At our institution, this agent is used as a second-line drug, after lorazepam has failed to control status epilepticus. Clinically significant hypotension is rare even at very high doses that are often required to address tachyphylaxis. Respiratory depression is uncommon after a loading dose, but should be anticipated with infusions of any duration. Sedation is quickly reversed after short-term infusions are discontinued. However, terminal half-lives of three to eight times normal have been reported with extended administration.[66] In addition, prolonged elimination times have been associated with critical illness and hepatorenal dysfunction. Others have recently discussed its use in this setting.[67]

Although intravenous paraldehyde has been abandoned, this agent is still useful. The current formulation is licensed only for enteral use. It can be given every 3 hours through a Teflon-coated nasogastric tube or rectally via a rubber catheter. The enteral form can be filtered for intramuscular injection; it should be given deeply into the lateral gluteal muscles, with special care taken to avoid the sciatic nerves. This route of administration should be confined to a few doses, when rectal or oral treatment is not feasible.

Isoflurane, an inhaled anesthetic, controls refractory status epilepticus; however, it is difficult to deliver such a gas outside of the operating suite or the recovery area. It has no

known advantage over intravenous anticonvulsants and can raise ICP.

Propofol has been reported to be effective in the treatment of refractory status epilepticus, but direct comparisons with other agents have shown mixed results.[68,69] It may offer a lower risk of ventilatory depression and promote more rapid awakening compared with other drugs when it is discontinued. Early fears of a possible proconvulsant effect appear to be unfounded, although withdrawal convulsions may occur if the drug is abruptly terminated. A dosage range of 1 to 15 mg/kg/hr has been studied,[70] although the actual upper limit is not known. Acidosis and oxygenation difficulties have been reported in children.[71] Mortality with its use appears to be greater than with midazolam.[72] Careful monitoring of creatine kinase and oxygen saturation would be prudent.[73]

The role of the newer anticonvulsant agents has yet to be determined. Intravenous valproate may emerge as an important drug for the treatment of several forms of status epilepticus.[74] Topiramate may also be useful for refractory status epilepticus,[75] especially when an intravenous form becomes available.

ACKNOWLEDGMENT

The authors would like to recognize the contributions of Christopher Dunatov, MD, to the previous edition of this chapter.

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Shneker BF, Fountain NB: Assessment of acute morbidity and mortality in nonconvulsive status epilepticus. Neurology 1996;47:83-89.

A retrospective review of 100 patients with nonconvulsive status epilepticus found a mortality rate of 18% that correlated with the underlying cause, severe impairment of mental status, and development of acute complications. Generalized spike-and-wave discharges did not correlate with mortality. This is the largest series to date.

Towne AR, Waterhouse EJ, Boggs JG, et al: Prevalence of nonconvulsive status epilepticus in comatose patients. Neurology 2000;54:340-345.

A retrospective review of the EEG recordings of 236 comatose ICU patients without clinical signs of status epilepticus found that nonconvulsive status epilepticus occurred in 18%. These findings suggest that EEG is an essential part of the coma evaluation.

Treiman DM, Meyers PD, Walton NY, et al: A comparison of four treatments for generalized convulsive status epilepticus. N Engl J Med 1998;339:792-798.

This 5-year randomized, double-blind, multicenter trial of four intravenous regimens in the first-line treatment of generalized convulsive status epilepticus demonstrated that lorazepam is more effective than phenytoin. Although lorazepam was not found to be more efficacious than phenobarbital or diazepam and phenytoin, it was easier to use and therefore recommended for initial intravenous treatment. There were no significant differences in side effects among the four treatment groups.

Chapter 54

NEUROMUSCULAR DISORDERS IN THE ICU

Vern C. Juel • Thomas P. Bleck

KEY POINTS

1. Respiratory dysfunction due to neuromuscular disease typically presents with a combination of **upper airway dysfunction and diminished tidal volume** (V_T).
2. Along with vital capacity, **trended measurement of the maximum inspiratory pressure** (PImax or negative inspiratory force [NIF]) is a useful index of ventilatory capacity. Inability to maintain a PImax greater than 20 to 25 cm H_2O usually indicates a need for mechanical ventilatory assistance.
3. **Autonomic failure and pulmonary embolism** are now the major causes of mortality in Guillain-Barré syndrome.
4. **Evidence-based guidelines for Guillain-Barré syndrome immunotherapy** have been published by the Quality Standards Subcommittee of the American Academy of Neurology. Plasma exchange is recommended for adult patients who cannot walk within 4 weeks of symptom onset. Intravenous immune globulin (IVIg) is recommended in these patients within 2 or possibly 4 weeks of symptom onset. Plasma exchange and IVIg are considered equivalent in efficacy, and no additional benefit is conferred by combining these treatments. In light of the therapeutic equivalence, the decision whether to employ plasma exchange or IVIg in treating acute Guillain-Barré syndrome may be determined by resource availability and by avoiding potential side effects related to a patient's medical comorbidities.
5. **In the initial North American outbreak of West Nile virus,** about 10% of infected patients experienced flaccid weakness with clinical features resembling Guillain-Barré syndrome.
6. Approximately 20% of patients with myasthenia gravis develop myasthenic crisis with **respiratory failure requiring mechanical ventilation.**
7. **Critical illness polyneuropathy** is a widespread axonal peripheral neuropathy that develops in the context of multiple organ failure and sepsis. Critical illness polyneuropathy is possibly the most common neuromuscular cause of prolonged ventilator dependency in patients without prior known neuromuscular disease.
8. **Acute quadriplegic myopathy** has developed most frequently in the setting of severe pulmonary disorders, in which neuromuscular blockade is used to facilitate mechanical ventilation and high-dose corticosteroids are concurrently administered. Given the growing recognition of acute quadriplegic myopathy, the use of high-dose corticosteroids should be avoided, if possible, when neuromuscular blockade is required.

Abnormal neuromuscular function may precipitate a patient's admission to an ICU or may develop as a consequence of another critical illness and its treatment. This chapter focuses primarily on respiratory failure as a consequence of neuromuscular disease but also addresses autonomic dysfunction occurring in this setting. To facilitate understanding of the concepts involved, a brief review of the motor unit and its physiology is provided and specific muscles critical to ventilation are identified.

THE MOTOR UNIT AND ITS PHYSIOLOGY

Central nervous system activity designated for motor output is ultimately conducted to lower motor neurons, also known as alpha motor neurons. A motor unit is composed of a lower motor neuron and its distal ramifications, its neuromuscular junctions, and the muscle fibers it innervates. The cell bodies of the lower motor neurons are located in the brainstem for cranial musculature and in the anterior horn of the spinal cord for somatic muscles. At the level of the brainstem or spinal cord, the motor neurons receive various excitatory and inhibitory inputs. Motor axons project through the subarachnoid space and penetrate the dura mater as nerve roots. They may join with other motor axons and with sensory and autonomic fibers in a plexus and then travel in peripheral nerves to the muscles they innervate. Alpha motor neurons are myelinated, a feature that accelerates nerve impulse propagation. The multiple terminal ramifications of the motor neuron synapse on individual muscle fibers.

The motor axon communicates with muscle via a specialized area termed the neuromuscular junction. On the presynaptic side of the neuromuscular junction the neurotransmitter acetylcholine is synthesized, packaged in vesicles, and stored for release. Depolarization of the axon opens presynaptic voltage-gated calcium channels, which activate the molecular machinery responsible for drawing the vesicles

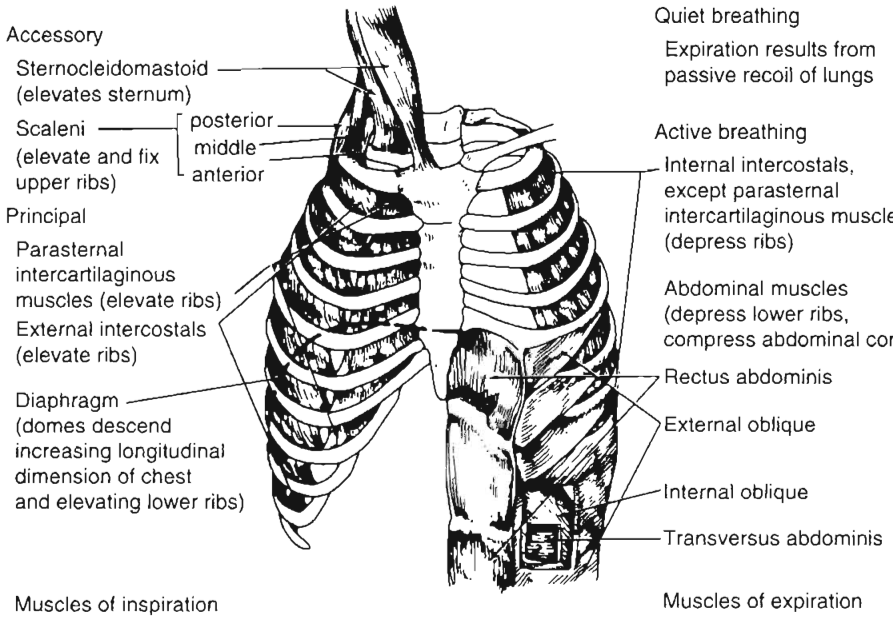

FIGURE 54–1. Major respiratory muscles. Inspiratory muscles are indicated on the left and expiratory muscles are indicated on the right. (From Garrity ER: Respiratory failure due to disorders of the chest wall and respiratory muscles. In MacDonnell KF, Fahey PJ, Segal MS [eds]: Respiratory Intensive Care. Boston, Little, Brown, 1987, p 313.)

to the presynaptic membrane. The vesicles then fuse with the membrane and release acetylcholine into the synaptic cleft. Acetylcholine molecules bind to receptors on the postsynaptic membrane and cause an influx of sodium, which in turn increases the muscle end-plate potential. When the end-plate potential exceeds the threshold level, the muscle membrane becomes depolarized. This depolarization releases calcium ions from the sarcoplasmic reticulum, and muscle contraction occurs through a process known as excitation-contraction coupling. After activating the acetylcholine receptor complex, the acetylcholine molecule is degraded by cholinesterase; the choline released by this reaction is then recycled by the presynaptic neuron.

MUSCLES OF RESPIRATION

Three muscle groups may be defined based on their importance for respiration, as follows (Fig. 54-1):[1]

1. *Upper airway muscles:* palatal, pharyngeal, laryngeal, and lingual
2. *Inspiratory muscles:* sternomastoid, diaphragm, scalenes, and parasternal intercostals
3. *Expiratory muscles:* internal intercostal muscles (except for parasternals) and abdominal muscles

The upper airway muscles receive their innervation from the lower cranial nerves. Sternomastoid innervation arrives predominantly from cranial nerve XI, with a small contribution from C2. The phrenic nerve originates from cell bodies located between C3 and C5, with a maximum contribution from C4, and innervates the diaphragm. Innervation to the scalenes arises from C4 to C8, whereas that of the parasternal intercostals is from T1 to T7. The intercostal muscles receive innervation from T1 to T12, and the abdominal musculature receive it from T7 to L1. Reference to this innervation scheme is important in understanding the effects of spinal cord and nerve root injuries on respiration and for the differential diagnosis of disorders producing apparently diffuse weakness.

CLINICAL PRESENTATION OF NEUROMUSCULAR RESPIRATORY FAILURE

Patients experiencing respiratory dysfunction due to neuromuscular disease typically present with a combination of upper airway dysfunction and diminished tidal volume (V_T). Difficulty with swallowing liquids, including respiratory secretions, is the most typical presentation of pharyngeal weakness, although some patients have an equal or greater degree of difficulty with solid food. A hoarse or nasal voice may also signal problems with the upper airway. These conditions are noted in patients who are at risk for aspiration and present with difficulty with attempts at negative-pressure ventilation (cuirass or iron lung), because the weakened muscles may not be able to keep the airway open as the pressure falls.[2] Paradoxical abdominal movement (inward movement of the abdomen during inspiration) is an important sign of diaphragmatic weakness.[3]

Loss of V_T occurs most dramatically with diaphragmatic weakness but also follows insults that affect the ability of the parasternal intercostals to keep the chest wall expanded against negative intrapleural pressure. This is most apparent in lower cervical spinal cord injuries where atelectasis commonly develops despite preserved phrenic nerve function. This problem usually diminishes over weeks as the parasternal intercostal muscles develop spasticity.

Patients with progressive generalized weakness (e.g., with Guillain-Barré syndrome) commonly begin to lose V_T before developing upper airway weakness. To maintain minute ventilation, and therefore carbon dioxide excretion, a patient's respiratory rate increases. Respiratory rate is thus one of the most important clinical parameters to monitor. As the vital capacity falls from the norm of about 65 to 30 mL/kg, a patient's cough weakens and clearing secretions becomes difficult. A further decrease of vital capacity to 20 to 25 mL/kg results in an impaired ability to sigh with progressive atelectasis. At this point hypoxemia may be present because of ventilation-perfusion mismatching and because an increasing percentage of V_T is used to ventilate dead space. Before the vital capacity reaches 15 mL/kg, a patient should

be in an ICU because respiratory failure is imminent and endotracheal intubation should be considered. The precise point at which mechanical ventilation is necessary varies with the patient, the underlying condition, and especially with the likelihood of a rapid response to treatment.

Regardless of the vital capacity, however, indications for intubation and mechanical ventilation include evidence of fatigue, hypoxemia despite supplemental oxygen administration, difficulty with secretions, and a rising $PaCO_2$. In the absence of hypercapnia, occasional patients (e.g., those with myasthenia gravis) can be managed under very close observation in an ICU with less invasive techniques (e.g., bilevel positive airway pressure [BiPAP]).[4]

In addition to vital capacity, trended measurements of the maximum inspiratory pressure (PImax, more typically recorded as negative inspiratory force [NIF]) are useful indicators of ventilatory capacity. Inability to maintain a PImax greater than 20 to 25 cm H_2O usually indicates a need for mechanical ventilation. Although the maximum expiratory pressure (PEmax) is a more sensitive indicator of weakness,[5] it has not proved to be as useful as an indicator of the need for mechanical ventilation. A more detailed discussion of these variables and their use may be found elsewhere.[6,7]

Because a patient with neuromuscular respiratory failure has intact ventilatory drive,[8] the fall in V_T is initially matched by an increase in respiratory rate, keeping the $PaCO_2$ normal or low until the vital capacity becomes dangerously reduced. Many patients initially maintain their $PaCO_2$ in the range of 35 mm Hg because of either (1) a subjective sense of dyspnea at low V_T or (2) hypoxia from atelectasis and increasing dead space. When the $PaCO_2$ begins to rise in this circumstance, abrupt respiratory failure may be imminent.

The modest degree of hypoxia in most of these patients worsens when the $PaCO_2$ begins to rise, displacing more oxygen from the alveolar gas. However, aspiration pneumonia and pulmonary embolism are also frequent causes of hypoxemia in these patients. To determine the relative contributions of these conditions to a patient's hypoxemia, one can use a simplified version of the alveolar gas equation as follows (derived elsewhere)[6,7]:

$$P_AO_2 = P_IO_2 - (PaCO_2/R)$$

where P_AO_2 is the alveolar partial pressure of oxygen, P_IO_2 is the partial pressure of inspired oxygen (in room air, 150 mm Hg), and R is the respiratory quotient (on most diets, about 0.8). This allows estimation of the alveolar-arterial oxygen difference ($P_AO_2 - PaO_2$). Under ideal circumstances in young people breathing room air this value is about 10 mm Hg, but it rises to about 100 mm Hg when the fraction of inspired oxygen (F_IO_2) is 1.0. The alveolar air equation allows one to factor out the contribution of hypercarbia to the decrease in arterial partial pressure of oxygen (PaO_2); it should be used to determine whether there is a cause of significant hypoxemia in addition to the displacement of oxygen by carbon dioxide.

Patients with orbicularis oris weakness may have artifactually low vital capacity and NIF measurements because they cannot form a tight seal around the spirometer mouthpiece. The need for nursing and respiratory therapy personnel who are experienced in the care of these patients is thus underscored. It is also important for physicians to observe these patients directly rather than relying solely on reported measurements. The physical findings associated with neuromuscular respiratory failure are reviewed elsewhere.[6,7] Among the most important findings are rapid, shallow breathing,[9] the recruitment of accessory muscles, and paradoxical movement of the abdomen during the respiratory cycle. Fluoroscopy of the diaphragm is occasionally valuable for the diagnosis of diaphragmatic dysfunction.[10]

Autonomic dysfunction commonly accompanies some of the neuromuscular disorders requiring critical care, such as Guillain-Barré syndrome, botulism, and porphyria (Table 54-1). In Guillain-Barré syndrome (discussed later) dysautonomia is common and may arise in parallel with weakness or may follow the onset of the motor disorder after a week or more.

NEUROMUSCULAR DISORDERS

Many chronic neuromuscular disorders and other central nervous system conditions affecting the suprasegmental innervation and control of respiratory muscles eventually compromise ventilation. In this chapter, however, we emphasize the more common acute and subacute neuromuscular disorders that precipitate or prolong critical illness due to ventilatory failure and autonomic dysfunction. A more complete listing of neuromuscular diseases appears in Table 54-1; reviews of this subject[11,12] or the references listed in Table 54-1 may be consulted for details of the more rare disorders. Some of the diseases listed (e.g., Lambert-Eaton myasthenic syndrome) rarely cause respiratory failure in isolation but may be contributing causes in the presence of other conditions,[13] such as neuromuscular junction blockade intended only for the duration of a surgical procedure.[14]

NEUROMUSCULAR DISEASES PRECIPITATING CRITICAL ILLNESS

Guillain-Barré Syndrome

Guillain-Barré syndrome, or acute inflammatory demyelinating polyradiculoneuropathy, is typically a motor greater than sensory peripheral neuropathy with subacute onset, monophasic course, and nadir within 4 weeks. Although the precise etiology is unknown, Guillain-Barré syndrome is immune mediated and related to antibodies directed against peripheral nerve components. Approximately 1.7 cases occur per 100,000 population per year.[28] Most patients suffer a demyelinating neuropathy, but in about 5% of cases the condition is a primary axonopathy.[29] Numerous antecedents have been implicated[30]; the more frequent ones are listed in Table 54-2. The association with antecedent infections suggests that certain agents may elicit immune responses involving antibodies that cross-react with peripheral nerve gangliosides. In particular, the development of ganglioside antibodies has been observed in Guillain-Barré syndrome after *Campylobacter jejuni* infections, such as GM_1 antibodies in axonal forms of Guillain-Barré syndrome[31] and GQ_{1b} antibodies in the Miller-Fisher variant of Guillain-Barré syndrome.[32]

The initial findings of patients with Guillain-Barré syndrome are subacute and progressive weakness, usually most marked in the legs, associated with sensory complaints but without objective signs of sensory dysfunction.[33] Deep tendon reflexes are often significantly reduced or absent at presentation, though this finding may take several days to develop.

TABLE 54–1. NEUROMUSCULAR CAUSES OF ACUTE RESPIRATORY FAILURE

Location	Disorder	Associated Autonomic Dysfunction?
Spinal cord	Tetanus[15]	Frequent
Anterior horn cell	Amyotrophic lateral sclerosis[16]	No
	Poliomyelitis	No
	Rabies	Frequent
	West Nile virus flaccid paralysis	No
Peripheral nerve	Guillain-Barré syndrome	Frequent
	Critical illness polyneuropathy	No
	Diphtheria	No, but cardiomyopathy and arrhythmias may occur
	Porphyria	Occasional
	Ciguatoxin (ciguatera poisoning)	Occasional
	Saxitoxin (paralytic shellfish poisoning)	No
	Tetrodotoxin (pufferfish poisoning)	No
	Thallium intoxication	No
	Arsenic intoxication[17,18]	No
	Lead intoxication	No
	Buckthorn neuropathy	No
Neuromuscular junction	Myasthenia gravis	No
	Botulism[19]	Frequent
	Lambert-Eaton myasthenic syndrome[20]	Yes, frequent dry mouth and postural hypotension
	Hypermagnesemia[21]	No
	Organophosphate poisoning	No
	Tick paralysis	No
	Snake bite	No
Muscle	Polymyositis/dermatomyositis	No
	Acute quadriplegic myopathy	No
	Eosinophilia-myalgia syndrome[22]	No
	Muscular dystrophies[23]	No, but cardiac rhythm disturbances may occur
	Carnitine palmitoyl transferase deficiency	No
	Nemaline myopathy[24]	No
	Acid maltase deficiency[25]	No
	Mitochondrial myopathy[26]	No
	Acute hypokalemic paralysis	No
	Stonefish myotoxin poisoning	No
	Rhabdomyolysis	No
	Hypophosphatemia[27]	No

The cerebrospinal fluid (CSF) typically reveals an albuminocytologic dissociation or elevated protein content without pleocytosis; this may not evolve until the second week of illness. The major reason to examine the CSF is to preclude other diagnoses. Although mild CSF lymphocytic pleocytosis (10 to 20 cells/mm^3) may suggest the possibility of associated human immunodeficiency virus (HIV) infection, in most patients, the nucleated cell count is less than 10 cells/mm^3.[34] Although they may be normal initially, results of electrodiagnostic studies (motor and sensory nerve conduction studies and needle electromyography) often reflect segmental nerve demyelination with multifocal conduction blocks, temporally dispersed compound muscle action potentials, slowed conduction velocity, and prolonged or absent F waves.[35] Differential diagnostic considerations for patients with suspected Guillain-Barré syndrome are primarily those listed in the "Peripheral Nerve" section of Table 54-1.

The components of treatment for patients with Guillain-Barré syndrome are as follows:

- Management of ventilatory failure
- Management of autonomic dysfunction
- Meticulous nursing care
- Psychologic support
- Physical and occupational therapy
- Prevention of deep venous thrombosis
- Nutritional support
- Early planning for rehabilitation
- Immunotherapy for the underlying autoimmune process

Patients with Guillain-Barré syndrome with evolving respiratory failure should generally be intubated when the vital capacity falls to about 15 mL/kg or when difficulty with secretions begins because the response to treatment is slow. If a patient has been immobile for several days before intubation and neuromuscular junction blockade is needed, a nondepolarizing agent should be used to avoid transient hyperkalemia. Oral intubation is again being viewed as preferable to the nasal route, because the endotracheal tube is frequently required for a week or longer, raising the risk of sinusitis with nasal intubation.

Many patients are too weak to trigger the ventilator; in such cases, the assist/control or intermittent mandatory ventilation mode is initiated. Weaning patients with Guillain-Barré syndrome from mechanical ventilation must wait for adequate improvement in strength. We usually shift to pressure support ventilation for weaning, although evidence of its superiority over intermittent mandatory ventilation or synchronized intermittent mandatory ventilation modes is only anecdotal. Although the majority of patients require mechanical ventilation for less than 4 weeks, as many as one fifth need 2 or more months of support before they can breathe without assistance. Improvement in vital capacity to greater than 15 mL/kg and in NIF to greater than 25 cm H_2O suggests that a patient has improved enough to begin

TABLE 54–2. MAJOR ANTECEDENTS OF GUILLAIN-BARRÉ SYNDROME

Frequent
Upper respiratory tract infections
Campylobacter jejuni enteritis
Cytomegalovirus (CMV) infection
Epstein-Barr virus (EBV) infection
Hepatitis A infection
Hepatitis B infection
Hepatitis C infection
HIV infection
Infrequent
Mycoplasma pneumoniae infection
Haemophilus influenzae infection
Leptospira icterohaemorrhagiae infection
Salmonellosis
Rabies vaccine
Tetanus toxoid
Bacille Calmette-Guérin immunization
Sarcoidosis
Systemic lupus erythematosus
Lymphoma
Trauma
Surgery
Questionable
Hepatitis B vaccine
Influenza vaccine
Hyperthermia
Epidural anesthesia

weaning from the ventilator. A formula using a combination of ventilatory and gas exchange variables may allow more accurate determination of a patient's ability to be weaned.[36]

Autonomic dysfunction related to Guillain-Barré syndrome most typically presents as a hypersympathetic state and is often heralded by unexplained sinus tachycardia. The blood pressure may fluctuate wildly. Patients may rarely experience bradycardic episodes, which may require temporary pacing. Autonomic surges during tracheal suctioning or due to a distended viscus may be very dramatic and should be minimized. Autonomic failure and pulmonary embolism are now the major causes of mortality in Guillain-Barré syndrome.

Nursing care for patients with Guillain-Barré syndrome is similar to that for other paralyzed and mechanically ventilated patients, but special care must be taken to remember that patients with Guillain-Barré syndrome are completely lucid. In addition to explaining any procedures carefully, arranging for distractions during the daytime (e.g., television, movies, conversation, visitors) and adequate sleep at right is very important. For the most severely affected patients, sedation should be considered. In concert with physical and occupational therapists, passive exercise should be performed frequently throughout the day.

Deep venous thrombosis is a significant danger for patients with Guillain-Barré syndrome. Episodic arterial desaturation is a common event, presumably owing to transient mucus plugging; submassive pulmonary emboli may therefore be overlooked. Adjusted-dose heparin (to slightly prolong the partial thromboplastin time) should be given, and sequential compression devices should be used on the legs; therapeutic anticoagulation may be considered. The risk of fatal pulmonary embolism extends through the initial period of improvement until patients are ambulatory.

Nutritional support should begin as soon as a patient is admitted, with appropriate concern for the risk of aspiration.[37] Most mechanically ventilated patients with Guillain-Barré syndrome can be fed via soft, small-caliber feeding tubes; autonomic dysfunction affecting the gut occasionally requires total parenteral nutrition.

Immunotherapy for Guillain-Barré syndrome includes removal of autoantibodies with plasma exchange or immune modulation with high-dose IVIg. The efficacy of plasma exchange has been evaluated in a Cochrane systematic review of six class II trials comparing plasma exchange alone with supportive care.[38] Most of the trials employed up to five plasma exchanges of 50 mL/kg over 2 weeks. In a large North American trial,[39] the time needed to improve one clinical grade (being weaned from the ventilator or being able to walk) was reduced by 50% in the plasma exchange group by comparison with the control group. There was no significant benefit when plasma exchange was begun later than 2 weeks after symptom onset. A meta-analysis demonstrated more rapid recovery in ventilated patients treated with plasma exchange within 4 weeks of onset.[38] The optimal number of plasma exchanges has been assessed in patients with mild (unable to run), moderate (unable to stand without assistance), and severe (requiring mechanical ventilation) Guillain-Barré syndrome by the French Cooperative Group.[40] On the basis of this trial, two exchanges are better than none in mild Guillain-Barré syndrome; four are better than two in moderate Guillain-Barré syndrome; and six are no better than four in severe Guillain-Barré syndrome. Albumin is the preferred replacement solution.[41] Treatment with IVIg for Guillain-Barré syndrome has also been examined in a Cochrane systematic review. Three randomized controlled trials demonstrated class I evidence that IVIg (2 g/kg over 2 to 5 days) is as effective as plasma exchange in Guillain-Barré syndrome patients with impaired walking.[42] Complication rates were somewhat higher in the plasma exchange groups. A large, international, multicenter, randomized trial compared plasma exchange (50 mL/kg × 5 exchanges over 8 to 13 days), IVIg (0.4 g/kg × 5 days), and plasma exchange followed by IVIg.[43] No significant outcome differences between these therapies were found with respect to functional improvement at 4 weeks or at 48 weeks.

Evidence-based guidelines for Guillain-Barré syndrome immunotherapy have been published by the Quality Standards Subcommittee of the American Academy of Neurology.[44] Plasma exchange is recommended for adult patients who cannot walk within 4 weeks of symptom onset. IVIg is recommended in these patients within 2 or possibly 4 weeks of symptom onset. Both treatments are deemed equivalent in efficacy, and no additional benefit is conferred by combining treatment with plasma exchange and IVIg. In light of their therapeutic equivalence, the decision whether to employ plasma exchange or IVIg in treating acute Guillain-Barré syndrome may be determined by resource availability and by avoiding potential side effects related to a patient's medical comorbidities. Patients with heart disease, renal insufficiency or failure, hyperviscosity, or IgA deficiency may be more susceptible to complications of treatment with IVIg, whereas plasma exchange may be complicated in patients with labile blood pressure, septicemia, and significant venous access problems.

Despite the autoimmune pathophysiology of Guillain-Barré syndrome and the efficacy of corticosteroids in more chronic forms of inflammatory neuropathy, corticosteroids

have not demonstrated effectiveness in Guillain-Barré syndrome and are therefore not recommended for Guillain-Barré syndrome treatment.[44] A large, multicenter trial failed to demonstrate efficacy of high-dose intravenous methylprednisolone,[45] and another large, multicenter trial demonstrated no added clinical benefit in combined treatment with IVIg and methylprednisolone.[46]

West Nile Virus Acute Flaccid Paralysis Syndrome

The large outbreak of West Nile virus encephalitis in the summer of 1999 in New York City marked the emergence of a relatively new cause for neuromuscular weakness with the potential for neuromuscular respiratory compromise. West Nile virus is a flavivirus transmitted between birds and mosquitoes. Humans may acquire West Nile virus from the bite of an infected *Culex* species mosquito, and a corresponding peak in human disease occurs in the late summer and fall. West Nile virus may also be transmitted to humans by organ transplantation,[47] blood and blood product transfusion,[48] transplacental exposure,[49] breast feeding,[50] and percutaneous laboratory injuries.[51] About 20% of humans experience a mild flulike illness lasting 3 to 6 days, and about 1 in 150 develop central nervous system disease, which usually presents as meningoencephalitis.[52]

In the initial North American outbreak of West Nile virus, about 10% of infected patients experienced flaccid weakness with clinical features resembling Guillain-Barré syndrome.[53] In one report from the original outbreak, a patient developed electromyographic evidence for segmental demyelination compatible with Guillain-Barré syndrome.[54] Although patients with West Nile virus infection exhibit a spectrum of clinical weakness,[55] the most prominent and distinctive syndrome documented in several subsequent reports of West Nile virus infection is an acute "poliomyelitis-like" or acute flaccid paralysis syndrome with pathology localizing to the ventral horns of the spinal cord and/or ventral roots.[56-62] These patients developed acute, asymmetrical, flaccid weakness in the absence of sensory abnormalities, diffuse areflexia, or bowel/bladder dysfunction. Some of the patients experienced concurrent meningoencephalitis, and a few required mechanical ventilation.[57,58] West Nile virus acute flaccid paralysis syndrome may occur in the absence of overt encephalitic signs (e.g., fever, confusion) or meningismus. Although the risk for West Nile virus encephalitis is significantly increased with age,[63] West Nile virus acute flaccid paralysis syndrome occurs in relatively younger patients.[56-62]

Electrodiagnostic studies in patients with West Nile virus acute flaccid paralysis syndrome demonstrate normal sensory potentials, the absence of findings suggesting segmental demyelination (e.g., motor conduction block, reduced conduction velocities, prolonged distal and F-wave latencies), low amplitude compound muscle action potentials in affected regions, and marked denervation changes in affected limb and in corresponding paraspinal muscles on needle electromyography. Corresponding MRI findings are sometimes observed and include abnormal signal in the spinal cord on T2-weighted images[60,61] and abnormal enhancement of the nerve roots and cauda equina.[59,60] CSF analysis usually demonstrates mild pleocytosis with lymphocytic predominance, mild to moderate protein elevation, and normal glucose.[64] Prognosis for recovery of strength in these patients appears poor.[65]

West Nile virus infection may be diagnosed by demonstrating West Nile virus RNA in serum, CSF, or other tissues by reverse-transcriptase polymerase chain reaction, although this is insensitive.[66] More commonly, a diagnosis is made by demonstration of West Nile virus IgM in CSF or serum by antibody-capture enzyme-linked immunosorbent assay. When serum West Nile virus IgM is present, diagnosis is confirmed by a fourfold increase in West Nile virus IgG titers between acute and convalescent sera obtained 4 weeks apart. Positive IgM and IgG antibody titers should be confirmed by plaque-reduction viral neutralization assay to exclude false-positive results related to other flaviviral infections such as St. Louis encephalitis. Serology may not become positive until 8 days after symptom onset.[52]

Particularly in the absence of a more typical encephalitic presentation of West Nile virus infection, a high index of clinical suspicion is needed to make a diagnosis of West Nile virus acute flaccid paralysis syndrome and to distinguish such cases from Guillain-Barré syndrome in patients presenting with acute weakness in the late summer or fall. Electrodiagnostic studies may help localize the pathology to the ventral horns of the spinal cord or ventral roots in West Nile virus cases and to exclude findings of segmental demyelination suggesting Guillain-Barré syndrome. CSF should also be evaluated to help discriminate between the albuminocytologic dissociation of Guillain-Barré syndrome and the lymphocytic pleocytosis observed in West Nile virus infection.

Although there is currently no specific treatment for West Nile virus acute flaccid paralysis syndrome, a multicenter study to evaluate the efficacy of Israeli IVIg in patients with West Nile virus meningoencephalitis or weakness began in the summer of 2003. The IVIg for this study contains high levels of West Nile virus antibodies because it was prepared from sera obtained after an Israeli West Nile virus epidemic in 2000.[67] Two candidate vaccines against West Nile virus are also being evaluated.[64]

Myasthenia Gravis

Myasthenia gravis is a consequence of autoimmune attack on the acetylcholine receptor complex at the postsynaptic membrane of the neuromuscular junction. This process results in clinical weakness with a fluctuating pattern that is most marked after prolonged muscle exertion. Myasthenia gravis occurs at a higher rate in early adulthood in women, but in later life the incidence rates for men and women become nearly equal. The reported prevalence is 14.2 cases per 100,000 population.[68] Myasthenia gravis typically involves ocular muscle weakness producing ptosis and diplopia, as well as bulbar muscle weakness resulting in dysphagia and dysarthria. This diagnosis should be considered in patients who have acute respiratory failure with these cranial nerve findings. A clinical diagnosis of myasthenia gravis may be supported by edrophonium testing, by electrophysiologic studies including repetitive nerve stimulation studies and single-fiber electromyography, and by acetylcholine receptor and muscle-specific receptor tyrosine kinase (MuSK) antibody testing.

Approximately 20% of patients with myasthenia gravis develop myasthenic crisis with respiratory failure requiring mechanical ventilation.[69] Intensivists may also encounter myasthenic patients for management of complications of immunomodulating treatment or for postoperative care after thymectomy. The most common precipitating factors for myasthenic crisis include bronchopulmonary infections

(29%) and aspiration (10%).[70] Other precipitating factors include sepsis, surgical procedures, rapid tapering of immune modulation, beginning treatment with corticosteroids, pregnancy, and exposure to drugs that may increase myasthenic weakness (Table 54-3).[71] Patients with myasthenia gravis are exceptionally sensitive to nondepolarizing neuromuscular blocking agents, but are resistant to depolarizing agents.[72] Thymomas are associated with more fulminant disease and have been identified in about one third of patients in myasthenic crisis.[70]

Although sometimes less appreciated than respiratory muscle weakness, upper airway muscle weakness is a common mechanism leading to myasthenic crisis.[73] Oropharyngeal and laryngeal muscle weakness may result in upper airway collapse with obstruction, along with inability to swallow secretions that may also obstruct the airway and become aspirated. Because direct assessment of oropharyngeal muscle strength is impractical, a focused history and examination to assess surrogate muscles in the head and neck region is important. Findings of bulbar myasthenia associated with upper airway compromise include flaccid dysarthria with hypernasal, staccato, or hoarse speech, dysphagia sometimes associated with nasal regurgitation, and chewing fatigue. Patients may exhibit facial weakness with difficulty holding air within the cheeks. Jaw closure is often weak and cannot be maintained against resistance. Patients with myasthenic tongue weakness may be unable to protrude the tongue into either cheek. Although neck flexors are often weaker, a dropped head syndrome due to neck extensor weakness may occur. Vocal cord abductor paralysis may produce laryngeal obstruction with associated stridor.[74,75]

Patients with features of impending myasthenic crisis including severe bulbar weakness, marginal vital capacity (less than 20 to 25 mL/kg), weak cough with difficulty clearing secretions from the airway, or paradoxical breathing while supine should be admitted to an ICU and made NPO to prevent aspiration.[76] Serial vital capacity and NIF measurements may be used to monitor ventilatory function in impending myasthenic crisis. However, with significant bulbar weakness, these measurements are often inaccurate, owing to difficulty sealing the lips around the spirometer mouthpiece and to inability to seal the nasopharynx. Vital capacity measurements may not reliably predict respiratory failure in myasthenia gravis, due to the fluctuating nature of myasthenic weakness.[77] The criteria for intubation and mechanical ventilation are similar to those discussed earlier for Guillain-Barré syndrome. If the upper airway is competent and there is no difficulty handling secretions or gross hypercapnia ($PaCO_2 > 50$ mm Hg), intermittent nasal BiPAP may be a useful temporizing measure.[4] The majority of patients who develop hypercapnia in myasthenic crisis require intubation, as do those who are becoming fatigued.

Plasma exchange is an effective short-term immunomodulating treatment for myasthenic crisis and for surgical preparation in symptomatic myasthenic patients. Significant strength improvement in myasthenic crisis is well documented in several series,[78-82] although there have been no controlled clinical trials. We perform a series of five to six exchanges of 2 to 3 L every other day. Onset of improved strength is variable but generally occurs after two to three exchanges.

IVIg may represent an alternative short-term treatment for myasthenic exacerbations or crises in patients who are poor candidates for plasma exchange owing to difficult vascular access or septicemia. Comparable efficacy for plasma exchange and IVIg was demonstrated in myasthenic exacerbations and crises in a relatively small randomized, controlled trial of IVIg at 1.2 and 2.0 g/kg over 2 to 5 days.[83] However, in a retrospective multicenter study of myasthenic crisis, plasma exchange proved more effective than IVIg in ability to extubate at 2 weeks and in 1-month functional outcome.[82] Treatment failures to IVIg subsequently responding to plasma exchange have also been reported.[84] Recent experience with preoperative IVIg for thymectomy in myasthenia gravis suggests that the time course of maximal response may be considerably delayed in some patients.[85]

Corticosteroids (e.g., prednisone, 1 mg/kg/day) are occasionally used in prolonged myasthenic crises that fail to respond to treatment with plasma exchange or IVIg. If begun early in the course of myasthenic crisis, the transient increase in myasthenic weakness associated with initiating corticosteroids may prolong mechanical ventilation. When preceded by unequivocal improvement in strength after plasma exchange or IVIg treatment, long-term treatment with corticosteroids may begin with reduced risk for corticosteroid-related exacerbations.

In the context of myasthenic crisis, excessive dosing of cholinesterase inhibitors may superimpose a cholinergic crisis owing to depolarization blockade and result in increased weakness. Other symptoms of cholinergic crisis include muscle fasciculations and prominent muscarinic symptoms, including miosis, excessive lacrimation and salivation, abdominal cramping, nausea, vomiting, diarrhea, thick bronchial secretions, diaphoresis, and bradycardia. Cholinergic crisis is rare in contemporary series of myasthenic crisis,[70] and it is now common practice to avoid repeated dose escalations of cholinesterase inhibitors in impending myasthenic crisis and to discontinue the use of cholinesterase inhibitors after intubation to reduce muscarinic complications. When there is a question of cholinergic excess contributing to respiratory insufficiency, it is most prudent to discontinue all cholinesterase inhibitors, protect the airway, and support respiration as necessary.

Thymectomy may result in long-term improvement in patients with a suspected thymoma or with a life expectancy of more than 10 years. However, a patient in acute respiratory failure is generally considered a poor operative risk, and thymectomy is generally delayed until the patient's condition has improved.[86] Post-thymectomy pain control and ventilatory function may be improved by postoperative administration of epidural morphine.[87]

TABLE 54–3. DRUGS THAT MAY INCREASE WEAKNESS IN MYASTHENIA GRAVIS

- Neuromuscular blocking agents
- Selected antibiotics
  - Aminoglycosides, particularly gentamycin
  - Macrolides, particularly erythromycin and azithromycin
- Selected cardiovascular agents
  - Beta-blockers
  - Calcium channel blockers
  - Procainamide
  - Quinidine
- Quinine
- Corticosteroids
- Magnesium salts
  - Antacids, laxatives, intravenous tocolytics
- Iodinated contrast agents
- D-Penicillamine

NEUROMUSCULAR DISEASES SECONDARY TO CRITICAL ILLNESS AND ITS TREATMENT

Critical Illness Polyneuropathy

Critical illness polyneuropathy is a widespread axonal peripheral neuropathy that develops in the context of multiple organ failure and sepsis. This entity was recognized by several investigators in 1983[88-90] and has been further characterized in large part by Bolton and colleagues.[91,92] In a prospective series of 43 consecutive patients with sepsis and multiorgan failure, 70% developed electrophysiologic evidence of a sensorimotor axonal neuropathy and 15 patients developed difficulty weaning from mechanical ventilation as a consequence of the neuropathy.[93] Critical illness polyneuropathy is possibly the most common neuromuscular cause of prolonged ventilator dependency in patients without prior known neuromuscular disease.[94] Given the limitations to detailed clinical motor and sensory examinations in the setting of critical illness, the clinical features of critical illness polyneuropathy (extremity muscle weakness and wasting, distal sensory loss, and paresthesias) may not be recognized. Deep tendon reflexes are generally reduced or absent. In the setting of superimposed central nervous system insult with pyramidal tract dysfunction, however, deep tendon reflexes may be normal or increased.[95]

Electrodiagnostic studies are important in establishing a diagnosis of critical illness polyneuropathy, because the clinical findings may be unobtainable or indeterminate in this setting.[95] Nerve conduction findings include normal or near-normal conduction velocity and latency values and significantly reduced compound muscle action potential and sensory nerve action potential amplitudes. Needle electrode examination reveals denervation changes that are most marked in distal muscles, including fibrillation potentials, positive sharp waves, and reduced recruitment of motor unit potentials.[96] With recovery over time, the denervation potentials abate and the motor unit potentials become polyphasic and enlarged. Peripheral nerve histopathology has revealed widespread, primary axonal degeneration in distal motor and sensory fibers, and skeletal muscle has exhibited fiber-type grouping.[92]

Although the clinical history is usually adequate to distinguish between critical illness polyneuropathy and Guillain-Barré syndrome, the latter has developed in the context of recent surgery complicated by infection.[97] In some such instances, it may be necessary to differentiate between these two peripheral neuropathic disorders in a patient with extremity weakness and inability to wean from mechanical ventilation. Although only a few severe cases of critical illness polyneuropathy have been associated with facial weakness,[98] facial and oropharyngeal weakness are common in Guillain-Barré syndrome.[97] Dysautonomia and, occasionally, external ophthalmoplegia are also observed in Guillain-Barré syndrome but have virtually never been attributed to critical illness polyneuropathy.[98]

Electrophysiologic findings are also helpful in distinguishing these two disorders. Features of segmental demyelination may be observed in Guillain-Barré syndrome on nerve conduction studies (e.g., reduced conduction velocity, prolonged distal and F-wave latencies, conduction block, and temporal dispersion of compound muscle action potentials); these findings are not observed in critical illness polyneuropathy. Needle electromyographic findings may differ in that relatively less spontaneous activity is observed in clinically weak muscles within the first few days in Guillain-Barré syndrome.[96] Although electrophysiologic studies are quite helpful in demonstrating the classic, demyelinating form of Guillain-Barré syndrome, an electrophysiologic distinction between axonal forms of Guillain-Barré syndrome and critical illness polyneuropathy may not be reliable. The mean CSF protein level in Guillain-Barré syndrome is significantly higher than in critical illness polyneuropathy, although there is overlap between these populations.[96] Peripheral nerve histopathology may also distinguish between these two groups, because segmental demyelination and inflammatory changes may be observed in Guillain-Barré syndrome and are not seen in critical illness polyneuropathy.[92]

Although overall prognosis in critical illness polyneuropathy is dependent on recovery from the underlying critical illness, most patients who survive experience a functional recovery from the neuropathy within several months.[92] Critical illness polyneuropathy may prolong ventilator dependence, but it does not worsen long-term prognosis.[95] Proper positioning and padding are important to prevent compression neuropathies, because prognosis from superimposed compression neuropathies in the context of critical illness polyneuropathy is less favorable.[95]

The pathophysiology of critical illness polyneuropathy is unknown. No clear metabolic, drug, nutritional, or toxic factors have been identified,[92] although the severity of critical illness polyneuropathy has been correlated with the amount of time in the ICU, the number of invasive procedures, an increased glucose level, a reduced albumin level,[93] and the severity of multiple organ failure.[99] Given the common antecedents of multiple organ failure and sepsis in which significant release of various cytokines occurs, increased microvascular permeability has been postulated to ultimately result in axonal hypoxia and degeneration as a consequence of endoneurial edema.[100]

Prolonged Effects of Neuromuscular Blocking Agents

Prolonged neuromuscular blockade may occur with nondepolarizing agents, particularly when hepatic or renal function is impaired. In one study, administration of vecuronium for 2 or more consecutive days resulted in prolonged neuromuscular blockade and paralysis lasting from 6 hours to 7 days.[101] Although vecuronium is hepatically metabolized, patients with renal failure were susceptible to prolonged effects due to delayed excretion of the active 3-desacetyl metabolite. Acidosis and elevated serum magnesium levels were also associated with prolonged paralytic effects of vecuronium. A peripheral nerve stimulator may be used to monitor muscle twitch responses to a train of four stimuli during use of neuromuscular blocking agents. Drug dosage should be titrated to preserve one or two twitches to avoid overdosing. Two- to 3-hertz repetitive nerve stimulation studies may also be used to confirm neuromuscular blockade when it is suspected.

ACUTE QUADRIPLEGIC MYOPATHY

The syndrome known as acute quadriplegic myopathy[102] or acute myopathy of intensive care[103] was originally described in 1977 in a young woman who developed severe myopathy after treatment of status asthmaticus with high doses of corticosteroids and pancuronium.[104] Subsequent to that report, there have been numerous citations of an acute myopathy

developing in critically ill patients without preexisting neuromuscular disease. Acute quadriplegic myopathy has developed most frequently in the setting of severe pulmonary disorders, in which neuromuscular blockade is used to facilitate mechanical ventilation and high doses of corticosteroids are concurrently administered. In a majority of reported cases, myopathy developed when nondepolarizing neuromuscular blocking agents were used for more than 2 days.[102-112] The development of acute, necrotizing myopathy with myosin loss also occurs in patients receiving high doses of corticosteroids and hypnotic doses of propofol and benzodiazepines to induce paralysis.[113] This observation highlights the significance of high-dose corticosteroid exposure in the development of this syndrome and suggests that paralyzed muscles may be generally susceptible to the toxic effects of corticosteroids. The occurrence of acute quadriplegic myopathy after organ transplantation may be caused by the use of high doses of corticosteroids to prevent graft rejection along with perioperative exposure to neuromuscular blocking agents.[114] Although most cases of acute quadriplegic myopathy have been associated with critical illness, high doses of corticosteroids, and paralytic agents, acute quadriplegic myopathy has developed after isolated corticosteroid exposure,[102,115-118] isolated nondepolarizing neuromuscular blocking agent use,[112,116,119] or neither.[120] Factors that may impair neuromuscular transmission (e.g., hypermagnesemia, aminoglycoside exposure), factors that may slow the elimination of nondepolarizing neuromuscular blocking agents (e.g., hepatic or renal failure), and factors associated with critical illness (e.g., sepsis and acidosis) have also been associated with acute quadriplegic myopathy.[105]

In typical cases, a diffuse, flaccid quadriparesis with involvement of respiratory muscles and muscle wasting evolves after several days of induced paralysis. External ophthalmoparesis has rarely been noted.[121] Sensation remains intact, but deep tendon reflexes are reduced or absent. The creatine kinase level is commonly elevated, but this may not be observed if creatine kinase is measured well after the myopathy has developed. Although the paralysis may be quite severe and may necessitate or prolong mechanical ventilation, the prognosis from the myopathy itself is good, with functional recovery over several weeks to months.[107] Electromyographic findings include reduced amplitude of compound motor action potentials with normal sensory nerve action potentials and normal nerve conduction velocities. M-wave amplitude improvement accompanies clinical recovery.[112] Repetitive nerve stimulation studies may yield significant decremental responses while residual effects of nondepolarizing neuromuscular blocking agents or their active metabolites persist.[105,112] Needle electromyography often reveals small, low-amplitude, polyphasic motor unit potentials exhibiting early recruitment, sometimes along with positive sharp waves and fibrillation potentials.

A spectrum of muscle histologic changes may be observed, ranging from type II fiber atrophy and loss of adenosine triphosphatase (ATPase) reactivity in atrophic fibers to fiber necrosis in severe cases. However, the distinctive finding in most cases of acute quadriplegic myopathy is an extensive loss of thick filaments corresponding to myosin loss.[102,106,111,115,120] This finding may be demonstrated with immunohistochemical staining or electron microscopy. The increased expression of steroid receptors in denervated and immobilized muscle[122] may render these muscles susceptible to toxic catabolic effects of steroids.[102] Given the growing recognition of acute quadriplegic myopathy, the use of high doses of corticosteroids should be avoided, if possible, when neuromuscular blockade or induced paralysis is required.

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This prospective series identified a 70% incidence of polyneuropathy developing in patients with multiorgan failure and sepsis.

Chapter 55
TRAUMATIC BRAIN INJURY

Steven M. Cohen • Donald W. Marion

KEY POINTS

1. **Severe traumatic brain injuries** are the leading cause of morbidity and mortality for Americans between the ages of 1 and 45 years.
2. **Outcome following traumatic brain injury** is determined not only by the primary injury, such as skull fracture and subdural hematoma, but also by secondary injuries initiated by post-traumatic ischemia.
3. **Secondary brain injuries** are primarily responsible for the development of delayed intracranial hypertension.
4. The **goal of critical care management** of patients with severe traumatic brain injury is to enhance cerebral perfusion and avoid therapy that may cause regional cerebral ischemia.
5. **Early assessment and triage** of patients with severe traumatic brain injury should use the advanced trauma life support protocol prescribed by the American College of Surgeons Committee on Trauma.
6. **Patients with severe traumatic brain injury** are best managed at a level I trauma center with immediate neurosurgical availability.
7. **All patients with contusions or hematomas** visible on head computed tomography scans and Glasgow coma scale scores of 8 or less will benefit from intracranial pressure monitoring.
8. **A ventricular catheter coupled to an external strain-gauge transducer** is the optimal means of monitoring intracranial pressure because it provides accurate measurements and allows for CSF drainage—the most benign way of treating elevated intracranial pressure.
9. **Prophylactic hyperventilation therapy**, particularly when the intracranial pressure is less than 20 mm Hg, should be avoided.
10. **Patients with subdural hematomas or contusions** benefit from anticonvulsive prophylaxis for 7 days after injury.
11. **Early evaluation of brain-injured patients** by a physical therapist and rehabilitation specialist is highly recommended and allows for their rapid mobility.
12. **Patients with mild or moderate brain injuries**, particularly those with sports-related concussions, benefit from careful neuropsychological evaluation before returning to contact sports.
13. **Athletes who have persistent headaches and focal neurologic deficits** should not be allowed to return to play until these symptoms have subsided.

An estimated 5.3 million people in the United States currently live with permanent disabilities due to traumatic brain injury (TBI). In addition to the personal toll, the direct and indirect costs of these disabilities are estimated to exceed $4 billion annually.[1] Americans sustain an estimated 1.6 million TBIs each year. Approximately 270,000 require hospitalization; 52,000 die of their injuries, and 80,000 are left with severe neurologic impairments.[2] Another 760,000 are treated and released, and an additional 400,000 mild or moderate TBIs are thought to occur but never come to medical attention.[3]

TBI is the leading cause of morbidity and mortality for Americans between the ages of 1 and 45 years. Teenagers and the elderly are most at risk, although the primary causes vary demographically. Motor vehicle crashes are the main cause of head injuries in those 5 to 64 years old, whereas falls are most common in people aged 65 years and older. The primary cause of penetrating head injury is gunshot wounds. Males have twice the risk of TBI as females across all age groups.

TBI death rates in the United States fell 22% from 1979 to 1992, according to one study.[4] A substantial decline in motor vehicle–related fatalities was primarily responsible. At the same time, however, the incidence of gunshot wounds to the head rose, and in 1990, firearms surpassed motor vehicle crashes as the single largest cause of death due to TBI in some urban areas.

PATHOPHYSIOLOGY

Trauma to the head causes primary injury, such as skull fracture, cerebral contusion, and hemorrhage, that is a direct physical consequence of the impact. Hours or days after the traumatic incident, secondary injury usually occurs and may be a major determinant of the patient's ultimate neurologic outcome.

PRIMARY INJURY

Injury to the brain is caused by external forces to the head that strain the tissue beyond its structural tolerance.[5] These forces

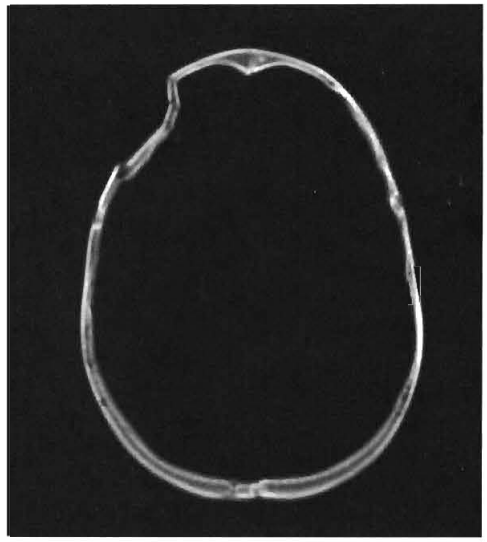


FIGURE 55–1. Right frontal depressed skull fracture caused by an assault with a hammer (axial CT scan, bone window).

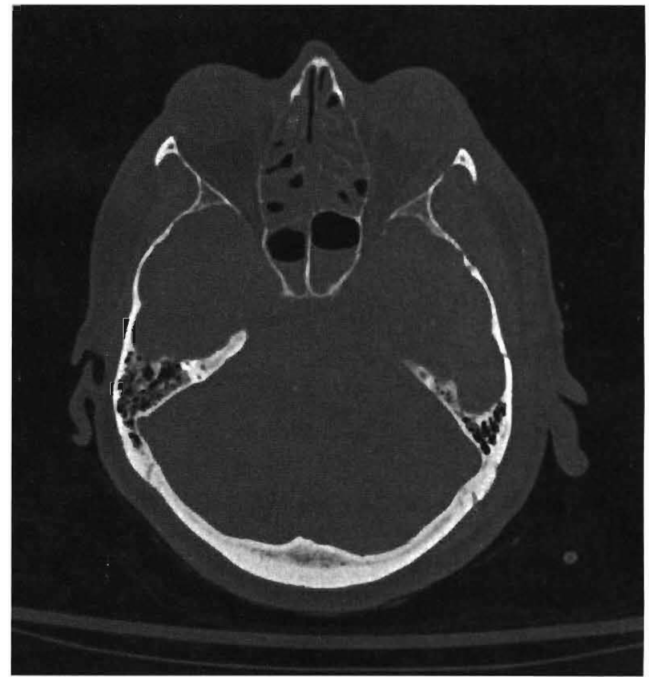


FIGURE 55–2. Basilar skull fractures through the anterior skull base typically cause cerebrospinal fluid rhinorrhea and tears in the adjacent dura. CT scans through the base of the skull may not show the fracture itself but often show fluid in the sphenoid sinus or the other paranasal sinuses (axial CT scan, bone window).

can be classified as contact or inertial.[6] Contact forces typically produce focal injuries such as skull fractures, contusions, and epidural or subdural hematomas. Inertial forces result from the brain undergoing acceleration or deceleration (translational, rotational, or both) and can occur without head impact. Inertial forces can cause focal or diffuse brain injuries: pure translational acceleration leads to focal injuries such as contrecoup contusions, intracerebral hematomas, and subdural hematomas, whereas rotational or angular acceleration, common with high-speed motor vehicle crashes, usually causes diffuse injuries. Although external signs of head injury, such as scalp abrasions, lacerations, and hematomas, are common with blunt-force trauma, the brain can also be severely injured solely by inertial forces, without accompanying scalp injuries.

Skull fracture results from a contact force to the head that is usually severe enough to cause at least brief loss of consciousness. Linear fractures are the most common type of skull fracture and typically occur over the lateral convexities of the skull. Most often, they are nondisplaced cracks in the skull, but a particularly intense impact can cause a gap (diastasis) between the edges of the fracture. A depressed skull fracture, in which skull fragments are pushed into the cranial vault, usually results from blunt force by an object with a relatively small surface area, such as a hammer (Fig. 55-1). The base of the skull can be fractured by severe blunt trauma to the forehead or the occiput. Basilar skull fractures are most common in the anterior skull base and often involve the cribriform plate, disrupting the olfactory nerves (Fig. 55-2). Posterior basilar skull fractures may extend through the petrous bone and internal auditory canal, thereby damaging the acoustic and the facial nerves.

Skull fractures per se are less detrimental than the associated damage to underlying tissues or vessels. For example, linear skull fractures that involve the squamous portion of the temporal bone are frequently accompanied by a tear of the middle meningeal artery, causing an epidural hematoma. Depressed skull fractures are often associated with contusions of the underlying brain tissue, and a scalp laceration overlying a depressed skull fragment can contaminate the fragment with bacteria from the scalp and hair. With a basilar skull fracture, the dura underlying the fracture is often disrupted, resulting in a cerebrospinal fluid fistula and leakage of cerebrospinal fluid from the nose or ear. Such fistulas allow bacteria to enter the intracranial space from the normally colonized nose, paranasal sinuses, or external auditory canal.

Common post-traumatic intracranial lesions are hemorrhage (epidural, subdural, and intraparenchymal), contusion, and diffuse brain injury. Subdural hematomas are seen in 20% to 25% of all comatose victims of TBI (Fig. 55-3). They develop between the surface of the brain and the inner surface of the dura and are believed to result from the tearing of bridging veins over the cortical surface or from disruption of major venous sinuses or their tributaries. The hematoma typically spreads over most of the cerebral convexity; the dural reflections of the falx cerebri prevent expansion to the contralateral hemisphere. Swelling of the cerebral hemisphere is common in those with subdural hematomas, given the associated damage to underlying brain tissue. Underlying cerebral contusions were found in 67% of patients with subdural hematomas in one series.[7] Subdural hematomas are classified as acute, subacute, or chronic, each having a characteristic appearance on computed tomography (CT): acute hematomas are bright white, subacute lesions are isodense with brain tissue and are therefore often overlooked, and chronic hematomas are hypodense relative to the brain.

Epidural hematomas develop between the inner table of the skull and the dura, usually when the middle meningeal artery or one of its branches is torn by a skull fracture. They occur in 8% to 10% of those rendered comatose by TBI.[8,9] The majority of epidural hematomas are located in the temporal or parietal regions, but they can also occur over the frontal or occipital lobes and, rarely, in the posterior fossa. They appear as hyperdense mass lesions on CT. Unlike subdural hematomas, their spread is limited by the suture lines of the skull, where the dura is very adherent. Because an

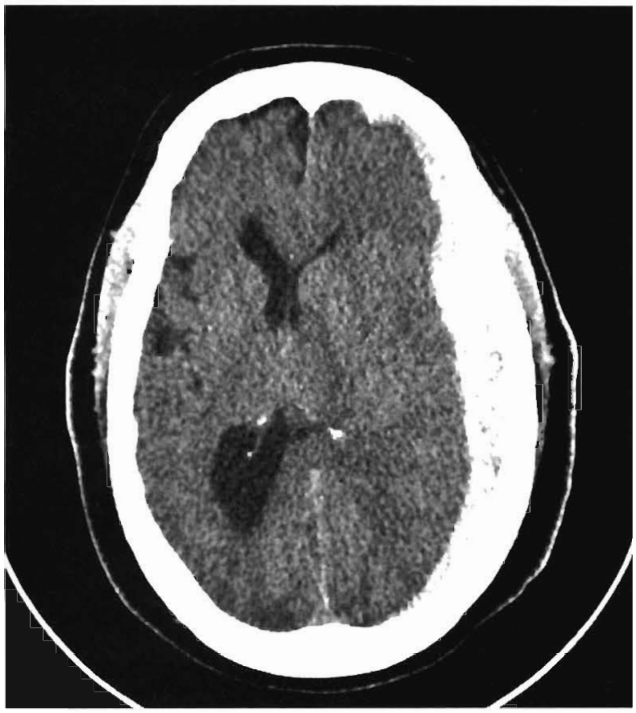


FIGURE 55–3. Acute subdural hematomas typically spread over the entire surface of the hemisphere.

epidural space normally does not exist, the clot must strip the dura from the inner table of the skull as it enlarges, resulting in its classic biconvex or lenticular shape (Fig. 55-4). Epidural hematomas are uncommon in infants and toddlers, presumably because their skulls are more deformable and less likely to fracture, and in TBI victims older than 60 years, because the dura is extremely adherent to the skull.

An intraparenchymal hematoma is a hemorrhage within the brain substance that occurs after a very severe TBI. It is usually associated with contusions of the surrounding tissue. Duret's hemorrhage, or hemorrhage into the base of the pons or midbrain, is thought to result from disruption of the perforating arteries at the time of uncal herniation. Such brainstem hemorrhage almost always leads to death or vegetative survival.

Though common after severe TBI, subarachnoid hemorrhage does not produce a hematoma or mass effect.[10] However, it may be associated with an increased risk for post-traumatic vasospasm.[11]

Contusions are heterogeneous lesions comprising punctate hemorrhage, edema, and necrosis and are often associated with other intracranial lesions. One or more contusions occur in 20% to 25% of patients with severe TBI. Because they evolve over time, contusions may not be evident on the initial CT scan or may appear as small areas of punctate hyperdensities (hemorrhages) with surrounding hypodensity (edema) (Fig. 55-5). Local neuronal damage and hemorrhage lead to edema that may expand over the next 24 to 48 hours. With time, contusions may coalesce and look more like intracerebral hematomas. Depending on their size and location, they may cause significant mass effect, resulting in midline shift, subfalcine herniation, or transtentorial herniation. Contusions are most common in the inferior frontal cortex and the anterior temporal lobes,[12] where the surface of the inner table of the skull is very irregular; they result from shifting of the brain over this irregular surface at the time of impact. Direct blunt-force trauma to the head can produce a contusion in the tissue underlying the point of impact (coup contusion). If the head was in motion upon collision with a rigid surface, a contusion may occur in the brain contralateral to the point of impact (contrecoup contusion).

Diffuse axonal injury refers to lacerations or punctate contusions at the interface between the gray and white matter. Such punctate contusions are thought to result from the disparate densities of the gray and white matter and the

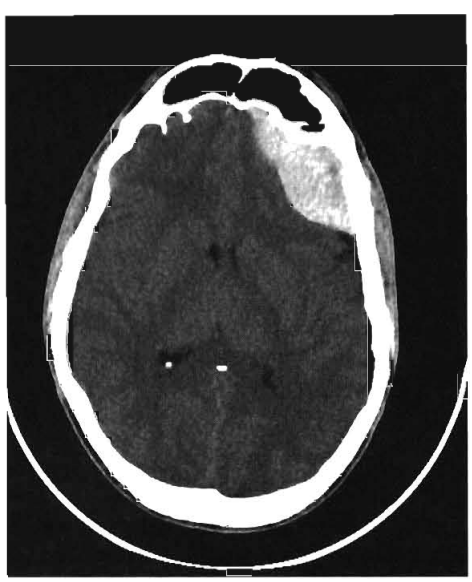


FIGURE 55–4. Epidural hematomas have a lens shape and a smooth inner border because they strip the dura from the inner table of the skull as they enlarge (axial CT scan).

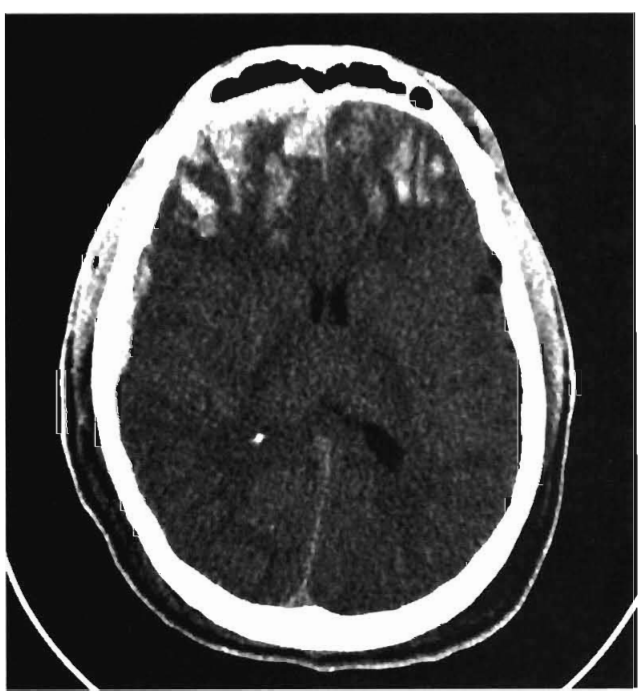


FIGURE 55–5. Contusions are most common in the inferior temporal and frontal lobes. In the first few hours after injury, they appear only as areas of hemorrhage mixed with edematous brain. Within 24 to 48 hours after injury, further hemorrhage may occur, causing significant enlargement of the contusion and hematoma (axial CT scan).

consequent difference in centripetal force associated with a rotational vector of injury.[13] Thus, diffuse axonal injury most often occurs after a high-speed motor vehicle crash, during which severe angular and rotational forces are applied to the head. Diffuse axonal injury was once thought to result solely from mechanical disruption at the time of impact; however, more recent research has identified cases in which the histologic footprints of diffuse axonal injury, such as fragmentation of axons and axonal swelling, do not appear until 24 to 48 hours after the incident, suggesting that some cases are a secondary manifestation of trauma.[14,15] Diffuse axonal injury is present in almost half of all patients with severe TBI and in one third of those who die, and it is a common cause of persistent vegetative state or prolonged coma.

Post-traumatic intracranial lesions cause neurologic dysfunction via direct and, in some cases, indirect mechanisms. By destroying brain tissue, contusions and intraparenchymal hemorrhage cause deficits directly related to the function of the damaged tissue. Uncal herniation is also an important mechanism of temporary or permanent neurologic deficits.[16,17] Semirigid dural reflections divide the intracranial contents into compartments. The tentorium cerebelli separates the anterior and middle cranial fossae from the posterior cranial fossa. The brainstem, specifically the midbrain, traverses an opening, the tentorial foramen, in the anterior central portion of this partition. The medial portion of the temporal lobe, the uncus, lies on both sides of the tentorial foramen. Because the most common TBIs, such as hematomas and contusions, are usually located over the lateral surfaces of the brain, and because the brain's extreme lateral surface is the rigid skull, such lesions tend to depress the brain medially. Therefore, a subdural hematoma over the surface of the temporal lobe or a hemorrhagic contusion of the temporal lobe itself is likely to displace the medial portion of the temporal lobe (uncus) into the tentorial foramen (i.e., uncal herniation). Such displacement compresses the midbrain, which contains neurons that are part of the reticular activating system. At the base of the midbrain is the crus cerebri, which contains pyramidal fibers from the cortex, and the third cranial nerve, which exits the midbrain through the interpeduncular cistern. Midbrain compression due to uncal herniation damages the reticular activating system, causing loss of consciousness; stretches the third cranial nerve and its associated parasympathetic fibers, causing pupil dilatation and loss of the light reflex; and injures the pyramidal fibers in the crus cerebri, causing abnormal posturing responses in the contralateral arm and leg.

Medial displacement of a cerebral hemisphere resulting from hemispheric swelling or a subdural or epidural hematoma also can cause herniation of the cingulate gyrus under the falx cerebri. Permanent neurologic dysfunction usually does not result, however.

Intracranial hypertension is a major cause of post-traumatic neurologic morbidity and mortality.[18] The intracranial pressure (ICP) is defined by the volume of cerebrospinal fluid, blood, and brain tissue in the cranial vault. The volume of these components is dynamic, and the brain can accommodate moderate changes in any of the three. For example, the blood volume can rise or fall by as much as 30% to 40%; cerebrospinal fluid absorption can increase to reduce the size of the ventricles by up to 90%; and brain tissue itself is compressible. Thus, the intracranial volume can gain 100 to 150 mL, equivalent to a moderate-sized subdural hematoma, without the ICP increasing significantly. When these buffering mechanisms have been exhausted, however, even a small increase in the size of a hematoma will cause a rapid rise in ICP. If appropriate treatment is delayed, the ICP may approach the mean arterial pressure (MAP), causing a hydrostatic block of blood flow to the brain and brain death. Intracranial hypertension, particularly if refractory to medical or surgical treatment, is the most common cause of death after severe TBI.

SECONDARY INJURY

Post-traumatic ischemia initiates a cascade of metabolic events that lead to the surplus production of oxygen free radicals,[19-21] excitatory amino acids,[22,23] cytokines,[24,25] and other inflammatory agents.[26] Glutamate and aspartate are the excitatory amino acids most commonly implicated in excitotoxic injury,[27] which is mediated by activation of *N*-methyl-D-aspartate, α-amino-3-hydroxy-5-methylisoazole-4-proprionic acid, or kainic acid receptors.[23] Overactivation of these receptors causes an excessive influx of ionized calcium into the cytosol, and elevated amounts of ionized intracellular calcium play a key role in neurodegeneration after injury to the central nervous system (CNS).[28,29] In addition, post-traumatic nonischemic events, such as an increase in intracellular free Ca^{++} via receptor-gated or voltage-dependent ion channels, induce the release of oxygen free radicals from mitochondria.[30] Excessive levels of highly reactive oxygen free radicals cause lipid peroxidation of cell membranes, oxidation of intracellular proteins and nucleic acids, and activation of phospholipases A_2 and C, which hydrolyze membrane phospholipids, thereby releasing arachidonic acid. The liberation of arachidonic acid triggers the generation of free fatty acids, leukotrienes, and thromboxane B_2, all of which are associated with neurodegeneration and poor outcome after experimental TBI.[31-33] Inflammatory cytokines, particularly interleukin (IL)-1, IL-6, and tumor necrosis factor, also are overproduced after TBI.[34-36] In animal models, post-traumatic activation of microglia is a principal source of these cytokines.[25] IL-1 and IL-6 provoke an exuberant cellular inflammatory response believed to be responsible for astrogliosis, edema, and tissue destruction.[26,37]

TBI also increases extracellular potassium levels,[38] leading to an imbalance of intracellular and extracellular K^+, disruption of the Na^+,K^+-ATPase cell membrane regulatory mechanisms, and subsequent cell swelling.[39,40] Astrocyte swelling has been attributed to the clearance of excessive extracellular K^+.[41] High levels of extracellular K^+ have also been implicated as the cause of widespread neuronal depolarization and spreading depression seen after experimental TBI.[27,38,42] Moreover, potassium stimulates increased oxygen uptake in glial cells, potentially depriving adjacent neurons of oxygen.[43,44] Severe TBI also causes a substantial decrease in extracellular magnesium (Mg^{++}) levels, thereby impairing normal glycolysis, cellular respiration, oxidative phosphorylation, and the biosyntheses of DNA, RNA, and protein.[45-47] Because Mg^{++} competes with Ca^{++} at voltage-gated cell membrane–associated Ca^{++} channels, reduced levels of Mg^{++} will result in an abnormal influx of Ca^{++} into the cell.

PREHOSPITAL CARE

The acutely injured brain is vulnerable to further damage from systemic hypotension, cerebral hypoperfusion, hypercarbia,

hypoxemia, and elevated ICP. Preventing these physiologic insults is crucial to limiting secondary brain injury. Care of the TBI victim always should begin with evaluating and securing a patent airway and restoring normal breathing and circulation. Early endotracheal intubation usually benefits comatose patients. Securing and maintaining an airway are essential to optimal oxygenation and ventilation, and early intubation has been found to reduce mortality after severe TBI.[48]

The airway is usually most easily and safely secured by orotracheal intubation, a method in which most emergency medical personnel are trained and experienced. Patients with severe maxillofacial trauma may require nasotracheal intubation, but this is less desirable because it is a relatively blind procedure; the nasal passageways can be irritated, causing blood pressure and ICP to surge; and, in those with severe anterior skull base fractures, the tube can inadvertently be passed into the brain. A third alternative for securing the airway is the laryngeal mask airway, an easily learned and rapidly applied device that has undergone successful field trials.[49] However, it does not protect against aspiration and cannot be used to achieve high airway pressures. A surgical airway (cricothyroidotomy) should be performed only after other attempts to secure an airway have failed, and only by an experienced provider.

The patient should be sedated and pharmacologically paralyzed before intubation, because irritation of the oropharynx typically causes transient hypertension, tachycardia, increased ICP, and agitation that can interfere with the procedure. Fentanyl, a short-acting opioid agonist that produces analgesia and sedation, is the most commonly used sedative. The usual dose is 3 to 5 μg/kg body weight, administered intravenously 3 minutes before intubation. Etomidate, an alternative to opioids, provides adequate sedation and is less likely to cause hypotension. Some prefer thiopental because it is an ultra-short-acting barbiturate and is thus less likely to conceal the neurologic status when the patient reaches the trauma center; however, it is more likely than other agents to cause hypotension. Neuromuscular blocking agents commonly used for endotracheal intubation include succinylcholine (1.5 mg/kg i.v.), which has the advantages of rapid onset, complete reliability, and very short duration of action. This last attribute is particularly important in the prehospital setting, where attempts at intubation sometimes fail. Vecuronium (0.01 mg/kg i.v.), an alternative paralytic agent, offers the theoretical advantage of being a nondepolarizing muscle relaxant. Because it has a relatively long duration of action (1 to 2 hours), however, it is less forgiving of failed intubation attempts. Table 55-1 shows a recommended rapid-sequence intubation pathway.

TABLE 55–1. RECOMMENDED RAPID-SEQUENCE INDUCTION FOR SEVERELY HEAD-INJURED PATIENTS

1. Preoxygenation
   100% oxygen for 5 min or four vital capacity breaths
2. Pretreatment
   Fentanyl (3 to 5 μg/kg i.v.)
3. Wait 2 to 3 min if possible
   Continue preoxygenation
4. Paralysis and sedation
   Succinylcholine (1.5 mg/kg i.v.)
5. Intubation with in-line cervical spine immobilization
6. Positive-pressure ventilation and possibly reparalysis with vecuronium if prolonged transport time is anticipated

Supplemental oxygen should be provided before and immediately after intubation. Ventilatory rates of 10 to 12 breaths per minute for adults, 20 breaths per minute for children, and 25 breaths per minute for infants should supply adequate oxygenation.[2] Therapeutic hyperventilation is inadvisable unless neurologic deterioration is clearly evident during evaluation and transport. Aggressive hyperventilation can cause cerebral vasoconstriction, reducing already low cerebral blood flow (CBF) and potentially causing or exacerbating cerebral ischemia.

Rapid fluid resuscitation and restoration of a normal blood pressure are critical in the prehospital setting, because hypotension has been associated with doubling of the mortality rate after severe TBI.[50] The most likely cause of hypotension is hemorrhage, usually in the abdomen or chest; therefore, hypovolemia should be assumed. Lactated Ringer's or normal saline solutions should be infused through a large-bore intravenous catheter as quickly as possible until normotension is achieved. Although preclinical studies suggest that hypertonic saline may be more effective than isotonic solutions for rapid volume resuscitation,[51,52] results of several small clinical trials have not been convincing.[53,54]

In all cases of severe TBI, defined as a Glasgow coma scale (GCS) score of 3 to 8 and an inability to follow commands, patients should be treated as if they have a spinal fracture until an adequate examination of the spine proves otherwise. Among those who survive long enough to reach the emergency department, the likelihood of a cervical spine fracture is 2% to 6%. More troubling, however, is that an estimated 10% to 25% of all post-traumatic spinal cord injuries are iatrogenic, occurring during transport to the hospital.[55] After respiratory and hemodynamic stabilization, the patient should be placed in a neutral position on a flat, hard surface. If the patient requires immediate endotracheal intubation, it should be performed while another person provides in-line cervical spine immobilization. A rigid cervical spine collar should be placed as soon as possible. Next, the patient should be placed on a backboard; the cervical spine can then be further immobilized with a buttress of foam or towels placed on both sides of the head. To prevent any movement during transport, the patient should be strapped to the board in several locations.

The organization of emergency medical services and regional trauma programs has improved outcomes for victims of trauma, particularly those with severe TBI.[56] Designation as a level I or II trauma center by the American College of Surgeons Committee on Trauma or a state health department ensures the availability of immediate neurosurgical care when the patient arrives. Therefore, every effort should be made to transport severely injured patients directly to a designated trauma center. Nonetheless, if an adequate airway or venous access cannot be obtained in the field, some patients may need to undergo respiratory or hemodynamic stabilization at a nearby emergency department en route to the trauma center.

EMERGENCY DEPARTMENT CARE

Upon arrival at the trauma center, the emergency medical personnel should concisely report their prehospital assessment and management, including mechanism of injury, stabilizing maneuvers, medications given, initial vital signs, GCS score, and hemodynamic stability during transport. A thorough physical and radiographic examination to identify all

life-threatening injuries should then be performed. Most trauma centers follow the Advanced Trauma Life Support protocol, a comprehensive routine that has proved successful in quickly detecting all major injuries.[57] First, the airway is reassessed, and the need for endotracheal intubation is carefully reconsidered. For patients intubated in the field, proper placement of the endotracheal tube is verified both clinically and radiographically. When the airway is secure and adequate oxygenation is confirmed using a percutaneous oxygen saturation monitor or arterial blood gas analysis, two large-bore intravenous catheters are inserted to provide sufficient venous access for high-volume fluid resuscitation. An isotonic saline solution is infused to continue volume replacement, which probably began at the scene. Any life-threatening injuries, such as overt hemorrhage, tension pneumothorax, or cardiac tamponade, should be treated immediately upon discovery. A brief neurologic examination is performed, including assessment of the GCS score (Table 55-2), pupillary size and reaction to light, and symmetry and extent of extremity movements. The head is palpated to detect fractures, lacerations, or penetrating wounds, and lacerations are probed gently to ascertain the presence of a depressed skull fracture or foreign body. Large lacerations are compressed with pressure dressings or temporarily sutured to prevent further hemorrhage. Careful inspection of the head should reveal hemotympanum, periorbital or mastoid ecchymosis, and cerebrospinal fluid rhinorrhea or otorrhea.

Oxygen saturation is monitored continually, and blood pressure is measured frequently during this primary examination. A Foley catheter is placed to help monitor the fluid status, and an orogastric tube is inserted and connected to suction to decompress the stomach. Blood specimens are obtained and analyzed for glucose, electrolytes, complete blood count, platelets, prothrombin and partial thromboplastin times, and International Normalized Ratio. Type and crossmatch of a blood specimen should be considered, and an arterial blood gas obtained. Serum and urine toxicology screens are advisable if alcohol or substance abuse is suspected, and women of childbearing age should undergo a pregnancy test.

TABLE 55–2. GLASGOW COMA SCALE

Speech	Points
Alert, oriented, and conversant	5
Confused, disoriented, but conversant	4
Intelligible words, not conversant	3
Unintelligible sounds	2
No verbalization, even with painful stimulus	1
Eye Opening	
Spontaneous	4
To verbal stimuli	3
To painful stimuli	2
None, even with painful stimuli	1
Motor	
Follows commands	6
Localizes painful stimulus	5
Withdraws from painful stimulus	4
Flexor posturing with central pain	3
Extensor posturing with central pain	2
No response to painful stimulus	1

From Teasdale G, Jennett B: Assessment of coma and impaired consciousness: A practical scale. Lancet 1974;2:81-84.

The initial x-ray evaluation is usually performed in the trauma bay during the primary survey and includes chest, pelvis, and lateral cervical spine films. If the lower cervical spine is not visible on the lateral cervical spine film, a swimmer's view can be obtained, or this area can be imaged with axial CT.

After all life-threatening injuries have been identified and stabilized, the immediate concern is whether the patient requires a craniotomy to evacuate an intracranial mass lesion. A CT scan of the head should be performed, at intervals of 10 mm or less, from the C2 vertebra to the vertex. In addition to post-traumatic intracranial lesions, the scan should be examined for brain swelling, patency of the basal cisterns, and other characteristics that will guide subsequent treatment. If no surgical intracranial mass lesion is evident on the scan of the head, CT scans of the chest and abdomen can be performed to detect occult hemorrhage in these cavities. If a surgical mass lesion is seen on the head CT scan, however, it should be evacuated immediately, postponing any other imaging studies. Diagnostic peritoneal lavage is often performed during the craniotomy to detect abdominal bleeding. Conversely, if hemodynamic instability necessitates an emergent laparotomy or thoracotomy before a head CT scan can be obtained, several diagnostic procedures can be performed in the operating room to confirm a suspected intracranial injury. These procedures include an air ventriculogram or diagnostic burr holes and are most appropriate if the patient has lateralizing neurologic deficits, particularly a unilateral fixed and dilated pupil.

An air ventriculogram can detect most large hematomas. With the patient in the supine position, a right coronal ventriculostomy is inserted, and an anteroposterior radiograph of the skull is obtained. Just before the x-ray is performed, 3 mL of air is injected into the ventricles. The air outlines the ventricles on the film; a distorted or shifted outline suggests the presence and location of a hematoma.

An alternative to air ventriculography is the placement of diagnostic burr holes. The first burr hole should be placed over the temporal lobe ipsilateral to the dilated pupil. If no clot is detected, burr holes can be placed over the frontal and parietal lobes. If a hematoma is encountered, the burr hole is enlarged to a craniotomy, and the clot is evacuated.

DEFINITIVE TREATMENT

Critical to determining the severity of the brain injury and the appropriate treatment are CT findings combined with a reliable post-resuscitation GCS score and assessment of pupil size and reactivity. In the case of an acute subdural hematoma, for example, a patient with a moderate-sized lesion who has normal pupil size and reactivity and is able to follow commands might safely be treated nonoperatively. Conversely, surgery is unlikely to benefit an elderly patient with fixed and dilated pupils and a GCS score of 3 or 4, regardless of the CT findings. Other determining factors include the size and location of the hematoma, the presence and extent of an underlying contusion or brain swelling, and the results of the neurologic examination. Neurologic deterioration, particularly a decline in mental status, suggests enlargement of the hematoma, and a new CT scan should be obtained promptly. Hematomas less than 10 mm thick that cause a midline shift of less than 5 mm can usually be observed, especially if they do not involve the middle cranial fossa.[58] If nonoperative management is chosen for an intracranial hematoma, the

patient should be monitored with frequent neurologic assessments in the ICU. If the patient cannot follow commands, ICP monitoring is recommended.

The classic presentation of a patient with an epidural hematoma is a period of unconsciousness immediately after impact to the head, followed by a so-called lucid interval in which consciousness returns for a few minutes to an hour or more before the patient lapses into a coma. This lucid interval actually occurs in less than one third of patients with epidural hematomas, however; most either remain conscious after the injury (smaller clots) or remain comatose.

A hematoma that compresses the temporal lobe is particularly ominous and can rapidly cause uncal herniation with minimal enlargement. Thus, such lesions warrant a lower threshold for evacuation compared with hematomas in other locations. If the clot is small enough not to require evacuation, it should be monitored with frequent CT scans during the first several days after injury. Enlarging middle fossa hematomas, even those large enough to cause herniation, do not always cause an increase in the ICP; therefore, ICP monitoring should not be relied on to follow their status.

The initial signs and symptoms of contusions vary greatly, depending on their size and location and the presence of other associated lesions. A small contusion may cause only a headache or no symptoms at all. If located in an eloquent area of the brain, such as the speech or motor areas, it may cause focal neurologic symptoms. Larger contusions, especially those involving the frontal lobes, typically cause elevated ICP and coma. Patients with small or deep-seated contusions without mass effect initially can be managed nonoperatively. The contusion should be followed closely with serial CT scans, however, because there is a 20% to 30% risk that the contusion will enlarge during the next 24 to 48 hours. The ICP should be monitored if the patient cannot follow commands. As with hematomas in the middle cranial fossa, contusions of the temporal lobes should be closely watched with CT scans. A temporal contusion can enlarge to the point of uncal herniation without a significant rise in ICP; thus, the threshold for evacuation of these lesions should be low (Fig. 55-6). Unilateral frontal or temporal lobectomies are usually well tolerated, do not cause measurable neurologic deficits, and provide space for further brain swelling.

In the ICU, the primary goal is to prevent cerebral ischemia and thereby limit secondary brain injury. The most common preventable causes of cerebral ischemia are hypotension, hypoxia, and intracranial hypertension. Thus, comprehensive physiologic monitoring should be performed so that these physiologic insults can be detected and treated promptly.

PHYSIOLOGIC MONITORING

Continual monitoring of the end-tidal partial pressure of carbon dioxide (PCO_2) and frequent analyses of arterial blood gases enable the early detection of deteriorating ventilatory status, which should prompt appropriate ventilator adjustments. Oxygen saturation should also be monitored continually with pulse oximetry. Blood pressure monitoring is best accomplished with an indwelling arterial catheter coupled to a pressure transducer. The catheter is usually inserted into the radial artery and can also be used to obtain arterial blood samples for blood gas analysis. Hypovolemia is a common cause of post-traumatic hypotension. It can result from overt hemorrhage, which is usually detected soon after injury; from occult hemorrhage, which may not be recognized for several hours or days; or from soft tissue inflammation and swelling. Consequently, central venous pressure monitoring should be considered for patients with severe TBI, particularly those with significant non-CNS injuries. Indwelling subclavian or internal jugular venous catheters are used, coupled to pressure transducers. In elderly patients or those with severe pulmonary contusions, intravascular volume may be more accurately assessed by pulmonary artery catheterization with a Swan-Ganz catheter. Monitoring urine output with an indwelling Foley catheter is essential for determining the patient's fluid status.

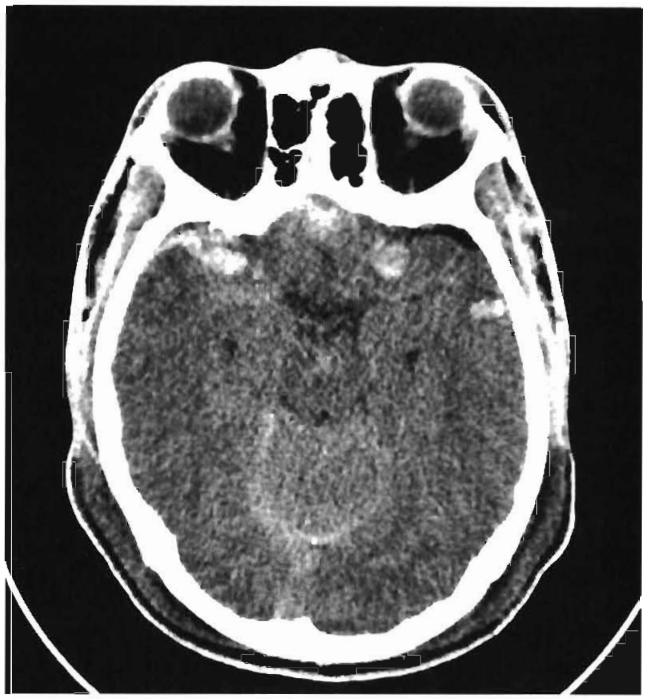


FIGURE 55–6. Temporal lobe contusions must be monitored closely, because even a slight enlargement can cause uncal herniation, often without an increase in intracranial pressure (axial CT scan).

Continuous ICP monitoring is essential for all patients who have severe TBI and abnormal CT findings, because intracranial hypertension develops in 53% to 63% of such patients.[59] ICP monitoring is also recommended for comatose patients who are older than 40 years and have unilateral or bilateral motor posturing or a systolic blood pressure less than 90 mm Hg, even if no abnormalities are seen on the initial CT scan.[60] The gold standard for ICP monitors is the ventricular catheter, coupled to an external strain-gauge transducer.[61] It is accurate, reliable, and far less expensive than newer self-contained pressure-sensing devices. In addition, ventricular pressure is considered more reflective of global ICP than is subdural, subarachnoid, or epidural pressure. Catheters placed in these extracerebral spaces are more prone to occlusion and, owing to the effects of compartmentalization, typically record a pressure that is lower than the global ICP. Other advantages of the ventriculostomy method of ICP monitoring are that the system can be rezeroed after insertion, which is not possible with most of the newer self-contained devices, and cerebrospinal fluid can be withdrawn to treat intracranial hypertension. The overall complication rate for ventricular ICP monitoring is 7.7% (infection, 6.3%; hemorrhage, 1.4%),[59] and some studies

indicate that the infection rate increases significantly when a catheter remains in place for more than 5 days.[62]

Alternatives to the ventriculostomy technique have been developed that provide relatively accurate measurements of global ICP, are easier to insert, and may cause fewer complications. They include devices that contain a pressure-sensing transducer (either strain-gauge or fiber-optic technology) within the tip of the catheter.[61] These pressure sensors provide reliable ICP measurements even if they are inserted into the white matter and are often used when a ventricular catheter is difficult to insert because of small or collapsed ventricles. The primary disadvantage is that cerebrospinal fluid drainage is not possible. In addition, these devices can be calibrated only once, before insertion, and with some of them, measurement drift is as much as 1 to 2 mm Hg per day.

The cerebral perfusion pressure (CPP), defined as the difference between MAP and ICP, is a calculated physiologic measurement that is used to describe actual cerebral perfusion. Some have suggested that maintaining the CPP above a certain threshold is more important than any particular MAP or ICP.[63]

Devices that monitor the oxygen partial pressure (PO_2) of brain tissue can be used to determine whether cerebral oxygenation is adequate. These monitors continually measure the tissue PO_2 in the small region of brain into which they are inserted. The probes have been found to be very sensitive to changes in arterial PO_2 and PCO_2, as well as to medically induced or physiologic changes that may cause focal cerebral ischemia.[64] Although no methods are available for continuously monitoring global CBF, transcranial Doppler insonation of the middle cerebral arteries can provide indirect information. Positron emission tomography or CBF measurements with xenon, either as a radiolabeled agent or as a CT contrast medium, can provide periodic snapshots of the blood flow.

MEDICAL TREATMENT

Hypoxia is best avoided with the use of endotracheal intubation and mechanical ventilation. The fraction of inspired oxygen should be titrated to provide an arterial PO_2 of 100 mm Hg. Maintaining an arterial PCO_2 of approximately 35 mm Hg is advised to avoid the cerebral vasoconstriction associated with aggressive hyperventilation. A form of acute respiratory distress syndrome (ARDS) can develop in patients with severe chest injuries. In such cases, adequate oxygenation requires the use of positive end-expiratory pressure (PEEP). Concern has been raised that the use of PEEP in patients with TBI may increase the ICP. However, clinical studies have shown that, in the presence of ARDS, up to 14 to 15 cm H_2O of PEEP can be used without measurable changes in ICP, most likely because ARDS significantly reduces pulmonary compliance.

Hypotension, defined as a MAP of less than 90 mm Hg, should be treated aggressively. Normovolemia should be restored by infusing isotonic saline as needed to achieve a central venous pressure of 7 to 12 cm H_2O. Hypotonic intravenous solutions can exacerbate cerebral edema and should be avoided. If the patient is anemic, packed red blood cells should be transfused to restore the hematocrit to at least 30%. If hypotension is refractory to volume resuscitation, the patient should be given a continuous intravenous infusion of a vasopressor medication, with the dose titrated to raise the MAP above 90 mm Hg. Dopamine and norepinephrine are the preferred vasopressor agents.

Although some advocate the used of induced hypertension to raise the CPP above 70 mm Hg, particularly if the ICP is elevated and difficult to reduce,[65] others do not support this practice. A prospective, randomized clinical trial of patients with TBI compared a group whose CPP was kept above 70 mm Hg via induced hypertension with a group whose CPP was allowed to drift to 60 mm Hg.[66] Six-month clinical outcomes did not differ between the two groups. Moreover, the group whose CPP was kept above 70 mm Hg required more vasopressor agents and had a significantly higher incidence of ARDS and other pulmonary complications. Others have found that the brain tissue PO_2 in patients with TBI typically does not fall until the CPP drops below 60 mm Hg.[67] Based on these findings, the current recommendation is to maintain a CPP above 60 mm Hg.

Intracranial hypertension is defined as sustained ICP greater than 20 mm Hg. Several clinical studies have found that mortality and morbidity increase significantly when the ICP persistently remains above this threshold.[68] Based on this association and the widely accepted premise that elevated ICP can compromise cerebral perfusion and cause ischemia, the aggressive treatment of intracranial hypertension is almost uniformly endorsed. Before beginning therapy for intracranial hypertension, however, medical or physiologic conditions that can increase ICP should be considered and, if present, treated. These include seizures, fever, jugular venous outflow obstruction (e.g., poorly fitting cervical collars), and agitation.

Several medical and surgical options are available to reduce ICP. Depending on the type of brain injury, some may be more effective than others, and each is associated with potential adverse effects. A stepwise approach is usually followed, with the least toxic therapies being tried first and more toxic therapies added only if the initial treatment is unsuccessful. Sedation and pharmacologic paralysis are often an effective first treatment, particularly if the patient is agitated or posturing. A narcotic, such as morphine or fentanyl, is used for sedation, and vecuronium bromide is the paralytic agent. Narcotic-induced hypotension can be averted by using relatively low doses and ensuring that the patient is normovolemic before treatment. Because the ability to obtain an accurate GCS score is lost during this treatment, the pupil status, ICP, and CT scans must be closely monitored.

If intracranial hypertension is refractory to sedation and paralysis, intermittent ventricular cerebrospinal fluid drainage is used. Intermittent rather than continuous drainage enables reliable measurement of the ICP. If these measures fail to reduce the ICP, a bolus administration of mannitol is recommended (0.25 to 1 g/kg every 3 to 4 hours as needed). This osmotic diuretic lowers ICP and increases CPP by expanding the blood volume, reducing the blood viscosity, and increasing CBF and oxygen delivery to the tissues within a few minutes of infusion. Its duration of effect averages 3 to 5 hours. Continuous infusion is less desirable than bolus infusion, because the former is more likely to lead to extravasation of the drug into brain tissue, causing a reverse osmotic gradient and increased edema and ICP.[69] The serum osmolarity and sodium level should be monitored frequently during mannitol administration; to minimize the risk of acute tubular necrosis and renal failure, the drug should be discontinued if the serum sodium level exceeds 160 mg/dL or the osmolarity exceeds 320 mOsm. The intravascular volume should also be closely monitored to prevent dehydration.

If, despite these measures, the ICP remains above 20 mm Hg, the ventilatory rate can be adjusted to reduce the arterial PCO_2 to 30 mm Hg. Hyperventilation should be used cautiously during the first 24 to 48 hours after injury, however, because it will cause cerebral vasoconstriction at a time when CBF is already critically reduced. Recent evidence also suggests that even brief periods of hyperventilation can lead to secondary brain injury by causing an increase in extracellular lactate and glutamate levels.[70] Prophylactic hyperventilation is always contraindicated in the absence of elevated ICP.[71] If hyperventilation is used, the brain tissue PO_2 or jugular venous oxygen saturation should be monitored to detect any cerebral ischemia that the treatment might cause. The risk of tissue ischemia and poor outcome may increase if the brain tissue PO_2 falls below 10 mm Hg.[67]

If intracranial hypertension persists despite all these treatments, particularly if the ICP rises rapidly or if the patient's initial CT scan showed a small contusion or hematoma, another CT scan should be obtained immediately to determine whether there is a new mass lesion or a preexisting lesion has enlarged. Even if the lesion has enlarged only slightly, an emergent craniotomy and evacuation of the contusion or hematoma may be the best way to reduce the ICP quickly and effectively.

If the CT scan does not reveal an intracranial mass lesion requiring surgery, the next recommended treatment for intracranial hypertension is high-dose barbiturates. Barbiturates are thought to be effective by reducing cerebral metabolic demand and blood flow, and preclinical studies suggest significant cerebral protective effects.[72] Pentobarbital is the most commonly used drug for this purpose and is administered as an intravenous loading dose of 10 to 15 mg/kg over 1 to 2 hours, followed by a maintenance infusion of 1 to 2 mg/kg per hour. The dose can be increased until intracranial hypertension subsides or MAP begins to fall. Some recommend continuous electroencephalographic monitoring while increasing the dose until a burst suppression pattern is observed. Hypotension, the most common adverse effect of barbiturates, can usually be averted by ensuring a normal intravascular volume before administering the drug.

Only a few options remain when intracranial hypertension is recalcitrant to all these measures, and they are controversial and not uniformly embraced. Therapeutic moderate hypothermia has been used in several clinical trials over the past decade. The body temperature is lowered to 32°C to 33°C as soon as possible after injury and kept at that temperature for 24 to 48 hours using surface cooling techniques. Although some clinical trials have not found that this treatment improves neurologic outcome compared with normothermia, they have consistently shown that hypothermia significantly reduces ICP. Moreover, hypothermia does not cause significant medical complications when used for no longer than 48 hours.

Some advocate the use of decompressive craniectomies, such as large lateral or bifrontal bone flaps, with or without a generous temporal or frontal lobectomy. In one study of patients with severe TBI, 6-month outcomes were similar for a group that had large decompressive craniectomies and a group that did not, even though the craniectomy group had lower initial GCS scores and more severe radiographic injuries.[73] Importantly, the craniectomy group did not have a higher incidence of persistent vegetative state. Two studies reported good outcomes in 56% to 58% of patients whose refractory intracranial hypertension was treated with decompressive craniectomy as a last resort,[74,75] and another study suggested that decompressive temporal lobectomy, when performed soon after injury, improves the outcome for young patients.[76] However, others found that decompressive craniectomy does not improve ICP, CPP, or mortality rates.[77] The decision to perform decompressive surgery should take into account the patient's ultimate prognosis. Because age has such a profound impact on the likelihood of a meaningful recovery, these therapies are recommended only for patients who are younger than 40 years old.

Patients who have TBI, particularly those who are comatose or have significant non-CNS injuries, are at high risk for pneumonia and other infections, fever, malnutrition, seizures, deep venous thrombosis, pulmonary embolism, and other maladies endemic to the ICU. Most of these complications cause secondary brain injury and should be diagnosed and treated without delay. Fever is very common in the ICU and occurs in more than 90% of patients who are there for 10 days or more.[78] Preclinical studies have found that there is a log increase in neuronal death in ischemic brain regions for every degree of brain temperature above 39°C,[79,80] and this effect is observed for 24 hours or more after injury.[81] Clinical studies of TBI patients have shown that the brain temperature is often 1°C to 2°C higher than body temperature.[82] Consequently, the body temperature should be kept below 37°C at all times, and infectious or other causes of fever should be aggressively sought and treated.

Patients who are comatose, those being kept pharmacologically paralyzed, and those with pelvic or long bone fractures are at high risk for deep venous thrombosis and pulmonary embolism. They should receive early prophylaxis, which typically includes the use of lower extremity sequential compression devices as well as subcutaneous heparin or enoxaparin. The early (2 to 3 days after injury) use of mini-dose heparin or low-molecular-weight heparin is safe and has not been found to cause or worsen intracranial hemorrhage after TBI.[83,84]

Malnutrition is also common after severe TBI. The resting metabolic expenditure typically increases by 140% in a nonparalyzed patient with severe TBI.[85] Branched chain amino acids from muscle protein are used preferentially for energy metabolism, potentially compromising the effectiveness of physical therapy. Nitrogen wasting is also increased, with excretion of as much as 9 to 12 g/day. Thus, early enteral or parenteral feeding is advisable, with the aim of providing at least 140% of the daily basal metabolic caloric requirements by the third or fourth day after injury.[86] A normal-sized adult patient usually needs 2000 to 3000 kcal/day. Because parenteral feeding increases the risk of infection, enteral administration is preferable. For a patient expected to be in a prolonged coma, a surgical jejunostomy provides a convenient and well-tolerated route to administer tube feeding.

Post-traumatic contusions and subdural hematomas are well-known causes of generalized seizures. Anticonvulsant prophylaxis, usually with phenytoin, is therefore recommended for patients with these lesions. The drug should be given for the first 7 days after injury; a prospective clinical trial found no advantage to longer prophylactic treatment.[87] A common side effect of phenytoin is fever; this should be considered if infectious causes of fever have been ruled out. If a patient has seizures, especially if they are prolonged, the associated cerebral hypermetabolism will cause secondary brain injury; seizures should thus be treated aggressively,

up to and including the use of general anesthesia if necessary. Seizures may not be readily evident in patients undergoing pharmacologic paralysis for the treatment of intracranial hypertension, because tonic-clonic extremity movements are absent. Such patients should receive anticonvulsant prophylaxis, and continuous electroencephalographic monitoring should be considered. Clinically silent seizures are a possible cause of abruptly deteriorating cerebral oxygenation or a sudden increase in ICP, but enlarging intracranial mass lesions remain the most likely cause.

PHYSICAL THERAPY AND REHABILITATION

The number of survivors of TBI is increasing due to greater success in understanding and treating the disease and improved motor vehicle safety devices. Accordingly, the demand for high-quality, well-organized TBI rehabilitation programs is also increasing. The primary goal of these programs is to reintegrate patients into their communities by either restoring normal or near-normal ability to function or teaching them alternative strategies to function well despite their disabilities. Such programs should involve a multidisciplinary team of physical, occupational, and speech therapists; neuropsychologists; and social workers, ideally coordinated by a physiatrist or a neurologist with special training in physical medicine and rehabilitation. The team should be experienced in TBI rehabilitation and thoroughly understand the special needs of these patients. Programs that focus exclusively on TBI rehabilitation are far preferable to those that mix patients with TBI, stroke, neurodegenerative diseases, and tumors, because the typical age groups are very different, as are their rehabilitative needs.

Rehabilitation of TBI patients should begin in the ICU during the first few days after injury, with the consultation of a physiatrist and passive range-of-motion exercises of the extremities. Mobilization helps prevent deep venous thrombosis, and studies indicate that early sitting of comatose patients may hasten the return of consciousness. Supplementing physical therapy with central neurostimulant medications is being investigated for those with more severe injuries and minimal responsiveness.[88] Rehabilitation after a TBI entails many other factors that are critical to optimizing outcome, but a thorough review is beyond the scope of this chapter.

PENETRATING INJURIES

Gunshot wounds to the head, the predominant cause of penetrating head injury, usually cause massive destruction of brain tissue, severe brain swelling, and death. The wounding potential of a bullet depends primarily on its velocity at impact and its mass, although the shape of the bullet and its lateral movements also play a role. The relationship of bullet mass and velocity to the energy imparted to the head is described by the equation $KE = {}^1/_2MV^2$, where KE is kinetic energy, M is the mass of the bullet, and V is the impact velocity of the bullet. According to this equation, the impact velocity is by far the most important determinant of a bullet's wounding potential. Consequently, high-velocity rifle wounds to the head are invariably fatal, whereas low-velocity open-chambered handgun wounds often are not. When a bullet enters the skull, it creates a variety of pressure waves within the brain, some of which can cause tissue pressures of nearly 100 atmospheres, resulting in further tissue injury. In addition to forward velocity, the bullet's lateral motion before and after impact affects the severity of tissue destruction. Such motion is described as yaw, or the angle between the bullet's path of flight and its long axis, and precession and nutation, which are circular rotations of the bullet around the center of its mass. These movements increase the bullet's relative surface area at the point of impact and enable it to pass more of its kinetic energy to the surrounding tissue. They increase the size of the entrance wound and cause greater cavitational injury. Bullets often fragment after they strike the skull, fracturing a portion of the skull into multiple fragments. Both the bullet and the bone fragments then become numerous secondary missiles that cause additional tissue damage.

Low-velocity missile wounds, such as those from knives, ice picks, or arrows, do not cause the massive brain injuries seen with bullets, as might be predicted by the kinetic energy equation. Usually, only the tissue in the immediate path of the missile is damaged, and patients often have a complete neurologic recovery after the missile is surgically extracted. Rarely, a missile injures a major intracranial artery or venous sinus, and these vascular injuries can result in large intracranial hematomas. Nonetheless, vascular injuries are always possible with high- or low-velocity missile injuries to the head, especially those in or near the skull base or the sylvian fissures.

The initial assessment and resuscitation of patients with penetrating head injuries are the same as for those with closed head injuries, as detailed earlier in this chapter. Prompt and aggressive cardiopulmonary resuscitation is critical. Knives or other missiles protruding from the head should never be removed in the field or emergency department; if they are tamponading a damaged intracranial vessel, removal could lead to massive intracranial hemorrhage. When a patient has a gunshot wound to the head, the neck, chest, and abdomen should be inspected carefully for other gunshot wounds, because wounds to the heart or great vessels in the chest or abdomen may be even more life threatening. A post-resuscitation GCS score should be obtained as soon as possible to guide future therapeutic decision-making. A CT scan of the head defines the intracranial path of the missile and related skull and tissue damage. More important, it identifies any large intracranial hematomas or contusions that may significantly affect outcome. If the missile trajectory is in or near the skull base or sylvian fissures and the patient is deemed salvageable, cerebral angiography should be performed.

Most patients who are expected to survive a penetrating head injury require at least limited operative treatment. Large intracranial hematomas should be evacuated promptly. A craniotomy is required for low-velocity missile wounds in which the object is still protruding from the head. After removing a segment of skull containing the missile and large enough to allow for intracerebral exploration, the surgeon can seek and immediately repair or occlude any vascular injuries caused by the missile. For gunshot wounds to the head, the surgeon should perform a limited debridement of the scalp and skull wound, removing scalp, bone, and bullet fragments penetrating the brain only if they lie near the surface. Easily accessible necrotic brain should be debrided, and meticulous hemostasis achieved. Dural closure is important because it reduces the risk of cerebrospinal fluid leak and infection, but it usually requires a pericranial graft. Artificial dural substitutes and allografts increase the risk of infection and therefore are not recommended.

Subsequent medical management of penetrating injuries is as described previously for closed head injuries. In addition, patients should receive prophylactic antibiotics for at least 14 days, because the missile usually carries skin and hair into the brain. Because a penetrating TBI, by definition, disrupts and contuses brain tissue, all patients with these injuries should also receive anticonvulsants for at least 7 days.

MILD AND MODERATE INJURY

A mild TBI is defined by an initial GCS score of 14 or 15; a moderate TBI, by a GCS score of 9 to 13. Often referred to as concussions, these injuries typically involve a brief loss of consciousness at the time of impact to the head and some degree of retrograde or post-traumatic amnesia; however, patients with such injuries can follow commands. They usually do not have the complex intracranial pathology associated with severe TBI and therefore are unlikely to die from the injury; mortality rates are near zero for those with mild TBI and approximately 4% for those with moderate TBI. Nonetheless, these injuries can cause long-term cognitive and neuropsychological impairment.[1] As many as 10% of those with mild injuries and 66% of those with moderate injuries suffer prolonged or permanent disabilities that prevent them from returning to work or school.

Rotational, acceleration, and deceleration forces are common causes of these injuries, particularly those that result in loss of consciousness. The impact usually is not intense enough to cause intracranial hematoma, cerebral contusion, skull fracture, or brain swelling. Although a small amount of subarachnoid hemorrhage may be present, usually in the sulci over the frontal or temporal lobes, CT findings are usually normal. Abnormal magnetic resonance imaging (MRI) findings have been reported in as many as 30% of these patients, most commonly diffuse hyperdense lesions on T2-weighted images. These lesions are thought to represent focal or punctate contusions.[89,90] Functional MRI often shows abnormal activation patterns, particularly if the patient has lost consciousness or is symptomatic at the time of the study.[90]

Several factors determine the appropriate level of medical evaluation and treatment after mild or moderate TBI. Any loss of consciousness at the time of impact or retrograde or antegrade amnesia of at least several minutes warrants a thorough medical assessment, as do persistent headache, confusion, dizziness, diplopia, weakness, or numbness. A formal examination in the emergency department is generally advisable. Patients who are neurologically normal and asymptomatic after at least an hour of observation and serial evaluations can usually be safely discharged, with clear instructions to return immediately if symptoms or signs of TBI develop. Ideally, these instructions are given to both the patient and a responsible companion.

A patient with persistent symptoms or neurologic deficits should have a CT scan of the head and be admitted to the hospital for observation. This is particularly important for those with GCS scores of 13 or less, because the risk of an intracranial hematoma or contusion large enough to require emergent craniotomy increases as the GCS score decreases. Among patients whose initial GCS scores are 9 to 13, as many as 40% have CT abnormalities, and 8% require neurosurgical intervention.[91]

Athletes—especially those involved in contact sports such as boxing, football, soccer, wrestling, and field hockey—are at high risk for mild and moderate TBI. One report estimated the incidence of concussion to be 40,000 per year for high school football players.[92] Athletes also have an increased risk for multiple concussions, which are much more likely to cause prolonged or permanent neurologic disability than is a single concussion, particularly if they occur over a short time span. Second impact syndrome is a rare but potentially lethal problem first noted in athletes in 1973 and later implicated as the cause of sudden death in several high school football players.[93,94]

Because sports-related concussions are associated with such disabling and potentially life-threatening consequences, coaches and athletic trainers must carefully consider whether an athlete should be advised to return to play or retire from athletic competition after a concussion. Several groups have devised concussion grading scales to evaluate concussion severity and developed guidelines to determine when an athlete can safely resume play. The most widely adopted scales are those developed by Kelly and colleagues at the University of Colorado,[95] Cantu,[96] and the American Academy of Neurology[97] (Tables 55-3 and 55-4). Most authorities recommend that athletes abstain from play for at least one season if, during that season, they sustain three or more grade I or II concussions or two grade III concussions.[98] In addition, many athletic organizations at the high school, college, and professional levels have adopted neuropsychological testing as a means of objectively evaluating the cognitive and neuropsychological consequences of each concussion.[99] The comparison of postinjury and preseason scores is a powerful tool for guiding return-to-play decisions.

A common sequela of mild or moderate TBI is postconcussion syndrome, a constellation of symptoms that can be disabling for weeks or even months.[100] The most common symptoms are headache, irritability, dizziness, tinnitus, lethargy, and sleep disturbance.[101] One or more of these symptoms develop in approximately 30% of patients 1 week after a mild or moderate TBI, but they usually subside within 3 months.[102] After 1 year, only 7% of patients report

TABLE 55-3. GRADING SCALES FOR CONCUSSION

Scale	Grade of Concussion		
	I	II	III
Colorado[95]	Confusion; no LOC; PTA <30 min	LOC <5 min; confusion; PTA >30 min	LOC >5 min; PTA >24 h
Cantu[96]	PTA<30 min; no LOC	LOC <5 min; PTA 30 min to 24 h	LOC >5 min; PTA >24 h
AAN[97]	Transient confusion; symptoms <15 min; no LOC	No LOC; transient confusion; symptoms >15 min	Any LOC

AAN, American Academy of Neurology; LOC, loss of consciousness; PTA, post-traumatic amnesia.

TABLE 55–4. RECOMMENDATIONS FOR RETURN TO PLAY

Concussion Grade	Colorado Guidelines[95]	Cantu Guidelines[96]	AAN Guidelines[97]
I	Return after 20 min if normal examination	Return same day if normal at rest and exertion	Return same day if normal at rest and exertion
II	Return after 7 days if asymptomatic	Return after 2 wk if asymptomatic at rest and exertion for 7 days	Return after 7 days if asymptomatic
III	Evaluation by neurologist or neurosurgeon; return after 2 wk if asymptomatic and cleared by specialist	Return after 1 mo if asymptomatic at rest and exertion for 7 days	Evaluation by neurologist or neurosurgeon; return after 2 wk if neurologically cleared

AAN, American Academy of Neurology.

residual symptoms, most commonly persistent headache. Postconcussion syndrome is best treated by a primary care physician or neuropsychologist who thoroughly understands the disorder. Cognitive testing is recommended for patients whose symptoms last more than a few weeks, because symptoms such as frustration and irritability are often linked to an inability to resume normal daily activities. If such testing identifies specific deficits, cognitive rehabilitation is recommended.[103] Persistent headaches, dizziness, and tinnitus should be treated symptomatically after a CT scan of the head establishes the absence of intracranial lesions. Post-traumatic disturbances of the ossicles of the inner ear semicircular canals can cause severe positional vertigo, and patients with vertigo or tinnitus may benefit from evaluation by an otolaryngologist. Factors associated with an adverse long-term outcome after a concussion include old age,[104] prolonged post-traumatic amnesia,[105] and a below-normal premorbid intellectual capacity.[106]

PROGNOSIS

Predicting outcome soon after a TBI can help guide acute and chronic care and help prepare family members for the typically protracted recovery process. Equally important is that further treatment may be deemed futile, and expensive critical care or surgery can be reserved for those who are likely to benefit. Of course, early prognostication must be reliable, especially when withdrawal of life support is a consideration.

Several clinical and radiographic characteristics have proved useful for outcome prediction, but they must be used in concert.[107] Moreover, these criteria are more reliable for predicting death or vegetative survival than for accurately predicting mild or no dysfunction and a complete return to normalcy. The most powerful outcome predictors are age, initial GCS score (particularly the motor component), pupil size and reaction to light, ICP, and the nature and extent of intracranial injuries.

Old age correlates most consistently with a poor outcome after TBI. In the Traumatic Coma Data Bank study of more than 700 patients with severe TBI, the incidence of death, persistent vegetative state, or severe disability was 92% for those older than 60 years, 86% for those older than 56, and 50% for younger patients.[108] The older groups had a higher incidence of traumatic intracranial mass lesions, midline shift, and subarachnoid hemorrhage, and the presence of these insults correlated strongly with poor outcome. Subsequent studies confirmed the low probability of a good recovery for patients older than 60 years whose initial GCS scores are 8 or less.[109]

The second most important predictor of outcome is the initial post-resuscitation GCS score. Among patients with severe closed head injuries in the Traumatic Coma Data Bank study, good outcomes occurred in 4.1% of those with an initial GCS score of 3, in 6.3% whose score was 4, and in 12.2% whose score was 5. Again, later clinical studies corroborated the strong direct correlation between initial GCS score and outcome.[110]

Unilaterally or bilaterally dilated pupils that are unreactive to light usually reflect uncal herniation and significant brainstem compression and damage; thus, this sign is ominous. Several large clinical studies found that patients with bilaterally fixed and dilated pupils had a greater than 90% likelihood of death or vegetative survival.[111,112] Also, intracranial hypertension refractory to medication is associated with a 43% mortality rate and 0% chance of a functional outcome.[113]

Various studies have analyzed the effect of the type and size of post-traumatic intracranial lesions on outcome, in terms of both the specific lesions and the CT-defined characteristics of their mass effect. Subdural hematomas are associated with the worst prognosis. One study found that only 26% of patients with these clots had a functional recovery.[114] However, the prognosis for patients with subdural hematomas is also related to how soon after injury the clot is evacuated, with the best outcomes in those who have surgery within 2 hours.[7]

Epidural hematomas pose a much lower risk of mortality because, unlike subdural hematomas, they usually are not associated with underlying cerebral contusions or swelling. If left untreated, however, epidural hematomas can cause uncal herniation and death. One report noted an increase in mortality from 17% to 65% if an epidural hematoma was not evacuated within 2 hours after the onset of coma.[8]

The presence of traumatic subarachnoid hemorrhage is associated with a 50% greater risk of death.[10,115] The link between traumatic subarachnoid hemorrhage and worse outcomes is controversial, however. Many believe that this condition merely indicates a more severe TBI and has no direct association with outcome.

Marshall and colleagues devised a CT-based classification scheme that proved prognostically useful when applied to the patients in the Traumatic Coma Data Bank study (Tables 55-5 and 55-6).[116] The classification emphasizes the mass effect of post-traumatic intracranial lesions. Not surprisingly, these investigators found the worst outcomes among patients with large intracranial mass lesions and uncal herniation.

TABLE 55–5. COMPUTED TOMOGRAPHIC CLASSIFICATION OF TRAUMATIC BRAIN INJURY

Category	Definition
Diffuse injury I	No visible intracranial pathology
Diffuse injury II	Cisterns present, with midline shift 0 to 5 mm; no high-density lesion >25 mL
Diffuse injury III (swelling)	Cisterns compressed or absent, with midline shift 0 to 5 mm; no high-density lesion >25 mL
Diffuse injury IV (shift)	Midline shift >5 mm; no high-density lesion >25 mL
Evacuated mass lesion	Any lesion surgically evacuated
Nonevacuated mass lesion	High-density lesion >25 mL; not surgically evacuated

From Marshall LF, Marshall SB, Klauber MR, Clark M: A new classification of head injury based on computerized tomography. J Neurosurg 1991;75:Σ14-Σ20.

Based on these studies, one can say with certainty that an 80-year-old patient who presents with bilaterally fixed and dilated pupils, a GCS score of 3 or 4, and a large subdural hematoma will not have a functional outcome regardless of treatment. However, the prognosis is much better for young patients with higher GCS scores, and aggressive surgical and medical management is usually warranted.

The patient's salvageability and prognosis after a penetrating injury are far clearer than for those with closed head injuries. Most victims of gunshot wounds to the head die before or shortly after hospital admission. Among 314 patients with civilian craniocerebral gunshot wounds, 92% died; 73% of them were pronounced dead at the scene of the injury, and 12% died within 3 hours of injury.[117] In the Traumatic Coma Data Bank study, the mortality rate was 88% for the 151 patients with gunshot wounds to the head.[118] No patient with an initial GCS score of 8 or less regained normal neurologic function, and only three recovered to the level of moderate disability, suggesting that the initial GCS score is an even more powerful predictor of outcome for these patients than for those with closed TBI. A meta-analysis of recent clinical studies examining civilian gunshot wounds to the head found that favorable outcomes (Glasgow outcome scale scores of 4 or 5) occurred in only 5 of 490 patients with initial GCS scores of 3 to 5.[119] Mortality rates ranged from 51% to 87% for patients with scores of 8 or less. In contrast, those whose initial GCS scores were 13 to 15 all survived and had favorable outcomes. Other clinical signs associated with death or a poor outcome are fixed and dilated pupils, intracranial hypertension, and hypotension. Also, a gunshot wound is more likely to be lethal if self-inflicted.

The CT-defined extent of intracranial injury caused by the missile also has prognostic significance. Hyperdense lesions with a volume greater than 15 mL, midline shift of more than 3 mm, compressed or absent basal cisterns, subarachnoid hemorrhage, and intraventricular hemorrhage are all associated with mortality rates of 80% to 90%, as is a bullet trajectory that traverses both hemispheres, the basal ganglia, or the posterior fossa.[118,120]

TABLE 55–6. RELATIONSHIP OF COMPUTED TOMOGRAPHIC CLASSIFICATION TO OUTCOME AT DISCHARGE

Category	No. of Patients	Unfavorable Outcome* (%)	Favorable Outcome† (%)
Diffuse injury I	52	38	62
Diffuse injury II	177	65	35
Diffuse injury III	153	84	16
Diffuse injury IV	32	94	6
Evacuated mass	276	77	23
Nonevacuated mass	36	89	11

*Death, persistent vegetative state, or severe disability.
†Moderate disability or good recovery.
From Marshall LF, Marshall SB, Klauber MR, Clark M: A new classification of head injury based on computerized tomography. J Neurosurg 1991;75:Σ14-Σ20.

ANNOTATED REFERENCES

Chestnut RM, Marshall SB, Piek J, et al: Early and late systemic hypotension as a frequent and fundamental source of cereberal ischemia following severe brain injury in the Traumatic Coma Data Bank. Acta Neurochir Suppl (Wien) 1993;59:121-125.

The authors reviewed blood pressure readings in a group of several hundred patients admitted to the Traumatic Coma Data Bank. They found that hypotension (systolic blood pressure <90 mm Hg) was associated with a twofold increase in the mortality rate compared with head-injury patients who did not have hypotension.

Dietrich WD: The importance of brain temperature in cerebral injury. J Neurotrauma 1992;9(Suppl 2):S475-S485.

This experimental study showed that in an ischemic rodent model, there was a log increase in the death of ischemic neurons for every degree centigrade the brain temperature exceeded 39°C. Subsequent studies from this laboratory showed that this effect is also observed 24 hours or more after injury.

Muizelaar JP, Marmarou A, Ward JD, et al: Adverse effects of prolonged hyperventilation in patients with severe head injury: A randomized clinical trial. J Neurosurg 1991;75:731-739.

This prospective, randomized, controlled clinical trial evaluated the effects of prophylactic hyperventilation therapy. Patients who had an initial GCS score of 5, 6, or 7 and were prophylactically hyperventilated to a mean PCO_2 of 25 mm Hg for the first 5 days after injury had a significantly worse outcome than patients who were kept at a mean PCO_2 of 35 mm Hg.

Narayan RK, Kishore PR, Becker DP, et al: Intracranial pressure: To monitor or not to monitor? A review of our experience with severe head injury. J Neurosurg 1982;56:650-659.

The authors reviewed their experience with more than 100 patients with severe TBI and identified indications for ICP monitoring. They found that patients who had GCS scores of 8 or less and abnormal CT scans were very likely to have problems with intracranial hypertension and would benefit from ICP monitoring.

Temkin NR, Dikmen SS, Wilensky AJ, et al: A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. N Engl J Med 1990;323:497-502.

In this randomized, controlled, double-blind study of the benefit of prophylactic anticonvulsant therapy for patients with TBI, the authors found a significant reduction in the incidence of post-traumatic seizures during the first week of therapy, but no subsequent benefit was observed when therapy was continued longer than 7 days. This study has led most to discontinue the use of anticonvulsants 1 week after TBI, regardless of the nature of the injury.

Chapter 56
SPINAL CORD INJURY

Elizabeth A. Vitarbo • Allan D.O. Levi

KEY POINTS

1. Most spinal injuries result from high-speed motor vehicle accidents.
2. Suspected spinal cord injury alters the basics of the "ABCs" of resuscitation in several important ways.
3. The primary injury mechanism results from a mechanical insult that occurs at the time of impact and includes acute compression, impaction, distraction, laceration, and shear. Secondary injuries occur after the initial injury and account for some of the progressive pathologic changes associated with spinal cord injury.
4. Respiratory complications are a major source of morbidity and mortality after spinal cord injury.
5. In the elderly patient with a spinal cord injury, careful attention to volume replacement is required so as not to precipitate heart failure.
6. The prognosis for recovery from spinal cord trauma is inextricably linked to age, with the younger patients fairing much better than their older counterparts for regaining neurologic function.

Despite substantial improvements in emergency, diagnostic, and surgical care, spinal trauma continues to present a challenging spectrum of diseases for the neurosurgeon to manage. When spinal trauma results in a spinal cord injury, the emotional and financial toll inflicted on individuals and their families is enormous. Improvements in the quality of care delivered over the past few decades are partially reflected in the recognition that centers of excellence that focus on the acute treatment and the rehabilitation of the spinal cord injury patient are best equipped to deal with the magnitude of services these patients require.

EPIDEMIOLOGY

Spinal cord injury typically occurs in males at the peak of their productive lives. The incidence of traumatic spinal cord injury is approximately 10,000 new cases each year in the United States,[1] with a prevalence of 191,000. The prevalence of spinal cord injury patients is increasing steadily owing to improved survival in both the acute and chronic stages of the disease. The amount spent on the treatment of spinal cord injuries in the United States is approximately 5.6 billion dollars each year and rising annually.[2] The cost of caring for the individual spinal cord–injured patient is directly related to the injury level of the spinal cord and to the patient's age, with the highest costs associated with the older quadriplegic patients who are dependent on a ventilator.[2]

ETIOLOGY

Most spinal injuries result from high-speed motor vehicle accidents (Fig. 56-1). Falls and work-related injuries are other important contributors. Spinal cord injury that is due to violence is on a dramatic rise secondary to increased incidence of assaults. These injuries include both blunt and penetrating injuries, such as gun and knife wounds. Sports-related injuries, which include football, horseback riding, and hockey injuries, are relatively rare but have received recent media attention.[3,4] Finally, recreational injuries from jet skis, snowmobiles, snow skiing, snow boarding, and parachuting, to name but a few, appear to be on the rise, as "extreme sports" become more prevalent.

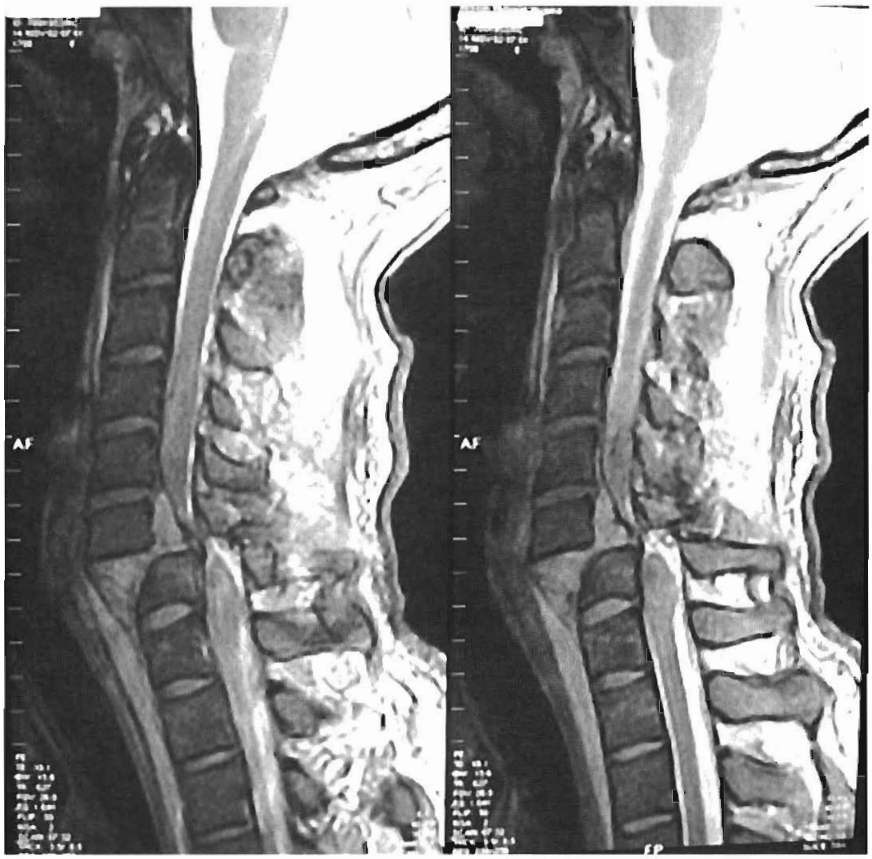
INITIAL MANAGEMENT

Suspected spinal cord injury alters the basics of the "ABCs" of resuscitation in several important ways. With respect to airway management, suspected spinal cord injury dictates in-line immobilization of the spine at all times. Therefore, hyperextension of the neck is contraindicated. A jaw thrust must be used to open the airway, and required intubation must be done with the head/neck in a neutral position. This is an important point to remember, because patients with a high spinal cord injury will have diminished or absent respiratory capacity and frequently require emergent intubation.

Aggressive resuscitation of spinal cord injury patients proceeds as with all trauma patients. As indicated earlier, however, upper spinal cord injury may be associated with neurogenic shock, requiring large volume fluid replacement. Although pressors are likely to be required in the setting of neurogenic shock, field management is commonly limited to fluid resuscitation. High incidence of associated head injury often requires use of colloid solutions in addition to normal saline/lactated Ringer's solution, in an effort to adequately resuscitate the patient while minimizing exacerbation of cerebral edema.

IMMOBILIZATION AND DIAGNOSTIC EVALUATION

Rigid immobilization is indicated if there is any doubt as to the presence of spinal cord injury. Presence of altered mental status in any way dictates the use of "spinal cord precautions."



A B

FIGURE 56–1. *A*, Sagittal T2-weighted MRI demonstrates a C6-C7 fracture-dislocation with severe cord compression in a patient who presented with complete C6 quadriplegia–ASIA. *B*, The patient was treated surgically to realign the spine and gained significant root recovery without any recovery of hand or lower extremity function.

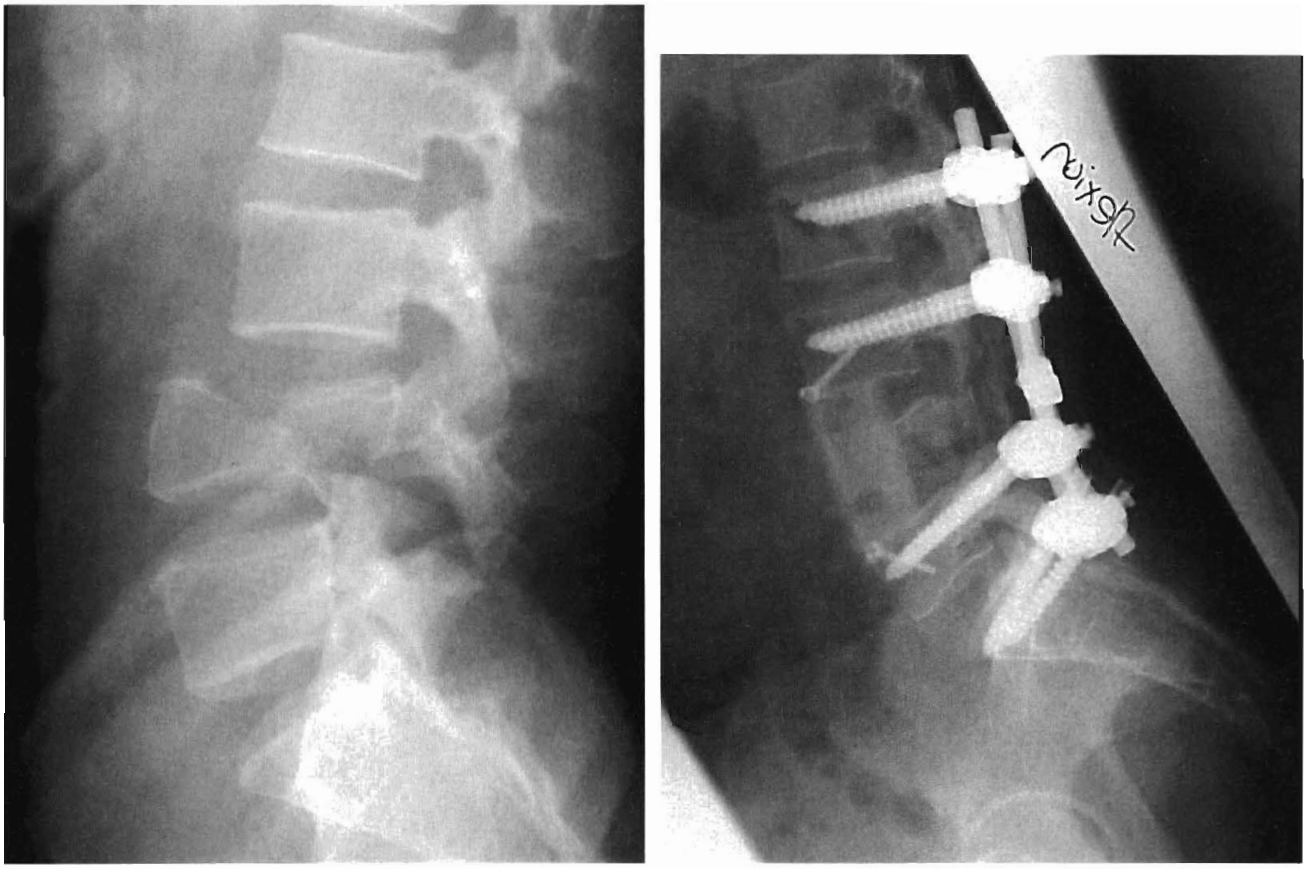
These include use of in-line immobilization, maintenance of neutral position, cervical immobilization with a rigid collar, and use of backboards for transport.

After initial resuscitative efforts, diagnostic studies are undertaken. Initial studies must include lateral cervical spine radiographs clearly demonstrating the cervical spine down to the C7-T1 junction in patients with altered mental status and/or suspected cervical spine injury. Additional spine studies may be obtained after the patient has been stabilized and more emergent diagnostic studies have been undertaken. During this time, rigid cervical collar and backboard immobilization must be continued.

Further diagnostic studies will be dictated by the findings of the initial and secondary surveys, as well as findings of initial diagnostic studies. Several points are important to keep in mind. First, important information can be obtained from studies performed for other reasons. For example, routine chest and abdominal radiographs may provide important information regarding the presence of significant thoracic/lumbar spine injury. Although these do not replace subsequent "formal" spine studies, these are often obtained as part of the routine trauma work-up and provide early "clues" regarding the presence of spine trauma and may help prioritize subsequent imaging studies.

Whereas anteroposterior/lateral spine radiographs are tailored to complaints of spine pain and the neurologic examination, altered mental status dictates that cervical, thoracic, and lumbar anteroposterior and lateral films be obtained (Fig. 56-2). When abnormalities are identified, and/or studies are limited by body habitus, plain radiographs must be supplemented by CT to further characterize bony abnormalities. Sagittal reconstructions may be obtained and are often useful adjuncts to plain radiographs. The radiographs and particularly the CT are the most sensitive tools in detecting a fracture of the spine, but occasionally it is difficult to clear the spine—even in the absence of a fracture—because an unstable ligamentous injury without fracture may exist.

Patients with a suspected spinal column injury who are unconscious, uncooperative, or intoxicated, or who have associated traumatic injuries that distract from their assessment, will often require further radiographic study of the cervical spine before the discontinuation of cervical spine immobilization. Several options exist and include (1) maintenance of the collar and/or spine precautions until the patient becomes coherent and responsive, (2) dynamic imaging of the spine with physician monitoring, and (3) MRI of the spine to rule out a purely ligamentous injury. Of the three options, we frequently use MRI to clear the spine because a completely negative MR image in the setting of trauma indicates that there is no instability of the cervical spine (Fig. 56-3). Malalignment and evidence of spine trauma on these imaging studies frequently determines subsequent management and diagnostic decision making. Cervical subluxations often require the use of traction and/or manual reduction of the fracture-dislocation. Diazepam (Valium) or lorazepam (Ativan), along with careful neurologic monitoring, often in the ICU setting, is required because application of traction can realign the spine but can also result in neurologic deterioration.



A B

FIGURE 56–2. A 45-year-old man sustained a (*A*) L4 fracture-dislocation and presented with a dense footdrop and underwent a (*B*) anteroposterior reconstruction with instrumentation.

PEDIATRIC SPINAL CORD INJURY

Pediatric spine trauma is relatively uncommon, representing approximately 5% of all spinal cord injuries.[5] For a specific discussion of pediatric spinal cord injury, please see Chapter 248. In addition, guidelines have been published on this topic.[6]

PHARMACOTHERAPY

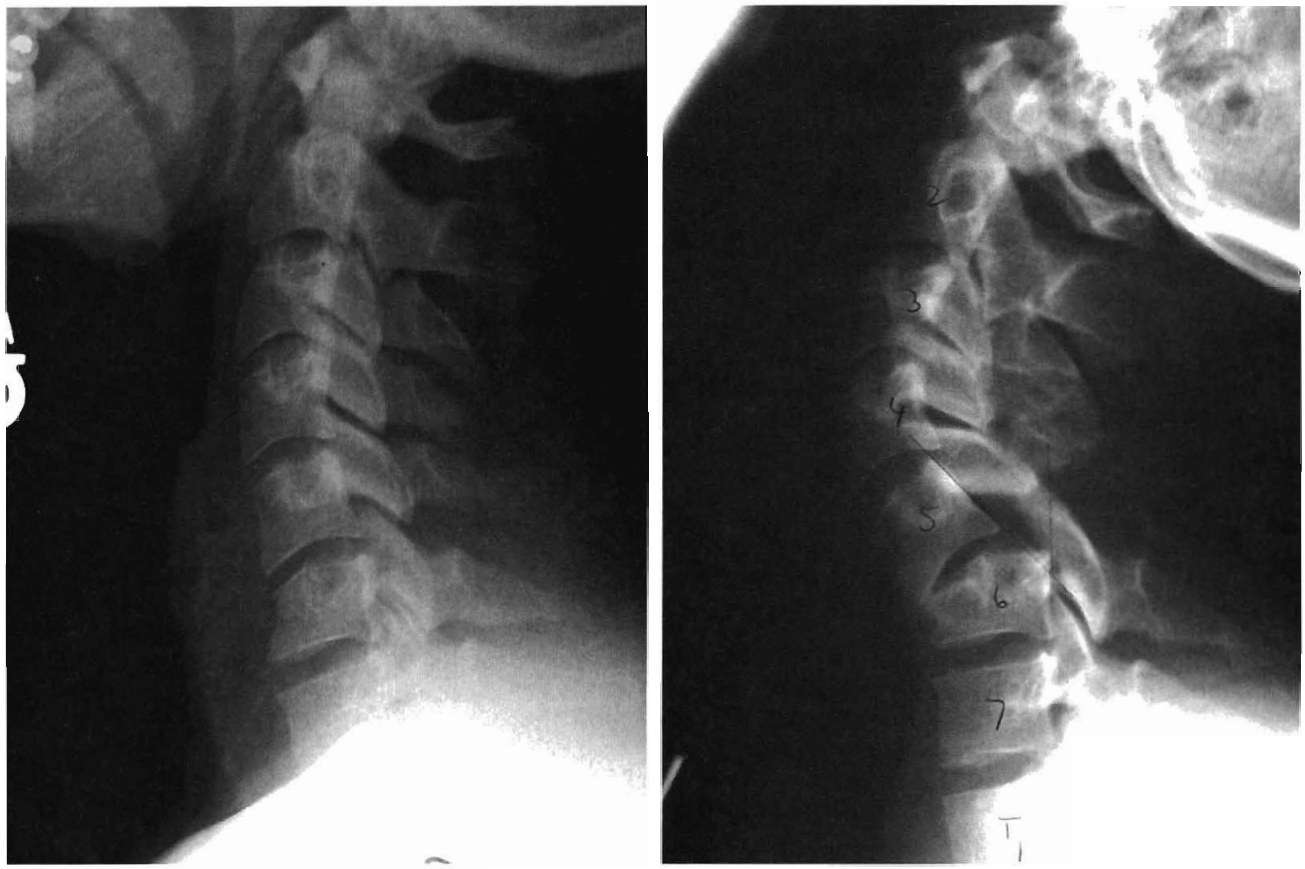
The concepts of primary and secondary spinal cord injury are important principles in understanding the pathophysiology and the role of pharmacotherapeutic agents in emergent treatment. The primary injury mechanism results from a mechanical insult that occurs at the time of impact and includes acute compression, impaction, distraction, laceration, and shear.[7] Secondary injuries occur after the initial injury and account for some of the progressive pathologic changes associated with spinal cord injury.[7] A number of drugs have been tested in the laboratory, but only a few of these agents have progressed to clinical trials to evaluate their efficacy. Five randomized controlled trials of pharmacotherapy for acute spinal cord injury have been conducted, focusing on the therapeutic effect of either corticosteroids or gangliosides.

CORTICOSTEROIDS

A number of studies have shown improved neurologic recovery in animals with spinal cord injuries that have received either dexamethasone or methylprednisolone.[8-12] Corticosteroid treatment initially held promise as a potential therapeutic agent for its putative role in reducing white matter edema and inflammation. Current evidence, however, suggests that the major mechanism of action is by reducing the effects of secondary injury and, in particular, the destructive effects of lipid peroxidation on cell membranes.[2] Other actions include improving spinal cord blood flow, enhancing the postinjury activity of Na^+, K^+-ATPase, and facilitating the recovery of extracellular calcium ion.[8,13]

The first NASCIS investigator (NASCIS I) examined low- (100 mg) and high- (1000 mg) dose methylprednisolone given for 10 days. Unfortunately, this trial had no control group, and no significant difference in outcome was found except for an increased number of wound infections among patients in the high-dose group.[14]

The second NASCIS trial (NASCIS II) was a prospective, randomized, double-blind, multicenter trial that demonstrated improved neurologic outcomes after 6 weeks, 6 months, and 1 year in patients with nonpenetrating spinal cord injury who had received a regimen of methylprednisolone, which included a bolus dose of 30 mg/kg.[15] The improvement in motor and sensory scores associated with administration of methylprednisolone was only observed if the drug was given within 8 hours of injury when compared with naloxone or a placebo. The results of this study have been criticized.[16,17] Some of the criticisms relate to difficulties in randomization, reporting methods, analysis of benefit limited to small subgroups within the larger study, and lack of replication of results by a completely independent group of investigators,



A B

FIGURE 56–3. A, A 31-year-old man was "cleared" in the emergency department after cervical spine series and CT failed to demonstrate a fracture. The patient had a Glasgow Coma Scale score of 11 on admission with significant facial fractures. He presented 1 year post admission with increasing neck pain and was diagnosed with a severe cervical kyphotic deformity with bilateral perched facets at C5-C6. **B**, MRI (gradient-echo sequence) done on admission in this obtunded patient would have easily demonstrated the posterior ligamentous injury between the C5 and C6 spinous process, which is relatively subtle on the admission lateral radiograph seen in A.

among others. However, the administration of methylprednisolone is believed to reduce the amount of secondary injury that occurs after spinal cord injury and has become an important tool in the treatment of spinal cord injury in most North American centers.

The results of NASCIS III have been published and compared the dosage of methylprednisolone used in the NASCIS II protocol with a longer dosing regimen (48 hours) as well as with a 21-aminosteroid. The 21-aminosteroids (lazaroids), a new class of steroids that are potent inhibitors of lipid peroxidation, lack much of the glucocorticoid activity of many of the traditional steroid compounds. The results of the study suggested that when patients are seen within 3 hours of their injury, they should receive a bolus dose of methylprednisolone (30 mg/kg i.v.) followed by 23 hours of treatment (5.4 mg/kg/h i.v.). Patients seen between 3 and 8 hours should receive the same bolus followed by a longer dosing regimen (48 hours). The complications from 48 hours of treatment included a significant increase in severe sepsis and pneumonia.[18]

GANGLIOSIDES

Gangliosides are a complex sialic acid containing glycosphingolipids, which are present in high concentrations in neural membranes. These compounds are involved in a variety of cell surface phenomenon such as cell-substrate binding and receptor functions.[19] Basic research in the past 15 years has demonstrated that these compounds can (1) promote the survival of neurons in cell culture; (2) increase the number, length, and branching of neuronal processes in cell culture; and (3) improve functional recovery after a variety of traumatic and ischemic insults to the peripheral and central nervous system. A limited number of animal studies has examined the role of gangliosides after spinal cord injury and has shown only a modest effect on the regeneration of serotonergic neurons.[20] A recent prospective, randomized, double-blind, single center study found a beneficial effect in functional neurologic outcomes when the ganglioside GM_1 was administered within 72 hours of human spinal cord injury.[21] However, a multicenter trial demonstrated no statistically significant benefit with administration of this agent at 26 and 52 weeks after injury.[22]

ICU MANAGEMENT

Spinal cord injury is associated with profound effects on all vital systemic functions. Through primarily class III medical evidence, numerous reports indicate lower morbidity and mortality rates in patients with spinal cord injury managed with ICU monitoring and aggressive medical management of these changes.[23-31] At the least, these studies taken together indicate that a systematic approach must be taken to evaluate and treat each of the potential complications. Early and late

complications will be seen, and the degree of involvement of each system is usually correlated with the level and severity of injury.

RESPIRATORY SYSTEM

Respiratory complications are a major source of morbidity and mortality after spinal cord injury, with an 18% to 30% mortality rate reported in patients with tetraplegia.[27,32] In a study by Hachen and associates,[23,25] most early deaths were related to pulmonary complications, with the likelihood of severe insufficiency related to spinal cord injury severity. Whereas most cervical spinal cord injuries occur below C4 with the phrenic nerves continuing to innervate the diaphragm, the respiratory system is frequently severely affected, particularly after cervical spinal cord injuries. Specifically, marked reductions in (forced) vital capacity, inspiratory capacity, and expiratory flow rates frequently result in a relative hypoxemia.[23,27,33-36] These changes may be attributed to variable paralysis of the intercostal muscles and accessory muscles of respiration. Loss of abdominal muscle tone and ileus also reduce the mechanical efficiency of breathing.

In general, there is a period of grace in which the patient with a cervical spinal cord injury will maintain his or her respiratory status. However, it is not uncommon for respiratory failure to ensue 24 to 48 hours after admission. Additional injuries such as rib fractures, hemathorax, and so on can accelerate this respiratory deterioration. Preparation for such events should be undertaken early so that if intubation is required it can be done with stabilization using in-line traction and often supplemented by fiberoptic technique using a bronchoscope. Measurements of arterial blood gases, negative inspiratory force, and forced vital capacity may provide a method of early detection of respiratory failure.

The most common respiratory complications include atelectasis, pneumonia, pulmonary embolus, pulmonary edema, and acute respiratory distress syndrome. In addition to difficulty with taking deep breaths and coughing, patients are often unable to clear airway secretions. Accumulation of secretions and/or mucus plugs can result in respiratory failure. Prevention includes respiratory treatment with bronchodilators, frequent pulmonary toilet, chest physiotherapy, increasing airway humidity, intubation, and mechanical ventilation including the use of continuous positive airway pressure. The use of the Roto-rest bed significantly decreases pulmonary complications associated with spinal cord injury[27,37] because it improves pulmonary blood flow and reduces the incidence of pulmonary emboli.

Pulmonary infections frequently complicate spinal cord injuries. Within days of admission, the normal flora of the oral cavity will contain increasing numbers of nosocomial organisms. Hospital-acquired pulmonary infections are heralded by fever, increased white blood cells both in the sputum and in the peripheral blood, and, lastly, by changes on the chest radiograph. After obtaining appropriate cultures, commencement of broad-spectrum antibiotics should be instituted.

Most patients can be discontinued or "weaned" from the ventilator after they have been medically stabilized, which usually means treatment of pulmonary infections, re-establishment of euvolemia, enhancement of respiratory muscle function, and nutritional supplementation to off-set the high caloric requirements of the trauma. Initially, weaning the intermittent mandatory ventilation rate is followed by weaning of the positive airway pressure (either continuous or end-expiratory). With prolonged periods of ventilation (greater than 2 weeks), and/or multiple failed extubations, one should consider a tracheostomy. The likelihood of requiring a tracheostomy increases after a high spinal cord injury, preexisting pulmonary disease, and the age of the patient. Tracheostomy effectively reduces the physiologic dead space. Northrup and colleagues[38] have demonstrated that a tracheostomy can be performed before anterior cervical instrumentation of the spine with a low risk of infection, but in our patient population early surgery for stabilization is advocated and, consequently, few patients undergo tracheostomy before anterior cervical stabilization surgery.

CARDIOVASCULAR SYSTEM

Significant confusion arises when the term *spinal shock* is used after spinal cord injury. The misunderstanding regarding its use stems from multiple causes. First, many physicians use the terms *spinal shock* and *neurogenic shock* interchangeably. Neurogenic shock, however, refers to a condition characterized by hypotension and bradycardia, resulting from interruption of the sympathetic nervous system pathways within the spinal cord. The incidence of significant neurogenic shock increases with injuries above the T6 level, because unopposed vagal tone slows the heart and reduces systemic vascular resistance, resulting in venous pooling. The condition responds to administration of fluids and/or colloids and occasionally requires the use of pressors. Neurogenic shock is distinct from hypovolemic shock, which may occasionally occur concomitantly in the multitrauma patient with a spinal cord injury who has evidence of either external or internal bleeding. Whereas isolated hypovolemic shock is characterized by hypotension with tachycardia, relative bradycardia (for a given degree of hypotension) is to be expected in the setting of multitrauma with spinal cord injury.

Spinal shock encompasses a number of different neurologic manifestations of spinal cord injury with varying time courses. Traumatic injuries to the spinal cord interrupt and/or temporarily damage a number of descending and ascending pathways. The most common initial presentation of a complete spinal cord injury with respect to reflex and autonomic function is a period of areflexia and flaccidity that is gradually replaced by hypertonia, exaggerated reflexes, and, in many cases, spasticity. The transition period may last from days to weeks. The immediate onset of hyperreflexia and spasticity is uncommon; and, when it occurs, it is a bad prognostic sign. The period of transition in reflex and autonomic function is often referred to as spinal shock. Concomitant changes in motor and sensory function are also common.

Animal studies indicate that ischemia underlies many of the secondary mechanisms of post-spinal cord injury, often dictating the resultant deficits.[23,39-41] Human studies suggest a direct correlation between the severity of spinal cord injury and the incidence and severity of cardiovascular problems.[23,42] Together, this suggests that reducing the magnitude of secondary injury should be at the forefront of medical management of spinal cord injury.

The typical patient with a spinal cord injury without associated vascular or visceral injury presents to the emergency department with a mean arterial blood pressure of 80 mm Hg and a heart rate of 65 beats/min.[30] Persistent bradycardia

is a frequent finding and is often profound enough to produce hemodynamic compromise.[23,43] The patient's blood pressure may respond to volume resuscitation, but not uncommonly these patients require low dose pressors. Aggressive medical management, including volume expansion and maintenance of mean arterial blood pressure above 85 mm Hg, is believed to potentially enhance neurologic outcome by maximizing spinal cord perfusion at the injury site and thus reducing the likelihood of secondary injury.[7] Invasive hemodynamic monitoring will demonstrate a normal cardiac index with a low systemic vascular resistance. In the elderly patient with a spinal cord injury, careful attention to volume replacement is required so as not to precipitate heart failure.

GASTROINTESTINAL SYSTEM

Hypoactive bowel sounds and impaired peristalsis are a common accompaniment after spinal cord injury owing to the lack of sympathetic modulation. To avoid gastric and small bowel dilatation, it is wise to delay enteral feeding. In any patient in whom gastric distention impairs respiratory function, a nasogastric tube is indicated. Most cervical cord injuries require nasogastric suction because of impaired bowel motility, air swallowing producing gastric distention, and respiratory compromise due to paralysis of intercostal muscles.

Patients with spinal cord injuries are at a high risk of developing gastric and duodenal stress ulcers. The use of steroids compounds the risk of developing significant gastrointestinal hemorrhage. All patients with spinal cord injuries should receive at minimum an H_2 blocker to prevent this dreaded complication. The reported risk of gastrointestinal hemorrhage in NASCIS II for the control group was 3% and for the methylprednisolone group it was 4.5%.[15]

URINARY SYSTEM

During the period of spinal shock after a cervical or thoracic spinal cord injury, the urinary bladder is atonic and flaccid. Over time it becomes an upper motor neuron bladder with small capacity. An indwelling Foley catheter is initially placed. After 3 to 4 days this is switched to intermittent bladder catheterization to maintain urinary volumes below 500 mL. Urinary tract infections are common, and if any fevers occur, urine cultures must be obtained and antibiotics selected based on culture sensitivities. Patients with spinal injuries above T6 may also develop autonomic dysreflexia if the bladder becomes overdistended; or, sometimes, with catheterization, sympathetic overactivity and thus headaches, hypertension, sweating, and reduced body temperature result. Long-term complications include chronic infections, obstructive uropathy, and renal calculi; and, if left untreated, renal failure may develop.

INTEGUMENT

The spinal cord–injured patient is extremely susceptible to developing decubiti. Frequent log rolling is invaluable in preventing skin breakdown. Additionally, the Roto-Rest bed[37] can reduce the incidence of skin breakdown by preventing pressure on a single area from frequent turning. Early intervention for skin breakdown frequently involves application of the Duoderm patch (Convatel, Princeton, NJ) to prevent progression.

THROMBOEMBOLIC COMPLICATIONS

Patients with spinal cord injury are at high risk of lower extremity venous thromboembolism, which may manifest by deep vein thrombosis in the lower or upper extremities resulting in leg swelling and/or pulmonary embolism. Depending on injury severity, age, and diagnostic methods, an incidence of thromboembolic events ranges from 7% to 100%.[44] The majority of these events occur within the first 3 months after injury, except in patients who are elderly, obese, or who have had prior thromboembolic events.[44]

Numerous studies have addressed the issue of preventive measures. Prevention has traditionally included the administration of low doses of heparin (5000 units subcutaneously) twice daily or more. However, meta-analysis of available literature suggests that better alternatives include the combination of pneumatic compression stockings with low-molecular-weight heparin (Lovenox, Rorers, Collegeville, PA) or adjusted-dose heparin.[44]

Current recommendations for the evaluation of suspected thromboemboli include use of Doppler ultrasound for suspected deep venous thrombosis and venography if a strong clinical suspicion exists for deep venous thrombosis despite a negative ultrasound or if pulmonary embolism is suspected.[44,45] Treatment of pulmonary emboli or above-knee deep vein thrombosis requires heparinization. Should there be a contraindication to heparinization, an inferior vena cava filter should be placed. Prophylactic placement of inferior vena cava filters has been advocated,[44,46-49] but these procedures are not without risk and no study thus far compares success rates to the aforementioned conservative prevention modalities.[44]

PROGNOSTIC FACTORS FOR RECOVERY

The clinician uses the neurologic examination, age, and the appearance of the spinal cord on MRI, as well as other clinical data, to guide the patient and his or her family on the expected outcome for a specific injury. In any traumatic spinal cord injury, it is important to ascertain whether the patient has a functionally complete or incomplete neurologic deficit. The distinction is important because the prognosis for neurologic recovery differs for these two conditions. Patients with no evidence of motor or sensory function below their spinal column injury are considered to have functionally complete injuries. Patients with no voluntary motor control and only slight sensory preservation in their lowest sacral dermatomes or some anal tone are still considered to have incomplete injuries. Functionally, patients with complete cervical spinal cord injuries, who remain complete within the first 24 hours of admission, are unlikely to regain significant ambulatory function (1% to 3%).[50,51] However, most patients who enter the hospital with an incomplete neurologic injury obtain some degree of recovery. The level and degree of an incomplete injury also provides important prognostic information. Cervical injuries have a higher potential for recovery when compared with thoracic and/or thoracolumbar injuries. The less severe the spinal cord injury, the more likely for the patient to recover.[52]

The majority of injuries occur in males, with well over half the injuries occurring in the 16- to 30-year-old age group. The prognosis for recovery is inextricably linked to age, with the younger patients fairing much better than their older counterparts for regaining neurologic function after

spinal cord injury.[53] The two most important potential neurologic explanations are the capacity of the "young" spinal cord to function with major deficiencies in the neural circuitry, as well as the possibility of some spontaneous regeneration of the central nervous system after injury.[54] The reverse also appears to be true. It is well recognized that patients with stable incomplete injuries who age may lose function, and this may simply be the result of the loss of the last few functioning neurons or axons within the damaged region of spinal cord.[55] Neuronal loss is a normal part of the aging process for both the brain and the spinal cord, and the clinical deterioration observed after spinal cord injury may be likened to the postpolio syndrome.

MRI after spinal cord injury allows visualization of the spinal cord in a noninvasive manner. The images provide immediate feedback to the surgeon as to the degree of spinal cord compression, as well as information regarding the stability of the spinal column through an assessment of the integrity of the ligaments, disks, and surrounding soft tissues. In addition, intramedullary hemorrhage may be easily discerned, and it provides important prognostic information. Intramedullary hemorrhage is more commonly observed after neurologically complete injuries, and hemorrhage signifies a worse neurologic and functional outcome.[56,57] MRI of spinal cord injury is discussed in greater detail in Chapter 57.

RESEARCH

Spinal cord injury research is an absolute priority of the National Institutes of Health. Models of spinal cord injury, mechanisms of secondary injury, treatment of the acute phase of spinal cord injury, as well as the development of transplantation strategies to repair the damaged spinal cord are ongoing across North America and around the world. The treatment arms of the research can be divided into two categories: (1) agents that can be given during the acute phase of injury and that may limit secondary injury mechanisms or (2) strategies to promote regeneration. Two of the most promising drugs, methylprednisolone and ganglioside GM_1, have only yielded modest results. Methylprednisolone, which is used in almost all major spinal cord injury centers, is coming under closer scrutiny as to its effectiveness.[17] Drugs of the future include neurotrophins, which can promote the survival and regeneration of injured nerve cells, drugs that prevent the inflammatory response to spinal cord injury,[58] and drugs that prevent apoptotic cell death.[59] In the transplantation arena, cellular therapies to treat the chronic injury are important. Cells of interest include Schwann cells, olfactory ensheathing glia, embryonic spinal cord, and neural progenitor cells. Antibodies that neutralize the inhibitory proteins within myelin have also demonstrated promise. Strategies that combine a number of the aforementioned treatments are most likely to have a beneficial effect in the future.

CONCLUSION

It appears that despite the enormous advancements in the diagnosis and treatment of spinal fractures over the past three decades there exists a number of unanswered questions regarding the most appropriate management of patients with traumatic spinal fractures. Although only a few aspects of the surgical management of spine trauma are raised in this chapter, it is clear that a number of issues remain unresolved. Technologic advancements in spinal instrumentation and pharmacotherapeutics will continue in the 21st century. It will be critical that both neurosurgeons and orthopedic surgeons work together to test both the efficacy and cost effectiveness of some of the newer treatment modalities, because both the best possible treatment and cost containment will be part of management equation in the future. Outcome assessment should be at the forefront of all new ideas. Only through a critical and open-minded analysis of our treatment strategies will we be able to provide the best care for those patients who will often be changed for the remainder of their lives by their injuries and the rapid sequence of events that revolve around their acute hospitalization.

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Clinical trial in 77 patients with acute spinal cord injury in which aggressive ICU care, including optimized volume expansion and pressor support, was associated with favorable outcome.

Chapter 57
NEUROIMAGING

Fred J. Laine

KEY POINTS

METHODS

1. Computed tomography (CT) is rapid and accurate and is the most widely used imaging modality in the acute setting.
2. Constant improvements in CT and magnetic resonance imaging (MRI) techniques not only afford greater sensitivity and specificity but also allow the evaluation of metabolic and physiologic functions of the brain.
3. Other modalities, such as nuclear medicine studies and angiography, have more specific indications and are generally not used as primary screening modalities.

BRAIN

1. The three types of brain edema—vasogenic, cytotoxic, and interstitial—can usually be differentiated, which helps in determining the underlying lesion.
2. The MRI appearance of hemorrhage is dependent on the age of the hemorrhage because the blood breakdown products have varying paramagnetic properties that influence the MRI signal.
3. Herniation can be identified on CT and MRI directly, by visualizing portions of brain that cross dural membranes and bony ridges, or indirectly, by noting the mass effect on adjacent structures.
4. Acute head injury is best evaluated initially with CT to rapidly establish the presence of surgical lesions; MRI is used secondarily to establish the presence of more subtle lesions.
5. The imaging evaluation of a patient suspected of having a stroke should include an anatomic study to determine the presence and type of infarct, as well as a physiologic study to evaluate parameters such as brain perfusion, blood volume, and vasculature status.
6. The distinction between recurrent tumor and postradiation necrosis is difficult on standard imaging but can be greatly facilitated by magnetic resonance spectroscopy and positron emission tomography.

SPINE

1. The possible causes of spinal disease can be significantly narrowed if the lesion can be placed into one of the three spinal compartments: intramedullary, extramedullary intradural, and extradural.
2. In the evaluation of spinal injury, CT is useful for evaluating bony pathology such as fractures and subluxation, whereas MRI is useful in soft tissue injuries such as cord contusion or acute disc herniation.
3. MRI is the modality of choice when evaluating patients suspected of having discitis, cord compression, or metastatic disease.

METHODS

PLAIN RADIOGRAPHS

Plain radiographs are rapid, inexpensive, and accurate but are of limited value in studying the central nervous system (CNS). Although useful in evaluating soft tissue abnormalities of the chest, abdomen, and pelvis, plain radiographs are inadequate for evaluating the soft tissues of the head and spine. Their main usefulness, with respect to the CNS, lies in their ability to depict osseous integrity and alignment. Therefore, they are typically the first studies obtained when evaluating traumatic injuries of the spine. Radiographs of the skull following head injury can demonstrate fractures but fail to provide significant information about intracranial injury.

COMPUTED TOMOGRAPHY

Computed tomography (CT) is the most widely used imaging modality for evaluating critical care patients with CNS pathology. CT is widely available, rapid, and accurate and has virtually no contraindications in the acute setting. The clinical utility of CT is increased by multiple modifications, including contrast administration, window techniques, and various reconstruction techniques. Iodinated contrast agents are available for intravenous injection. With their use, lesions that cause a breakdown in the blood-brain barrier, as well as normal or abnormal vascular structures, enhance or "light up" on CT scans. Varying the gray scale "window level" permits the evaluation of osseous structures with a wide window and soft tissue structures with a narrow window.

Spiral or helical CT scanners are now widely available, and this form of CT has many advantages over standard scans. It allows rapid imaging through a large volume of the body, usually with a single breath-hold. Rapid, thin-section axial images can be obtained with very little artifact, and they can be merged and reproduced in any plane. Three-dimensional reconstructed CT images can also be produced and rotated in any plane. CT angiography is one example of a technique that is possible with helical CT. Thin-section axial images, contrast bolus tracking, and elimination of background tissue allow accurate visualization of vascular structures. Reconstruction of these images allows a noninvasive CT evaluation of vascular structures.

Xenon CT involves the inhalation of xenon gas over a period of time, with sequential CT cuts and subsequent calculations of xenon uptake. This technique is valuable for measuring cerebral blood flow. Spiral CT has also allowed the development of perfusion CT techniques. Dynamic intravenous administration of contrast material is tracked with rapid serial imaging during its first-pass circulation through the brain tissue capillary bed. Post-processing mathematic models for computing perfusion maps allow the measurement of cerebral blood volume, cerebral blood flow, and mean transit time. This technique is becoming more valuable in the physiologic assessment of brain tissue in patients with stroke, tumor, trauma, dementia, vasospasm, and epilepsy.[1]

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) uses magnetic field gradients and radiofrequency pulses rather than ionizing radiation. Many sequences that vary the MRI signal parameters are obtained, allowing tissue characterization based on the tissue's inherent response to magnetic field and radiofrequency pulses. Continual refinements in MRI sequence techniques have drastically reduced imaging time and increased the conspicuity of pathologic changes. A gadolinium-based contrast agent can be injected intravenously, which allows better visualization of intracranial and intraspinal pathology. Magnetic resonance angiography (MRA) sequences use the property of flowing spins to create an angiographic image. These methods create greater signal intensity in flowing blood than in the surrounding stationary tissues. The background tissue is effectively subtracted from the tissue volume, and the resultant images can be "reconstructed" and simulate a standard angiogram.

A wide variety of MRI sequences are being investigated that are based on physiologic changes rather than anatomic changes. Functional MRI techniques are showing promise in the detection and assessment of cerebral pathophysiology and in the characterization and regional mapping of distinct human cognitive functions, such as vision, motor skills, language, and memory.[1] Diffusion-weighted MRI is based on the evaluation of free versus restricted movement of water molecules. Diffusion-weighted MRI is now considered a standard sequence in evaluating stroke, because it is more sensitive than standard MRI in identifying acute stroke and in differentiating stroke from other pathologies.[2,3] Magnetic resonance perfusion can be performed by different methods, but the final outcome allows the measurement of vascular supply to brain tissue. Perfusion can also be used to measure metabolic activity, because blood supply and tissue activity are related. Although evaluation of brain ischemia is the most common clinical application, perfusion studies are also proving useful in tumor characterization.[4]

Magnetic resonance spectroscopy can noninvasively measure numerous biochemicals in a small volume of brain tissue. Many nuclei can be detected, but phosphorous (^{31}P) and proton (^{1}H) spectroscopy have the most clinical utility. Phosphorous spectroscopy provides information concerning tissue energetics, phospholipid metabolism, and intracellular pH. Proton spectroscopy can provide information on neuronal density, membrane constituents, amino acid metabolism, and glycolysis. Current uses include characterizing tumors, differentiating recurrent tumor from radiation necrosis, and distinguishing intracranial tumor from infection.[5] However, many other disease processes are also being studied with spectroscopy.[6]

The disadvantages of performing MRI on critical care patients involve the preprocedural preparation and screening.[7] MRI is contraindicated in patients with pacemakers, certain cardiac valves, and intraocular metal fragments. Careful screening for the presence of cerebral aneurysm clips and other metallic devices, stents, and surgical implants is necessary. In addition, respirators and physiologic monitors must be MRI compatible. Only oxygen and nitrogen tanks composed of aluminum can enter the magnet suite. Frequently, patients must be switched from MRI-incompatible respirators to MRI-compatible ones before the procedure can take place. All these precautions and modifications can significantly delay imaging in the acute setting. In addition, such basic medical instruments as stethoscopes, hemostats, and scissors must remain outside the MRI suite.

NUCLEAR MEDICINE STUDIES

Evaluation of CNS pathology with nuclear medicine techniques is still undergoing investigation, but it is an area of rapid development because of its ability to provide physiologic imaging rather than standard anatomic imaging. Positron emission tomography (PET) generates cross-sectional images by quantitatively measuring administered compounds containing various cyclotron-generated positron emitters such as ^{18}F-fluorodeoxyglucose. PET can provide functional information such as glucose and oxygen utilization, as well as hemodynamic data about blood flow and blood volume.[8] Single photon emission computed tomography (SPECT), developed from PET, analyzes the distribution of radiopharmaceuticals that are incorporated into biologically active compounds. Cerebral blood flow, tissue metabolism, neuroreceptors, and glucose and amino acid metabolism can be evaluated with this technique.[9]

ANGIOGRAPHY

Percutaneous transfemoral catheterization is used to evaluate cerebral and spinal vascular anatomy and integrity. Cerebral angiography is an invasive procedure and imposes some risk. The overall complication rate is 2% to 4%, with the majority of complications being minor and transient, such as groin hematoma, subintimal injections, and minor allergic reactions.[10] More severe complications, such as cerebral infarction, seizure, and death, occur infrequently.

Although Doppler ultrasonography, CT angiography, and MRA have had a significant impact on the evaluation of cerebrovascular diseases, especially atherosclerotic disease,

cerebral angiography is still considered the gold standard. In the acute setting, in cases of intracranial hemorrhage, angiography is necessary to establish the presence of vascular malformations or aneurysms. In trauma, angiography is used to evaluate vascular integrity.

Interventional neuroradiology has made great strides in the treatment of a variety of neurovascular lesions. Safer microcatheters and a wide variety of treatment options are now available that gain access to lesions through preexisting vascular paths. Therapeutic techniques include embolization of vascular tumors, aneurysms, and arteriovenous malformations; stent placement; angioplasty; and thrombolysis.

BRAIN

PATTERNS OF DISEASE

Edema

Cerebral edema or brain swelling is caused by a localized or diffuse abnormal accumulation of water and sodium. This differs from cerebral engorgement caused by vasodilatation or obstructed venous outflow. Both conditions lead to an increase in brain volume and are difficult to distinguish on routine imaging studies. Newer methods such as xenon CT and diffusion-weighted MRI are useful in this regard.

Three types of edema have been described:

1. *Vasogenic edema* is the result of increased capillary permeability and involves mainly the white matter. This type of edema is most often associated with tumor, abscess, or trauma but can also be seen with infarct and ischemia.
2. *Cytotoxic edema* is the result of cellular swelling and involves both gray and white matter. Ischemia, anoxia, and hypo-osmolar states are the primary considerations.
3. *Interstitial edema* is the result of cerebrospinal fluid migration into the periventricular white matter. This form of edema is secondary to conditions that impede cerebrospinal fluid absorption, such as hydrocephalus.

Except for location, the CT and MRI appearance of all types of edema is similar. On CT scans, increased water is seen as a decrease in density and appears dark. On MRI scans, an increase in water is seen as an area of decreased signal on T1-weighted images and an area of increased signal on T2-weighted images. The vasogenic form of edema extends along the fingers of white matter, interposed between normal gray matter (Fig. 57-1). This pattern has a nonvascular distribution and is often associated with mass effect. The cytotoxic form of edema involves gray and white matter, and the decreased density extends uniformly to the calvaria. Typically, this edema follows a vascular distribution and produces less mass effect for its size (Fig. 57-2). The interstitial form of edema involves the periventricular white matter and appears as a fairly symmetrical low-density rim in the periventricular region that masks the ventricular wall and gradually fades into the surrounding white matter.

Hemorrhage

Intracranial hemorrhage may be parenchymal or extra-axial (epidural, subdural, and subarachnoid spaces) in location. Parenchymal hemorrhage can be traumatic in origin but is more likely nontraumatic, from an underlying disease such as hypertension or neoplasm or from a vascular anomaly. Epidural and subdural extra-axial hemorrhage is most often a result of trauma. Subarachnoid hemorrhage is most often secondary to trauma but is also associated with ruptured congenital aneurysm.

The imaging appearance of hemorrhage is dependent on the age of the hemorrhagic event. On CT, acute hemorrhage typically appears hyperdense because of the high hematocrit and globin component (Fig. 57-3*A*). However, this pattern may vary in different clinical situations. Acute hematomas may be isodense to brain in anemic patients when the hemoglobin drops below 10 g/dL[11] or in patients with a coagulopathy who fail to produce clot retraction.[12] As the hemorrhage resolves, the CT appearance also changes. Initially, as the clot retracts, the CT density may rise for 2 to 3 days after the initial event. Thereafter, the clot begins to liquefy and then resorb. The CT appearance demonstrates gradually decreasing density through an isodense stage between 1 and 6 weeks (depending on size) and finally a hypodense stage. The final CT appearance of resolved hemorrhage may show no residual abnormality or demonstrate a focus of low attenuation or calcification.[13]

The appearance of hemorrhage on MRI is more complicated because of the varying paramagnetic properties of blood breakdown products. As hemorrhage resolves, fibrinolysis, leukocyte infiltration, hemoglobin denaturation, and changes in red blood cell morphology interact to alter the MRI appearance at different stages.[14] The progression of resolution represents a continuum of changing intensity values and is not an all-or-none phenomenon. It progresses through the following stages (during resolution, these stages may be present simultaneously):

1. During the first 24 hours after parenchymal hemorrhage, intact red blood cells containing oxyhemoglobin accumulate. The oxyhemoglobin is diamagnetic and appears slightly hypo- to isointense on T1-weighted images and iso- to hyperintense on T2-weighted images.
2. Within 3 to 5 days, the hemoglobin becomes deoxygenated. The deoxyhemoglobin is paramagnetic and appears similar to oxyhemoglobin on T1-weighted images but becomes hypointense to brain on T2-weighted images (see Fig. 57-3*B* and *C*).
3. Between 3 and 7 days, intracellular methemoglobin starts to accumulate, beginning peripherally and advancing toward the center of the clot. On T2-weighted images, the intracellular methemoglobin behaves similarly to deoxyhemoglobin and remains hypointense, but the T1 values begin to increase, causing the periphery of the clot to become hyperintense (see Fig. 57-3*B* and *C*).
4. Between 7 days and 2 to 3 months, the red blood cells lyse and release methemoglobin into the extracellular space. During this phase, signal intensities increase on both T1- and T2-weighted images. Hence, the hemorrhage appears bright on both sequences (see Fig. 57-3*B* and *C*).
5. During the final stage, which may begin within 2 weeks and last for years, conversion of methemoglobin to hemosiderin occurs as a result of phagocytic degradation. Iron is removed from the hematoma and deposited at the periphery. Signal intensities again decrease and give rise to hypointense signal on both T1- and T2-weighted images.

Most hematomas are associated with a surrounding area of edema that can be misinterpreted as an additional area of hemorrhage. Similar to oxyhemoglobin, edema is hypo- to isointense in comparison to brain on T1-weighted images

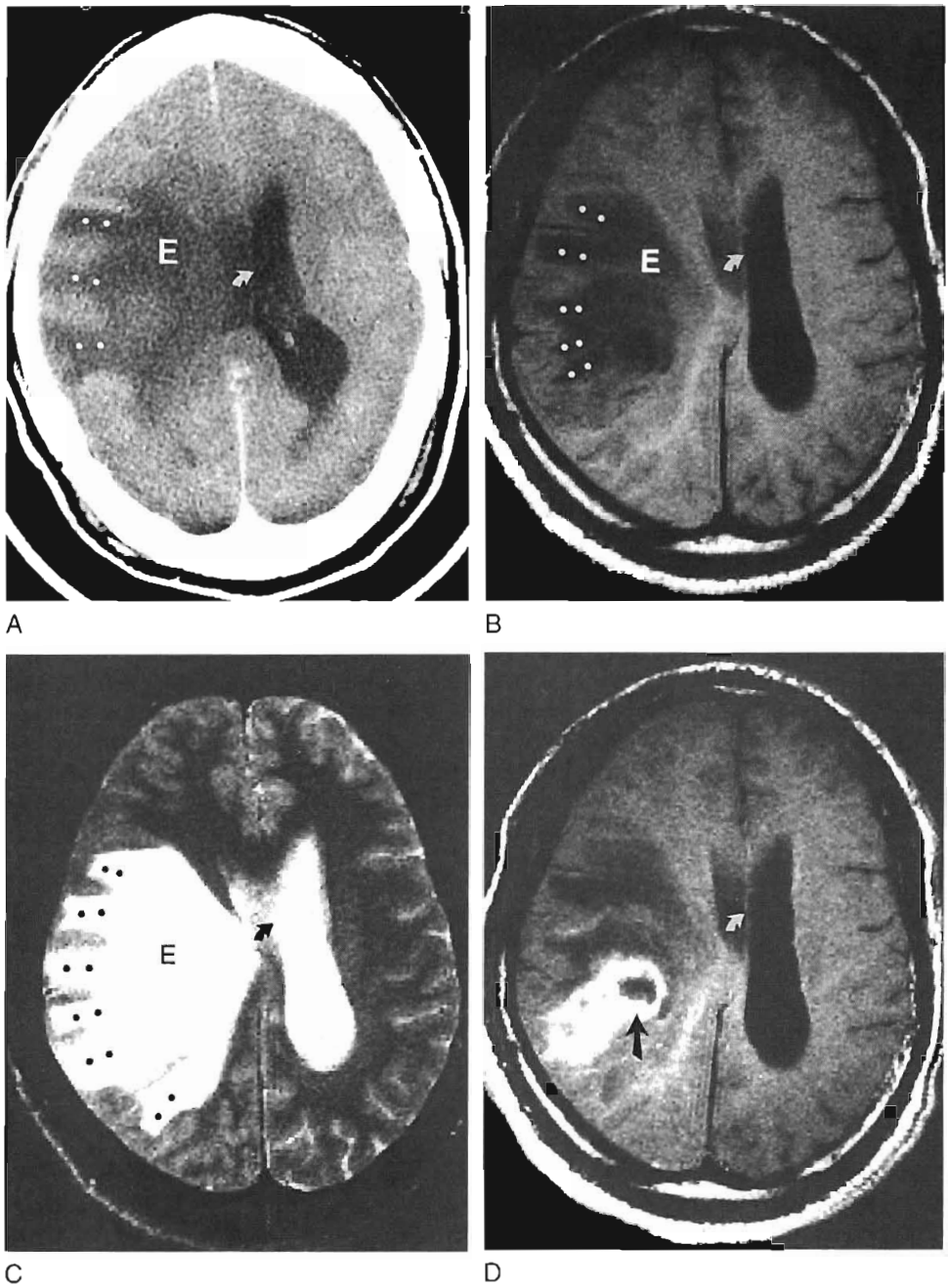


FIGURE 57–1. Vasogenic edema in glioblastoma. Non-contrast-enhanced axial CT scan *(A)*, axial T1-weighted MRI scan *(B)*, and axial T2-weighted MRI scan *(C)* all demonstrate an area of edema (E). The edema extends along the white matter fibers *(dots)*, with normal gray matter interposed. Axial T1-weighted MRI scan following contrast enhancement *(D)* demonstrates the enhancing tumor nidus *(arrow)*, distinct from the surrounding edema. Subfalcine herniation is also demonstrated on these images by displacement of the falx *(curved arrows)*.

and hyperintense on T2-weighted images. However, the signal characteristics of edema remain constant, and it gradually fades over time. Extra-axial blood collections resolve in an identical fashion, although the time required to resolve is slightly longer between stages.

Mass Effect, Shift, and Herniation

Lesions that increase intracerebral mass may eventually cause brain herniation.[15] This may be the direct result of an enlarging lesion, such as a tumor, or the indirect result of a lesion, such as edema caused by a tumor. Two relatively fixed dural partitions are present within the skull and create compartments across which brain substance may herniate. The falx cerebri separates the cerebral hemispheres, and the tentorium separates the cerebral hemispheres from the posterior fossa structures. Herniation is described in terms of location.

Subfalcine herniation occurs when the medial surface of a hemisphere, usually the cingulate or supracingulate gyrus, is compressed against or displaced beneath the falx. With CT or MRI, early signs may appear as compression or distortion of the lateral ventricles (see Fig. 57-1). Later stages are recognized by deviation of the falx and identification of the hemispheric structures that are crossing the midline.

Transalar herniation occurs when a mass, located in the frontal or temporal lobe, displaces brain tissue across the sphenoid ridge. When the mass arises in the temporal lobe and brain is displaced above the sphenoid ridge into the anterior cranial fossa, it is termed *ascending* transalar herniation. When the mass arises in the frontal lobe and displaces brain inferiorly into the middle cranial fossa, it is termed *descending* transalar herniation. With CT or MRI, displacement of the sylvian portion of the middle cerebral artery can identify the herniated brain directly or indirectly.

Transtentorial herniation occurs when a mass arising on either side of the tentorium results in brain herniation through the tentorial incisura. *Descending* transtentorial herniation is

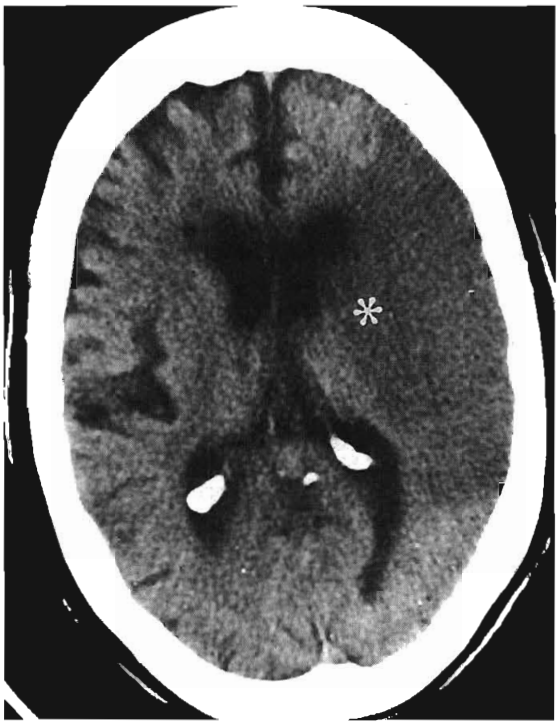


FIGURE 57–2. Cytotoxic edema and acute infarct. Axial non-contrast-enhanced CT scan demonstrates an area of decreased density *(asterisk)* involving the left middle cerebral artery territory. Gray and white matter structures are involved, and there is little mass effect.

caused by a supratentorial mass that displaces the medial temporal lobe through the incisura. On CT or MRI, the herniated brain pushes against and rotates the brainstem. This produces widening of the ipsilateral brainstem cistern and effacement of the contralateral cistern (Fig. 57-4). Associated findings may include dilatation of the contralateral temporal horn secondary to ventricular trapping. *Ascending* transtentorial herniation is caused by an infratentorial mass that displaces the pons, vermis, and adjacent portions of the cerebellar hemispheres upward through the incisura. On CT and MRI, the brainstem cisterns are symmetrically effaced as the cerebellar vermis bulges up through the incisura. There is often associated acute hydrocephalus caused by compression of the sylvian aqueduct.

Tonsillar herniation occurs when the cerebellar tonsils are pushed through the foramen magnum. This results in medullary compression and dysfunction of the vital respiratory and cardiac control centers. Sagittal MRI is the primary modality for demonstrating tonsillar herniation and the secondary effects on the brainstem.

SPECIFIC DISEASE PROCESSES

Head Trauma

In patients with acute head injury, management decisions must be made quickly. The critical issue is rapid and accurate detection of potentially treatable or surgically correctable lesions. In this regard, CT continues to be the primary modality for the initial evaluation of patients with head injury.[16] Its advantages include fast examination time, wide availability, fracture detection, lack of contraindications, and high accuracy.[17] Although MRI is more sensitive in detecting intracranial traumatic lesions, it is limited by a longer examination time, less conspicuity of hyperacute hematomas, and difficulty in monitoring patients.[17] For the evaluation of chronic head injury, MRI is the modality of choice. It can identify small foci of old hemorrhage and gliosis and evaluate the presence and extent of diffuse axonal injury (shear injury) with greater sensitivity than CT scan.[18]

Injury to brain parenchyma may result in contusion, axonal (shear) injury, or hematoma. The imaging appearance of hematomas has been described previously. Contusions are caused by the direct impact of parenchyma against bone and are most common along the gyral surface of the frontal and temporal lobes. Shear injuries are secondary to rotational forces that produce tears in axonal fibers and are most common within white matter (subcortical white matter, corpus callosum, internal capsule, brainstem). Except for

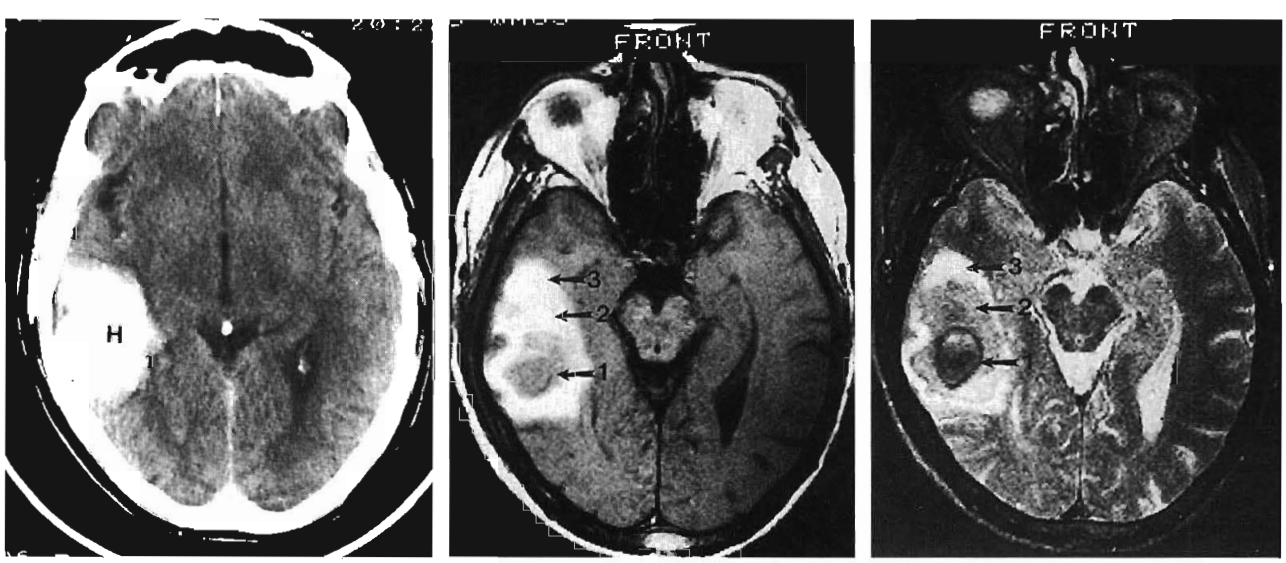


FIGURE 57–3. Hemorrhage. Axial CT image *(A)* demonstrates a large area of acute hemorrhage (H) in the right temporal lobe. T1-weighted *(B)* and T2-weighted *(C)* MRI scans demonstrate the hemorrhage in various stages of breakdown. The center of the lesion is dark on the T1- and T2-weighted images, indicating oxyhemoglobin (1). The intermediate zone is bright on the T1-weighted image and gray on the T2-weighted image, indicating intracellular methemoglobin (2). The outer rim is bright on both the T1- and T2-weighted images, indicating extracellular methemoglobin (3).

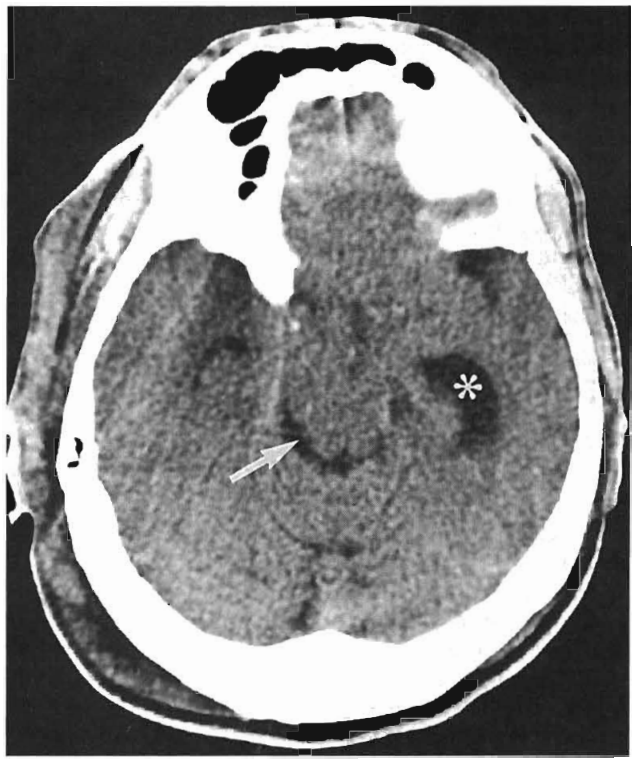
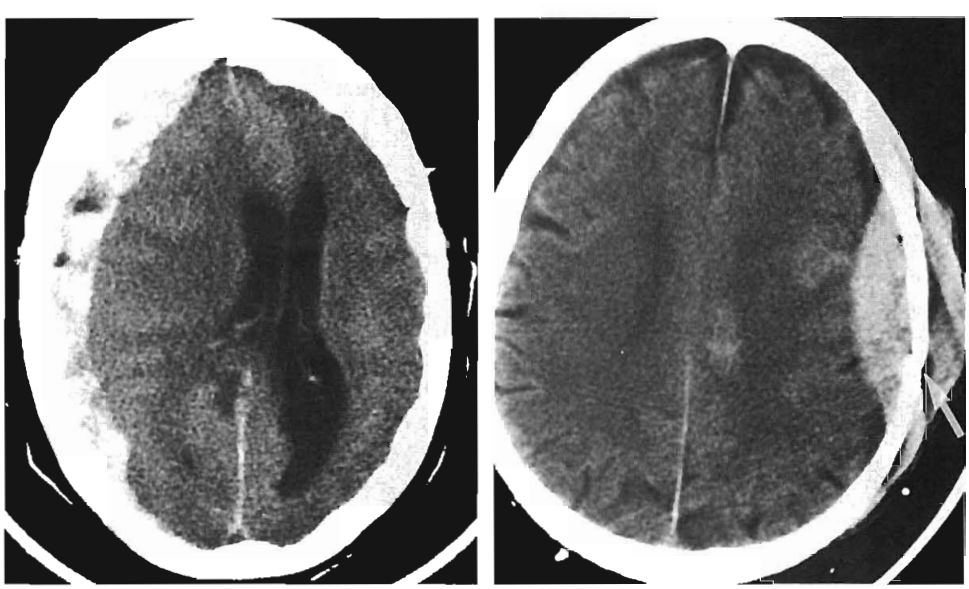


FIGURE 57–4. Right descending transtentorial herniation in a patient with a large right parietal subdural hematoma. Axial non-contrast-enhanced CT scan of the head at the level of the midbrain shows that the ipsilateral subarachnoid cistern is widened *(arrow)*, and the contralateral subarachnoid cistern is obliterated because of brainstem rotation. The left temporal horn is also dilated *(asterisk)*, indicating trapping of the left lateral ventricle.

location, the imaging characteristics of nonhemorrhagic contusions and shear injuries are similar. Initial studies may be normal or demonstrate small foci of edema. Shear injuries may remain nonvisible on CT but become more apparent on MRI. Larger contusions may contain petechial hemorrhage and appear as ill-defined heterogeneous lesions with little or no mass effect. Edema and mass effect may increase in the first 48 hours after trauma, making these lesions more evident on imaging studies.

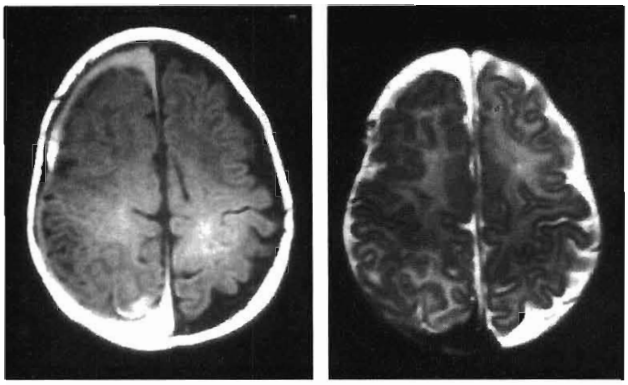
Damage to the brain coverings may lead to hemorrhage into the intraventricular, subarachnoid, subdural, or epidural spaces. On CT, intraventricular and subarachnoid hemorrhage is identified by replacement of the normal low-density cerebrospinal fluid by high-density blood. When subtle, subarachnoid hemorrhage can be mistaken for generalized edema, with loss of the basal cisterns. Subdural hematomas typically appear as crescentic mixed or hyperdense collections that cross suture lines but not dural attachments (Fig. 57-5*A*). Epidural hematomas appear as biconvex, hyperdense collections that cross dural attachments but not suture lines (see Fig. 57-5*B*). With rapid accumulation of blood, unretracted semiliquid clot may be present. In this situation, CT demonstrates hypodense areas within the hyperdense hematoma, the so-called swirl sign.[19] Distinction between these two collections is important, because an epidural hematoma is due to arterial bleeding and is a surgical emergency. Without surgery, these lesions resolve by gradually decreasing in density and appear hypodense at about 3 weeks' time.

Nonaccidental head injury is the leading cause of morbidity and mortality in abused children younger than 2 years old.[20] Mechanisms include direct impact, asphyxia, and shaking or whiplash injury. Injuries encountered include skull fracture, subdural hematoma, subarachnoid hemorrhage, and shear injuries. Cerebral infarction can also be seen secondary to numerous mechanisms, including smothering, strangulation, and shaking. Subdural hematoma is regarded as one of the most characteristic CNS lesions encountered in "shaken baby" syndrome. In fact, subdural hematomas are more often associated with nonaccidental injury than with accidental trauma.[21] The CT appearance of nonaccidental injury in children is similar to that in adults. However, subdural hematoma is more common along the posterior interhemispheric fissure and appears as increased attenuation along the falx. Other common locations include the anterior interhemispheric, tentorial, and parieto-occipital regions. MRI can determine the age of the blood products and provide an accurate estimate of the time the hemorrhage occurred because of the stages of resolution, as discussed earlier. The blood clot resolves similar to a parenchymal hemorrhage but at a different rate. MRI can also determine the coexistence of blood products of different ages, indicating repeated abuse (Fig. 57-6).



A B

FIGURE 57–5. Subdural and epidural hematoma. *A*, Axial CT scan of the head demonstrates a mixed-density subdural hematoma along the right frontoparietal lobes. The mixed-density appearance is most likely due to the presence of unretracted, semiliquid clot. *B*, Axial CT scan of the head demonstrates a left biconvex hyperdense collection that is classic for epidural hematoma. A fracture *(arrow)* can also be identified.



A B

FIGURE 57–6. Nonaccidental head injury. Axial T1- *(A)* and T2-weighted *(B)* MRI scans of an infant reveal bilateral subdural blood collections of different ages. The right collection shows blood in the late subacute phase (2 to 4 weeks old), and the left shows blood in the chronic phase (>1 month). This finding is almost proof positive of repeated abuse.

Vascular Lesions

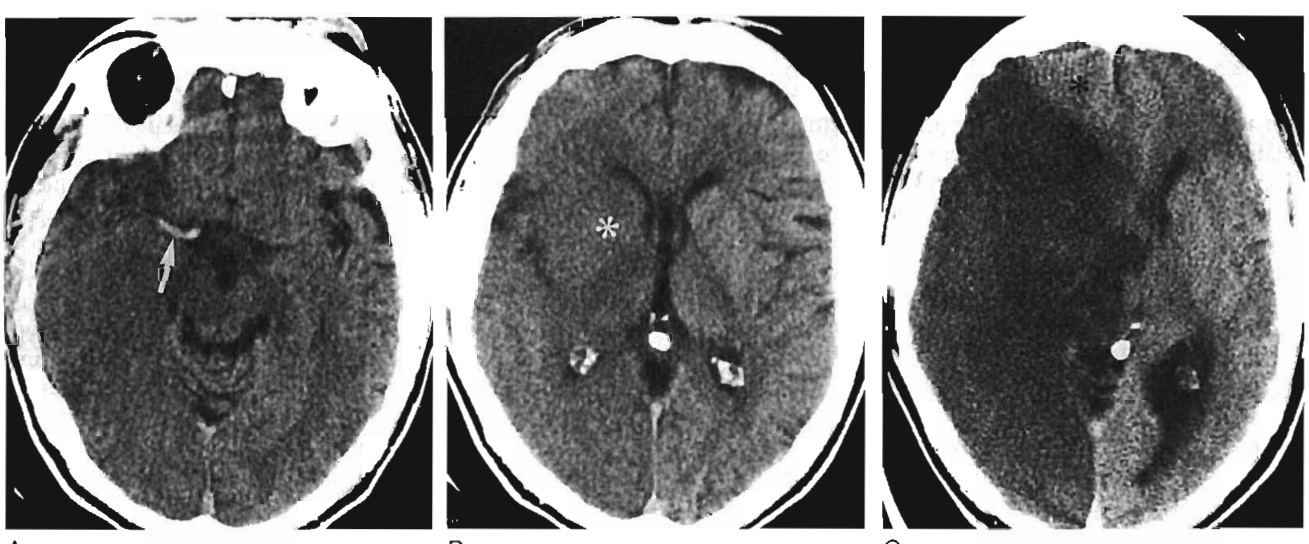
Ischemia, Hypoxia, and Infarct. Although CT demonstrates only about half of infarcts within the first 48 hours, it remains the imaging modality of choice in evaluating patients with symptoms of transient ischemic attack, reversible ischemic neurologic deficit, or completed stroke.[22] In the acute setting, CT can identify the location and extent of infarction; distinguish among ischemic stroke, hemorrhagic infarction, and primary intracerebral hemorrhage; and effectively exclude lesions that mimic stroke.

The CT appearance depends on the age of the infarct, as follows:

- In the hyperacute stage (first 24 hours), the CT scan may be normal or demonstrate a subtle decrease in density and loss of gray-white differentiation (Fig. 57-7).
- During the acute stage (within the first week), the infarct becomes more pronounced owing to the decreased density produced by cytotoxic edema (see Fig. 57-2). The infarct is better defined, involves both gray and white matter, and corresponds to a known vascular territory.
- The subacute stage may persist for 1 to 3 weeks, during which time the edema and mass effect begin to resolve.
- Chronic infarcts demonstrate parenchymal replacement, with well-defined, sharply marginated zones of cystic encephalomalacia and gliosis. The infarct behaves like a contracting, rather than an expanding, mass.

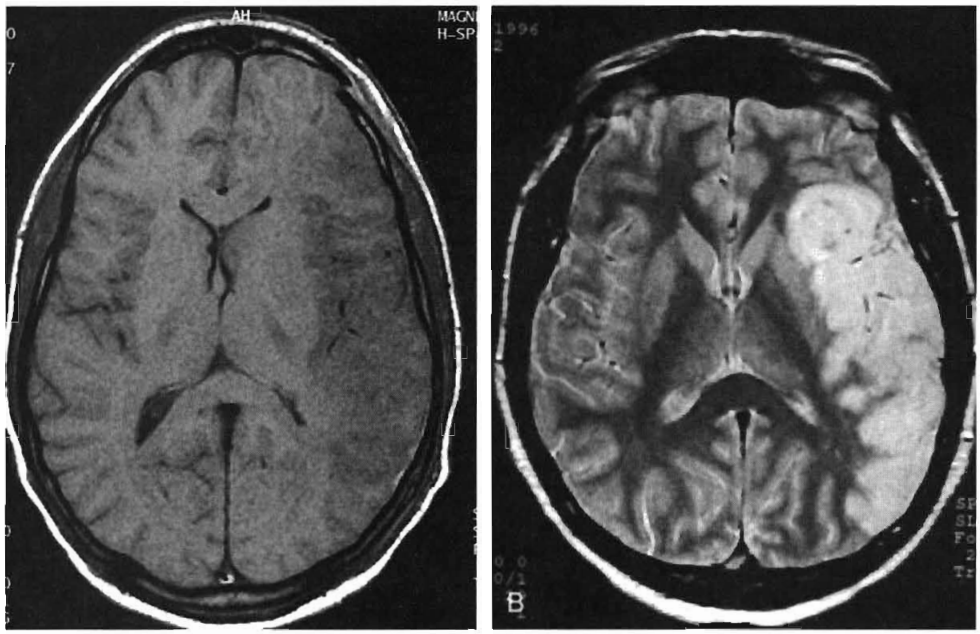
The MRI appearance reflects the changes of cytotoxic edema (Fig. 57-8). Nonhemorrhagic infarcts begin with subtle increased signal intensity on T2-weighted images and minimal changes on T1-weighted images. Subtle findings include stagnation of blood flow (arterial enhancement) and swelling of the involved gyri. Diffusion-weighted MRI has become a standard in the evaluation of acute ischemia (Fig. 57-9). Acute ischemia induces water influx into cells (cytotoxic edema), which results in an increased proportion of restricted water. The diffusion-weighted sequence is sensitive to this restricted water, which can be demonstrated on images as increased signal. The apparent diffusion coefficient values can be mapped and an additional image generated that confirms the acute nature of the infarct as an area of low signal.

CT and MRI perfusion techniques can demonstrate diminished blood perfusion within minutes of an insult. When MRI perfusion studies are coupled with diffusion images, a penumbra can be identified as a zone of decreased perfusion surrounding an area of absent perfusion. Only the central area shows the diffusion restriction. The penumbra represents viable tissue that is at risk for infarction but may still be salvageable.[23] Perfusion techniques can also demonstrate subtle areas of decreased perfusion without a completed infarct (Fig. 57-10).



A B C

FIGURE 57–7. Acute infarct. Axial non-contrast-enhanced CT images obtained at the level of the temporal lobe *(A)* and through the level of the basal ganglia *(B)* demonstrate an area of low density involving the gray and white matter of the right hemisphere. There is loss of gray-white matter differentiation, especially noticeable in the region of the basal ganglia *(asterisk, B)*. Compare the right and left sides. High density is identified within the right middle cerebral artery *(arrow, A)*, representing clot. Axial non-contrast-enhanced CT scan obtained 48 hours later *(C)* demonstrates marked edema involving the territories of the right, middle, and posterior cerebral arteries. Note the sparing of the right anterior cerebral artery territory *(asterisk, C)*.



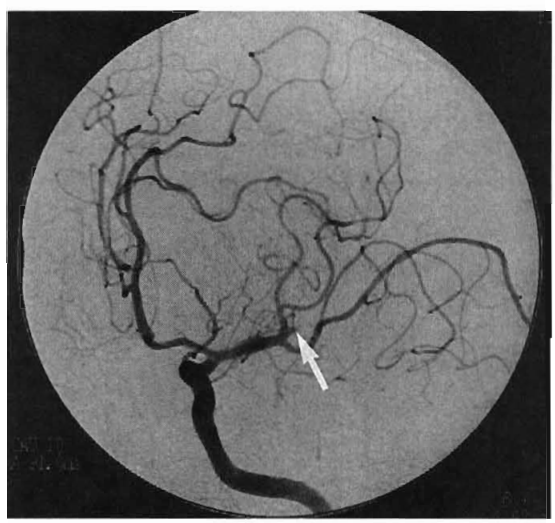


FIGURE 57–8. Infarct. Axial T1-weighted *(A)* and T2-weighted *(B)* MRI scans of a patient being evaluated for stroke. The initial CT scan (not shown) was normal. MRI demonstrates an area of cytotoxic edema involving the distal left middle cerebral artery territory. The edema is hypointense to brain on the T1-weighted image and hyperintense to brain on the T2-weighted image. Left internal carotid artery angiogram *(C)* demonstrates the occluded branch of the left middle cerebral artery *(arrow)*. Within the proper time frame, intra-arterial thrombolysis would be a method of management for this patient.

Treatment of acute embolic infarct with interarterial thrombolysis has been gaining momentum and is changing the role of imaging. Thrombolysis has a very narrow window (0 to 3 hours) for the initiation of treatment. Any delay decreases the positive outcome. Because of this time frame, many methods have been developed to replace routine CT as the initial imaging modality.[24] The goal is to increase the sensitivity for detecting early infarction and demarcating the area at risk. Standard CT coupled with CT perfusion and CT angiography is one alternative. MRI techniques can provide significant information regarding acute cerebral infarction.[24] Use of a series of MRI sequences, a "stroke protocol," can reveal changes in gross anatomy (standard MRI), metabolic alterations (magnetic resonance spectroscopy), water movement restrictions (diffusion-weighted MRI), vasculature status (MRA), and physiologic blood flow data (MRI perfusion) (see Fig. 57-10).[23] During the hyperacute and early acute stages, when CT is usually negative, MRI can readily demonstrate the zone of infarction. In addition, patterns of contrast enhancement in acute ischemia may have prognostic implications with regard to the completeness or reversibility of the ischemic insult.[25] Other methods being used include xenon CT, SPECT, Doppler ultrasonography, and PET. The advantages and disadvantages of these techniques and their future roles in stroke therapy are still under investigation.

Hypertensive encephalopathy is a syndrome that occurs in patients with elevated blood pressure of any cause. Severe preeclampsia and eclampsia of pregnancy are the most common causes, and CNS involvement is common. Typical MRI findings include nonspecific white matter hyperintensities on T2-weighted images at the gray-white matter junction. Cortical and subcortical white matter edema occurs primarily in the occipital lobes. Characteristically, these lesions resolve completely with treatment. Hypotensive encephalopathy can occur in patients who have suffered an episode of hypotension such as that seen after cardiac arrest. Typically, this results in infarction in the watershed distribution, basal ganglia nuclei, thalamus, hippocampus, cerebellum, and brainstem.

Venous infarction can occur in isolation and is associated with thrombosis of a dural sinus or large draining vein. In contrast to arterial infarctions, venous infarctions are typically

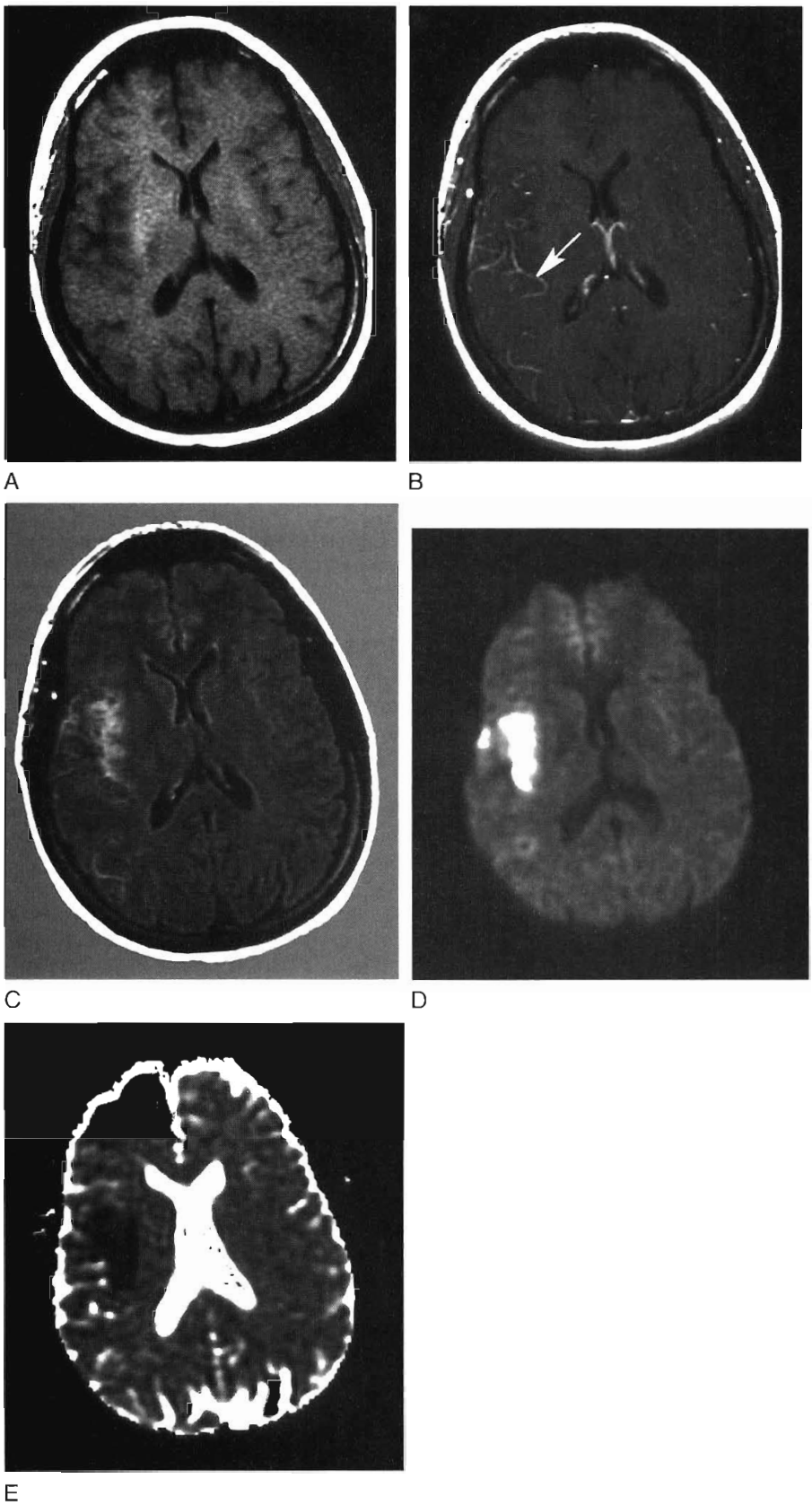


FIGURE 57–9. Hyperacute infarct. Axial T1-weighted images before *(A)* and after *(B)* contrast administration reveal subtle low intensity and arterial enhancement *(arrow)* in the right insular cortex. The fluid-attenuated inversion recovery (FLAIR) sequence *(C)* helps define the area of involvement. The diffusion-weighted sequence *(D)* shows the infarct to the best advantage. The acute phase is confirmed by the low signal on the apparent diffusion coefficient map *(E)*.

hemorrhagic and affect primarily the white matter. Pregnancy, dehydration, sepsis, and hypercoagulable states are common causes. CT can demonstrate the hemorrhagic infarct as well as the high-density clot in the venous sinus. MRI is very sensitive to the hemorrhagic foci and edema. Thrombosis of the venous sinus can be seen on routine MRI by identifying the clot in the vein. Magnetic resonance venography, performed similar to MRA, can also be helpful in identifying the occluded sinus.

Neonatal and pediatric stroke differs from adult stroke, and the imaging is more complex. The normal imaging appearance of the neonatal brain changes during development

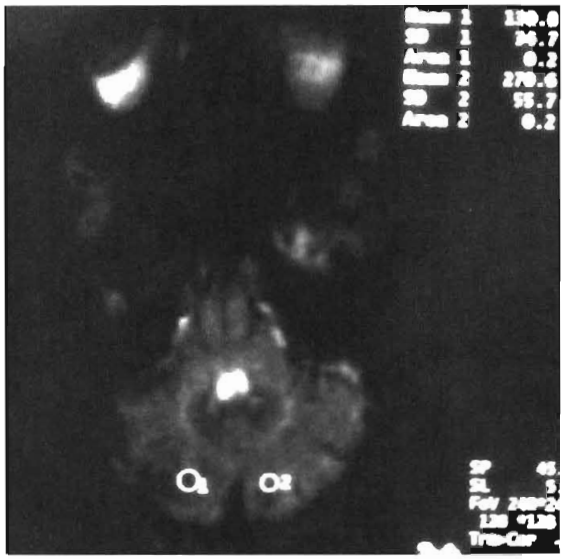


FIGURE 57–10. Perfusion deficit. MRI perfusion study shows hypoperfusion in the right posterior inferior cerebellar artery territory. The normal left side measured 270.6, and the abnormal right side measured 130.8.

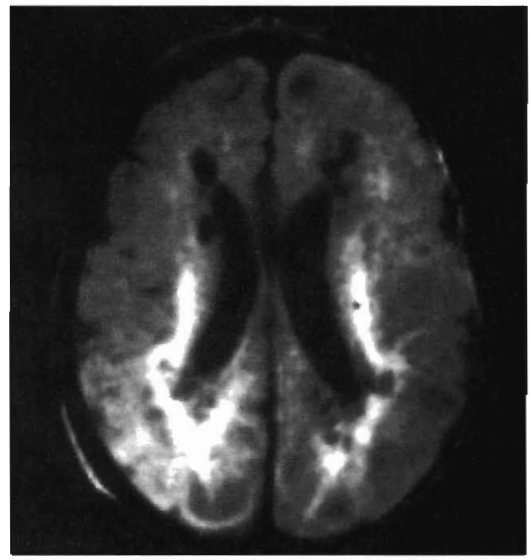


FIGURE 57–11. Periventricular leukomalacia. Axial fluid-attenuated inversion recovery (FLAIR) image obtained on a child with spastic diplegia and a history of prematurity and hypoxic episodes. Multifocal white matter hyperintensities, reduced white matter volume, irregular ventricular contours, and cystic changes are typical findings of periventricular leukomalacia.

because of the degree of myelination. In general, the brain of a term infant has myelinated fibers only in the brainstem and cerebellum. As the baby grows, myelination proceeds from inferior to superior and posterior to anterior. Myelination is typically complete at age 1 year. These changes create variable CT and MRI appearances, depending on the age of the baby. The differences among a preterm infant's brain, a term infant's brain, and an older child's brain are dependent on blood supply and metabolic demands, which differ at each stage. The imaging appearance is therefore dependent on the age of the child at the time of the insult and the duration of the insult.

In the preterm brain, the early imaging findings after an anoxic event include germinal matrix hemorrhage, periventricular venous infarction, and periventricular leukomalacia.[26] The germinal matrix is a rich vascular stroma in the subependymal caudothalamic groove that is very vulnerable to hemorrhage. When an insult occurs, the germinal matrix bursts, and blood leaks into the ventricles or parenchyma. Ultrasonography is used to stage the degree of hemorrhage. Venous infarctions are similar to those discussed earlier but occur in the periventricular region. These focal hemorrhages are readily seen with MRI and are frequently seen with CT. Periventricular leukomalacia represents areas of coagulation necrosis of the white matter, leading to reduction of the central white matter. CT and MRI demonstrate loss of white matter, primarily in the parietal and occipital regions, and enlargement of the ventricles, with ragged borders (Fig. 57-11). Cystic areas may be present, and the sulci extend almost to the ventricles.

In the term brain, diffuse or focal edema, basal ganglia necrosis, and lamina necrosis are the patterns typically seen. At this age, MRI is more sensitive to changes from ischemia than are other modalities. The earliest sign of infarct in the term infant is loss of the gray-white differentiation that is normally seen on T2-weighted images. Occasionally, subtle edematous changes, such as swollen gyri, are the only signs of an acute infarct. Diffuse high signal in the basal ganglia on T1-weighted images can be seen 7 to 10 days after the insult. Cortical lamina necrosis is identified as curvilinear high signal intensity on T1-weighted images in the deeper layers of the cortex and bases of the sulci.

Mention should be made of total anoxia in preterm and term infants. The pattern of injury in total anoxia involves primarily the brainstem, basal ganglia, thalamus, and perirolandic areas. On CT and MRI, changes reflecting edema are seen in these regions. In older children, there is involvement of the cerebral hemispheres. On CT, the cerebral hemispheres are of low density, with loss of gray-white matter differentiation secondary to the accumulation of water (Fig. 57-12). The cerebellum is spared and has normal blood flow that results in a "bright cerebellar" sign. On MRI, the

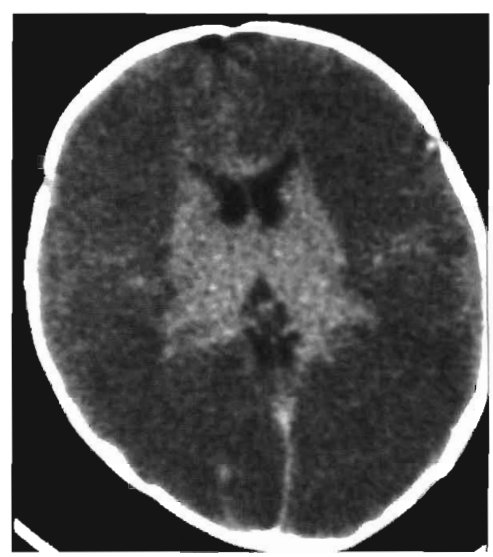


FIGURE 57–12. Global anoxia. Axial CT scan of a child following cardiac arrest. There is diffuse low density in the cerebral hemispheres and compression of the ventricles and sulci, reflecting the increased water accumulation (edema) and resultant mass effect. The basal ganglia and thalami appear bright, showing the "reversal" sign of global anoxia.

accumulation of water is reflected in the loss of gray-white matter differentiation, swollen gyri, and abnormal signal in the basal ganglia.

Congenital Aneurysm and Subarachnoid Hemorrhage. Evaluation of a patient with a suspected ruptured cerebral aneurysm should begin with a noncontrast-enhanced CT scan to demonstrate subarachnoid hemorrhage (Fig. 57-13). If the scan is positive and the patient is a surgical candidate, a cerebral angiogram is performed to identify the aneurysm, identify additional aneurysms, determine which aneurysm ruptured (when multiple aneurysms are present), and assess the presence or absence of associated vasospasm (see Fig. 57-13). MRI and MRA are increasingly important in the evaluation of aneurysms, but primarily in the nonacute setting to screen patients considered to be at high risk for aneurysms or those with focal cranial nerve deficits.[27]

Therapy of congenital aneurysms is undergoing significant changes. Intravascular techniques using detachable coils or balloons now play an important role in the management of certain ruptured and nonruptured aneurysms. Endovascular occlusion of intracranial aneurysms using detachable platinum coils provides a therapeutic alternative, especially in patients with aneurysms that are considered technically difficult or have a high surgical risk.[28,29]

For patients with suspected vasospasm, imaging modalities other than angiography have proved useful. Xenon CT can assess regional blood flow in patients symptomatic from vasospasm.[30] Transcranial Doppler ultrasonography provides an additional noninvasive method of measuring flow velocities and indirectly assessing vessel diameter.[31,32] Treatment of symptomatic vasospasm is also undergoing changes. Percutaneous transluminal balloon angioplasty and intra-arterial papaverine infusion have been effective in treating patients with vasospasm.[33]

Vascular Malformations. Four types of vascular malformations are described: (1) arteriovenous malformation (AVM), (2) capillary telangiectasia, (3) cavernous angioma, and (4) developmental venous anomaly (venous angioma).

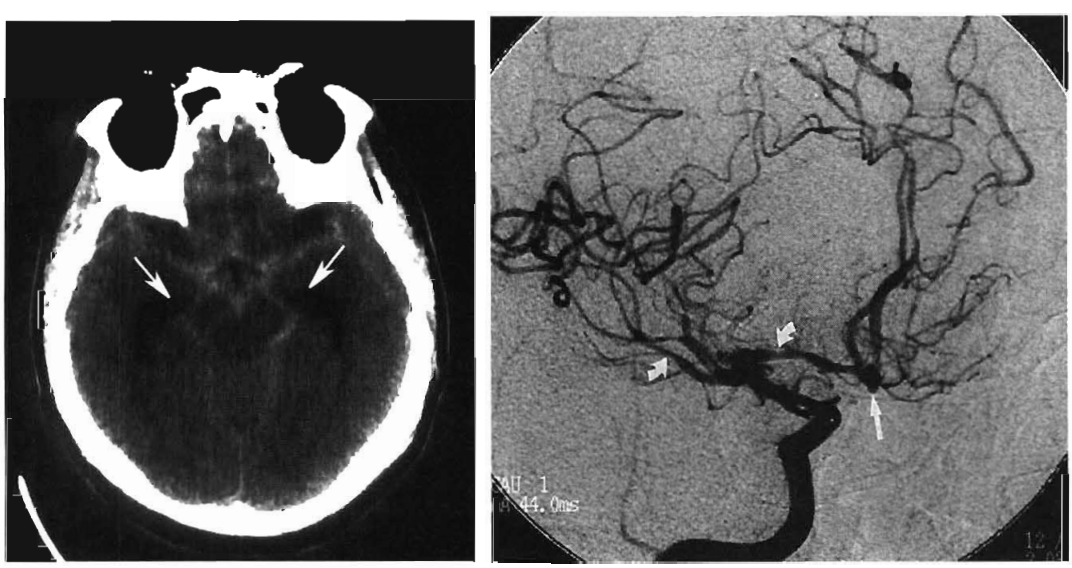
AVMs are the most common type. An unruptured AVM may not be apparent on non-contrast-enhanced CT or may appear as a subtle hyperdense region. After contrast administration, large, linear, tortuous, high-density structures representing the serpentine vessels are identified (Fig. 57-14). On MRI, these abnormal vessels appear as areas of absent signal (flow void) caused by rapid blood flow through the normal vessels. Angiography is performed to evaluate these lesions because it demonstrates the feeding arteries and draining veins and can establish pial, dural, or mixed supply (see Fig. 57-14). Intravascular embolization of all or a portion of the AVM may also be performed as a treatment option.[34] When an AVM ruptures, the imaging characteristics are those of hemorrhage, as described previously.

Capillary telangiectasia and cavernous angioma are best evaluated by MRI, because angiography is typically normal and CT is insensitive. The MRI signal characteristics are variable because of the presence or absence of blood products.

Developmental venous anomalies (venous angiomas) are typically not apparent on non-contrast-enhanced CT, but the large transcortical vein can be identified after contrast administration. The caput medusae or smaller feeding veins are frequently seen and are diagnostic. On MRI, the large vein and caput are seen as linear flow voids. Angiography is not necessary for the evaluation of venous angiomas because of the classic CT and MRI appearance and the untreatable nature of these lesions.

Neoplasm

Neoplasms are typically grouped according to location. This method helps narrow the differential diagnosis, because the imaging characteristic of tumors vary widely, based on their internal components. Knowledge of the imaging characteristics of specific tumors, the age and sex of the patient,



A B

FIGURE 57–13. Subarachnoid hemorrhage and aneurysm. *A*, Axial non-contrast-enhanced CT scan of the head reveals high density (blood) replacing the normal low density of cerebrospinal fluid within the suprasellar cistern and subarachnoid spaces. This indicates subarachnoid hemorrhage. Note also the dilated temporal horns *(arrows)*, indicating acute hydrocephalus. *B*, Right internal carotid artery angiogram demonstrates the presence of a congenital anterior communicating artery aneurysm *(arrow)*, as well as vasospasm *(curved arrows)*.

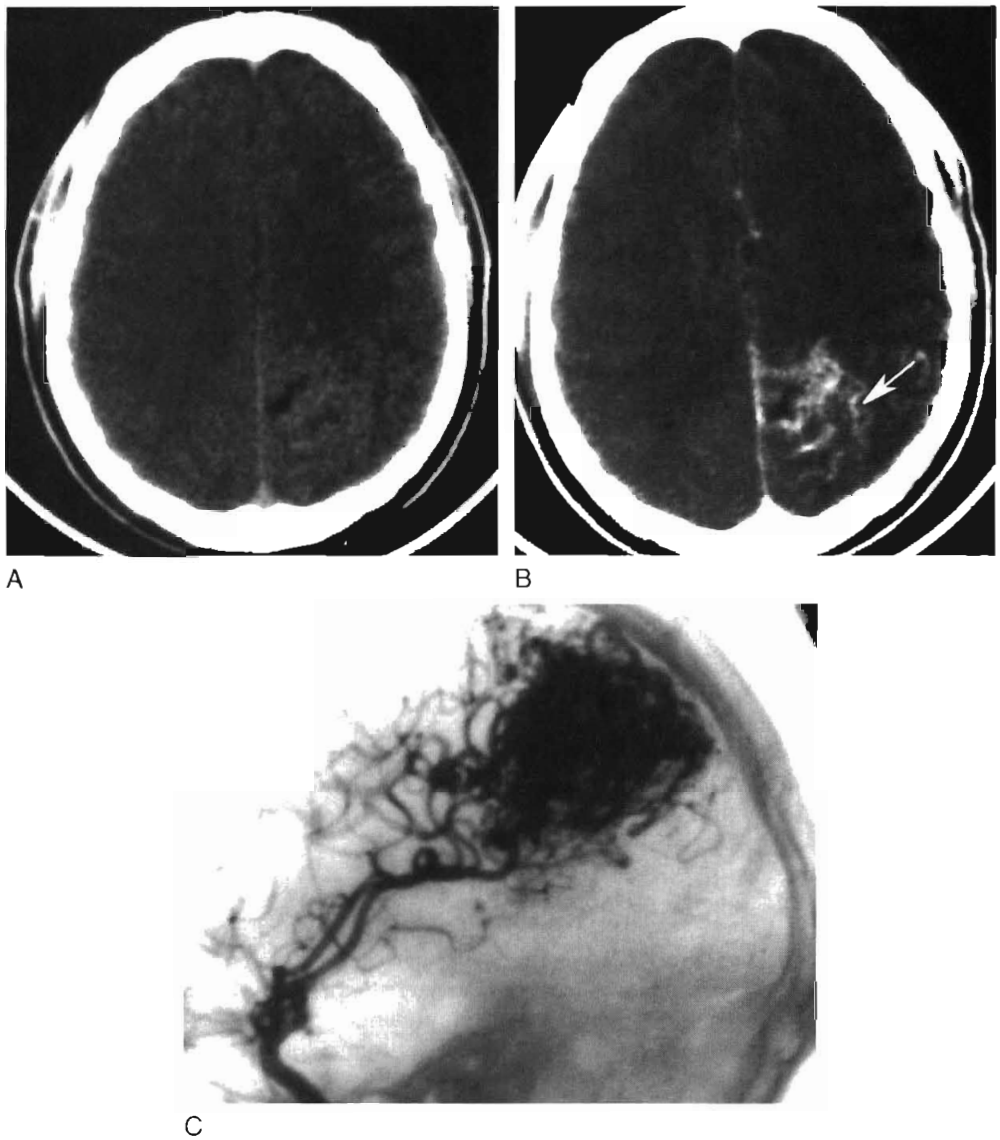


FIGURE 57–14. Arteriovenous malformation. *A*, Axial non-contrast-enhanced CT scan of the head reveals a vague area of hyperdensity in the posterior left parietal region. *B*, Contrast-enhanced CT scan demonstrates serpiginous enhancement of this lesion *(arrow)*. *C*, Internal carotid artery angiogram demonstrates an arteriovenous malformation being fed by the middle cerebral artery.

the clinical presentation, and the lesion location can narrow the differential diagnosis further and often provides a specific diagnosis.[35] On CT, low-grade gliomas may appear as subtle nonenhancing masses, but higher-grade gliomas often demonstrate heterogeneous enhancement, with large areas of necrosis and vasogenic edema (see Fig. 57-1). Metastatic lesions may be low-density and enhancing masses, as seen with lung or breast carcinoma, or they may have high density secondary to hemorrhagic components, as seen with melanoma and thyroid and renal cell carcinomas (Fig. 57-15). Cystic tumors, such as cystic astrocytomas, may be composed of large cysts with the density of cerebrospinal fluid. Epidermoid and dermoid tumors frequently contain areas of fat density and therefore appear very hypodense (less dense than cerebrospinal fluid).

MRI has high sensitivity but low specificity in the evaluation of neoplasms, because most tumors appear similar. Tumors are typically of low intensity on T1-weighted images and high intensity on T2-weighted images (see Fig. 57-1). There are a few notable exceptions, however, because the signal characteristics reflect tumor composition. For example, meningiomas, because of their homogeneous cellular makeup, tend to be isointense to brain on T1- and T2-weighted images. Epidermoid tumors appear bright on T1-weighted images and less bright on T2-weighted images, reflecting their high fat content.

Tumors that have been treated with radiation therapy present a special problem when trying to determine whether increasing mass effect and edema represent tumor recurrence or post-radiation necrosis. Routine imaging modalities are limited and are based on the observation of changes over time. This can delay further treatment or prematurely instigate unnecessary surgery. A variety of imaging modalities, including magnetic resonance spectroscopy and PET, are becoming increasingly important in this regard. With magnetic resonance spectroscopy, the diagnosis is based on the concentration of various metabolites. Recurrent tumors show an increase in choline levels and a decrease in *N*-acetyl aspartate, representing neuronal loss (Fig. 57-16), and radiation necrosis shows decreased levels of choline. Depending on the technique used, PET measures local glucose consumption, blood flow, or oxygen metabolism. These measurements are increased with recurrent tumor and decreased with radiation necrosis.

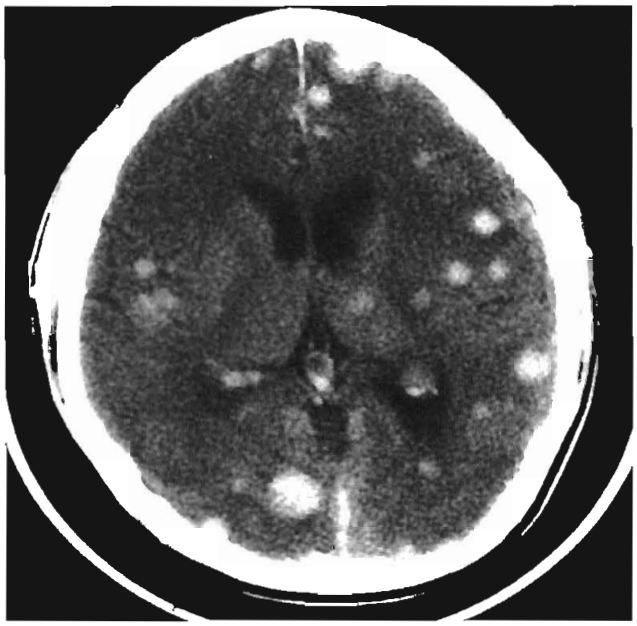


FIGURE 57–15. Intracranial metastatic disease. Axial contrast-enhanced CT scan of the head reveals multiple enhancing nodules throughout the gray and white matter structures, consistent with metastatic disease.

Infection and Inflammation

Infectious and inflammatory processes are considered according to their primary site of involvement: parenchymal or extra-axial.

Parenchymal Infection. Parenchymal infections include encephalitis, cerebritis, and abscess. Encephalitis, a diffuse inflammation of the brain, is often viral or toxic in origin. MRI is more sensitive than CT and demonstrates the changes earlier, making it the modality of choice when encephalitis is suspected clinically. On CT, there are vague areas of low density and subtle gyral enhancement after contrast administration. On MRI, affected brain typically appears hypointense on T1-weighted images and hyperintense on T2-weighted images, reflecting edematous changes. Herpes simplex virus (HSV) encephalitis is a common and specific form of encephalitis with fairly consistent imaging findings. HSV encephalitis is caused by HSV 2 in neonates and HSV 1 in children and adults. Imaging studies show gyral edema with a predilection for the temporal lobes, insular cortex, and cingulate gyri. Acute disseminated encephalomyelitis is an immune-related response to a previous viral infection or vaccination. MRI is the modality of choice and typically shows multifocal subcortical hyperintense lesions on T2-weighted images. Deep white matter can be affected, and lesions are typically bilateral and asymmetrical.

Cerebritis, an early phase of abscess formation, looks like encephalitis but is more focal in nature. Cerebral abscess results from liquefactive necrosis, producing a localized collection of pus or caseous material in a cavity surrounded by a fibrous capsule. On CT, an abscess cavity demonstrates central hypodensity (necrotic cavity); a thin, isodense wall (capsule); and surrounding low density (edema). Following contrast administration, there is enhancement of the capsule. Unlike the shaggy, irregular walls of a tumor, the walls of an abscess are typically smooth, well defined, and uniform in thickness; these are important differential features. MRI findings are similar to CT findings. The central cavity has variable signal characteristics, depending on the contents. The capsule is iso- to hyperintense on T1-weighted images,

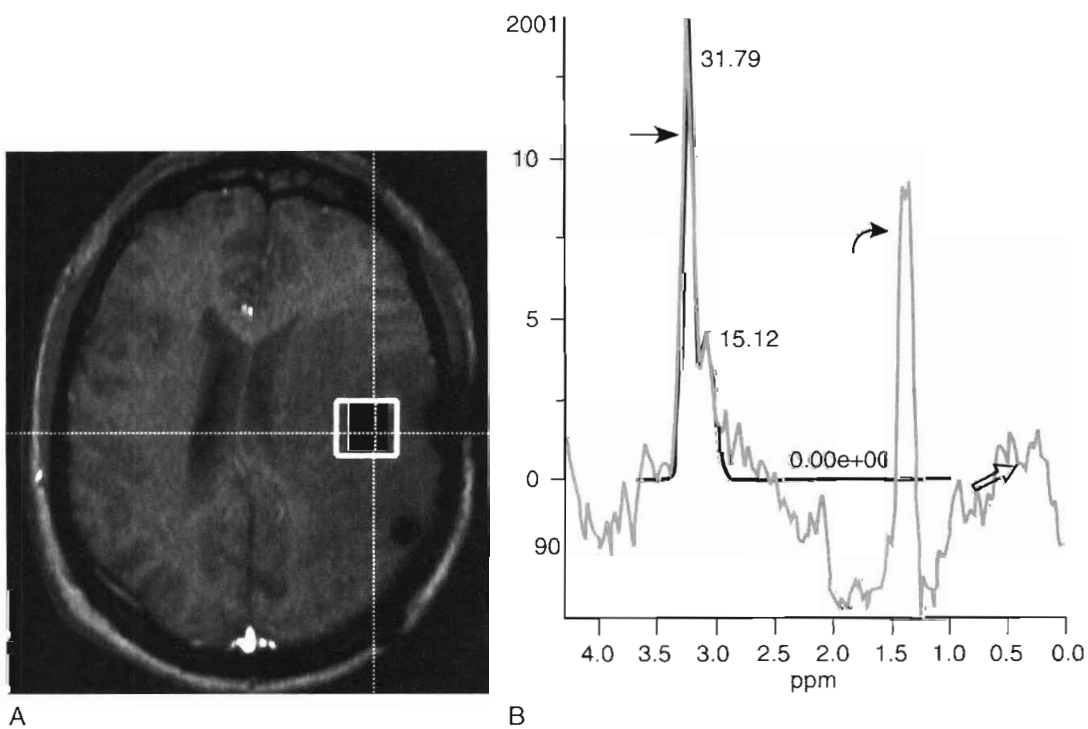


FIGURE 57–16. Recurrent high-grade astrocytoma. A study performed after radiation therapy (not shown) showed increased edema and mass effect, and the differential diagnosis included recurrent tumor and radiation necrosis. *A*, Axial MRI scan shows the volume of tissue *(box)* selected for spectroscopy. *B*, Proton spectroscopy reveals an increase in the choline peak *(arrow)*, a decrease in the *N*-acetyl aspartate peak *(curved arrow)*, and the appearance of a lactate peak (*open arrow*). This appearance is consistent with recurrent tumor, which was verified with repeat surgery and biopsy.

is hypointense on T2-weighted images, and enhances after contrast administration.

Extra-axial Infection. Extra-axial infections include ventriculitis, meningitis, and subdural or epidural empyemas. MRI is usually the modality of choice for extra-axial infections. In general, with both CT and MRI, contrast administration is necessary to establish the diagnosis of extra-axial infection. On CT and MRI, ventriculitis is characterized only by enhancement of the involved ventricular wall or walls. In meningitis, CT and MRI may be normal or demonstrate diffuse enhancement of the meningeal surfaces after contrast administration. The diagnosis of meningitis is made on clinical grounds and cerebrospinal fluid studies. Imaging is performed to exclude an associated abscess or empyema or to evaluate for complications, such as hydrocephalus and vascular thrombosis. Subdural and epidural empyemas are collections of pus that most often occur as complications of sinusitis, otitis, surgery, or trauma. On CT, the collections frequently have a density intermediate between cerebrospinal fluid and acute blood. On MRI, the collections are typically hypointense to brain on T1-weighted images and hyperintense on T2-weighted images.

White Matter Diseases

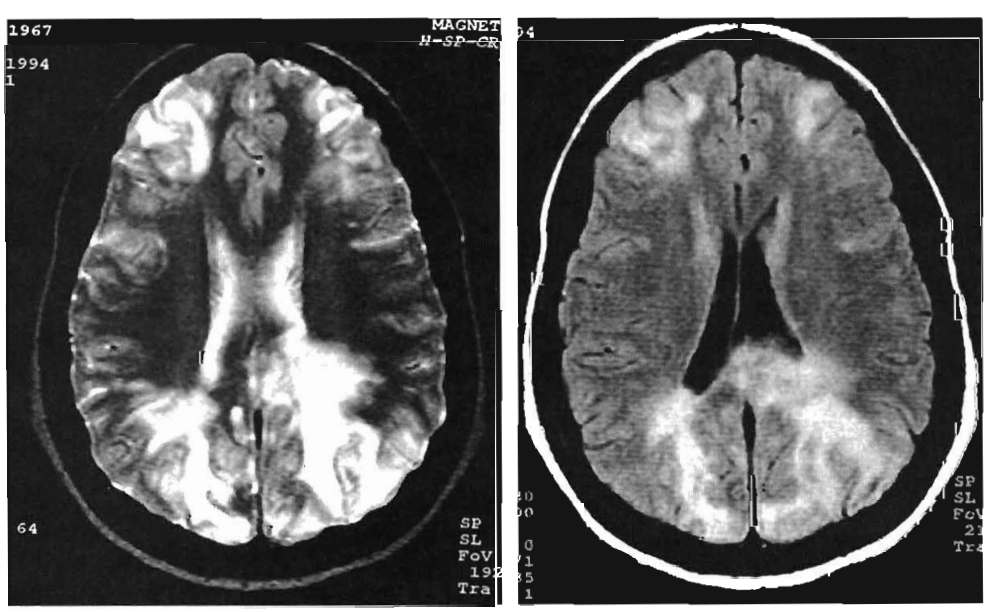
White matter diseases are classified as dysmyelinating (improper formation or maintenance of myelin) or demyelinating (normal myelin destroyed by exogenous or endogenous agents). Dysmyelinating disorders include the leukodystrophies and storage diseases. Demyelinating disorders can be idiopathic (multiple sclerosis), postinfectious (progressive multifocal leukoencephalopathy), toxic-degenerative, or vascular. MRI is much more sensitive than CT and is the study of choice for determining the presence and extent of white matter disease (Fig. 57-17). On T1-weighted images, these lesions appear as vague regions of low intensity. On T2-weighted images, white matter lesions appear hyperintense. Newer T2-weighted imaging sequences have the ability to suppress the bright signal produced by cerebrospinal fluid and increase the conspicuity of white matter lesions.[36] Although the majority of white matter diseases appear similar on imaging studies, occasionally the pattern of white matter involvement can lead to a more limited or specific diagnosis.

White matter diseases seldom present acutely; typically, they present as slow progression of neurologic deficits. When the presentation is acute, toxic and vascular diseases are the primary considerations (vascular disorders were already discussed). Toxic demyelination results from interaction of a chemical compound with the brain and may occur acutely. Radiation therapy or chemotherapeutic agents, such as cyclosporin A and methotrexate, may result in acute transient leukoencephalopathy. MRI demonstrates white matter lesions involving the deep white matter, with sparing of the cortex and underlying subcortical arcuate fibers.[37] Central pontine myelinolysis occurs in alcoholic or malnourished patients or in those who have undergone rapid correction of hyponatremia. On MRI, the white matter abnormalities are seen in the pons, with sparing of the corticospinal tracts. Acquired hepatocerebral degeneration occurs with many types of chronic liver disease, such as alcoholic cirrhosis, hepatitis, and portal systemic shunts.[38] MRI frequently demonstrates bilateral basal ganglia hyperintensities on T1-weighted images.

SPINE

PATTERNS OF DISEASE

It is often useful to classify spinal canal pathology according to the three spinal compartments, or spaces: intramedullary, extramedullary-intradural, and extradural (Fig. 57-18). Certain pathologic lesions occur with greater frequency in specific spaces; therefore, the diagnostic considerations can be significantly narrowed if a lesion can be localized to one of these spaces. In most instances, MRI is the modality of choice in evaluating spinal pathology, especially in the acute setting. The high degree of tissue contrast and spatial resolution can localize most lesions to a specific compartment, determine the extent of disease, and offer an accurate differential diagnosis. The only exception is acute trauma, in which case bony alignment and stability are best demonstrated by



A B

FIGURE 57–17. Progressive multifocal leukoencephalopathy. Axial T2-weighted *(A)* and fluid-attenuated inversion recovery (FLAIR) *(B)* images in a patient with human immunodeficiency virus (HIV). Multiple areas of white matter disease are identified; the FLAIR image increases their conspicuity. These findings in an HIV-positive patient indicate a postinfectious demyelinating process—progressive multifocal leukoencephalopathy.

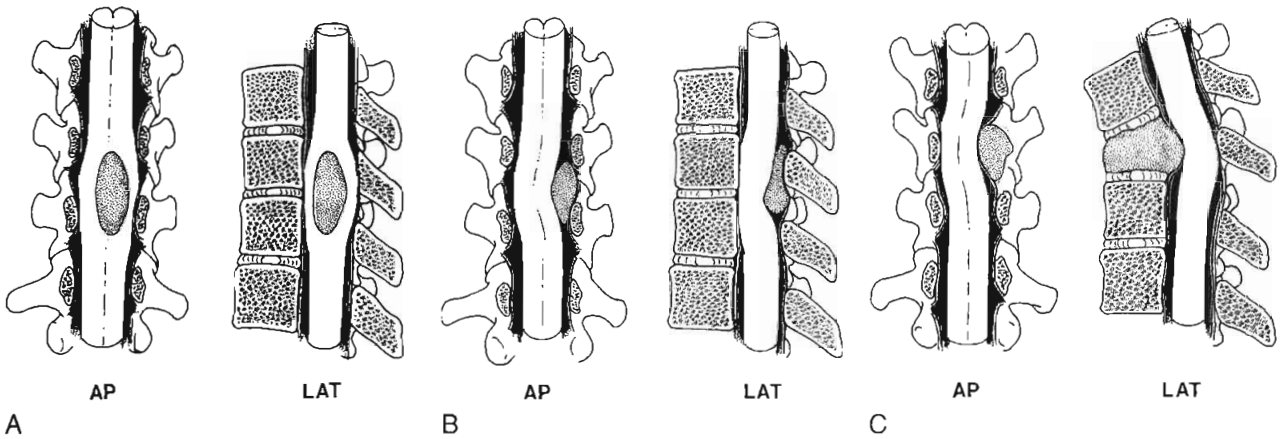


FIGURE 57–18. Spinal compartments. Anteroposterior (AP) and lateral (LAT) views of the spinal cord and canal demonstrate the appearance of an intramedullary lesion *(A)*, an extramedullary intradural lesion *(B)*, and an extradural lesion *(C)*.

plain films, and fracture evaluation and fragment displacements are best demonstrated with CT.

Intramedullary lesions expand the spinal cord as they enlarge, gradually thinning the subarachnoid space, usually symmetrically (see Fig. 57-18*A*). If of sufficient size, the intramedullary expansion may produce changes in the bony spinal canal, including posterior scalloping of the vertebral bodies, flattening of the spinous processes, widening of the interpeduncular distance, and overall widening of the canal. Intramedullary disease is usually secondary to a variety of neoplasms, most often gliomas (ependymoma, astrocytoma, glioblastoma). Other tumors include dermoid cysts, sarcomas, hemangioblastomas, and intramedullary metastases. In the acute setting, infectious processes such as transverse myelitis, granulomas (sarcoidosis, tuberculosis), and abscesses must be considered. Traumatic injuries such as cord contusion and hematomas can also produce an intramedullary pattern.

Extramedullary-intradural lesions are contained within the subarachnoid space but are external to the cord (see Fig. 57-18*B*). These lesions displace the arachnoid layer of the meninges but leave the dura in place. On imaging studies, the subarachnoid space flares out to form a "cap" at its interface with the lesion. Tumors, mostly benign, account for the majority of lesions in this space, particularly meningiomas and nerve sheath tumors. Less common lesions occurring in this space include arachnoid cysts, drop metastases, lymphomas, and dermoid and epidermoid tumors.

Extradural lesions lie outside the subarachnoid space. Except for the absence of the subarachnoid cap at the interface with the lesion, the imaging pattern of extradural lesions may be indistinguishable from that of extramedullary-intradural lesions. Extradural lesions typically produce a more gradual displacement of the subarachnoid space and spinal cord (see Fig. 57-18*C*). Excluding disc disease, the most common extradural pathology is metastatic disease with epidural extension. Pathologic fractures of the involved vertebrae occur frequently and are often associated with spinal cord compression. Primary tumors of the spine and direct extension from paraspinal neoplasms make up the other malignant lesions of the extradural compartment; these include lymphoma, myeloma-plasmacytoma, sarcoma, and vertebral body chordoma.[39] Benign lesions are uncommon in this compartment and include nerve sheath tumor, meningioma, lipoma, and primary bone lesions such as osteoblastoma, giant cell tumor, and aneurysmal bone cyst. Discitis-osteomyelitis with epidural abscess is an additional consideration.

SPECIFIC DISEASE PROCESSES

Spinal Cord Injury

The sequence of performing the various imaging studies to evaluate spine injury remains controversial and is usually based on their availability at the particular trauma center. Initial evaluation usually involves a plain film series. Plain radiographs are rapid, accurate, and widely available and provide a confident diagnosis of stable or unstable injuries. However, only bony injuries are seen directly with this technique; soft tissue injury can be inferred by identifying changes in bone alignment (Fig. 57-19*A*). With cervical spine injury, a single lateral view is often obtained. If alignment is normal, a complete series is obtained, including oblique and odontoid views. With suspected thoracic and lumbar injuries, lateral and anteroposterior films suffice, but oblique views can be added if questionable areas are identified.

Indications for CT include further evaluation of detected fractures, further evaluation of suspected fractures or confusing plain film findings, and evaluation of areas not well imaged on standard plain films.[40] The sensitivity of CT for fracture detection is between 78% and 100%.[40] Higher resolution and sagittal and coronal reformations aid in the sensitivity (see Fig. 57-19*B* and *C*). However, meticulous attention to technique is needed, because subtle alignment abnormalities that suggest ligamentous injury may be missed. Because of the high sensitivity of CT for most types of bony injury, some studies recommend that CT be the primary modality in patients with suspected cervical spine injury.[41,42]

MRI is the only method that can directly visualize intrinsic spinal cord and soft tissue injuries (see Fig. 57-19*D*). It can identify and distinguish between cord hematoma and contusion (edema), which affects the prognosis. Cord hematoma has a poor prognosis and indicates a complete lesion, whereas localized edema has a better prognosis for recovery of motor function.[43] Traumatic disc herniations can be readily identified. The presence of disc herniation with cord compression can change management from nonsurgical to surgical or change a posterior stabilization approach to a combined anterior and posterior approach.

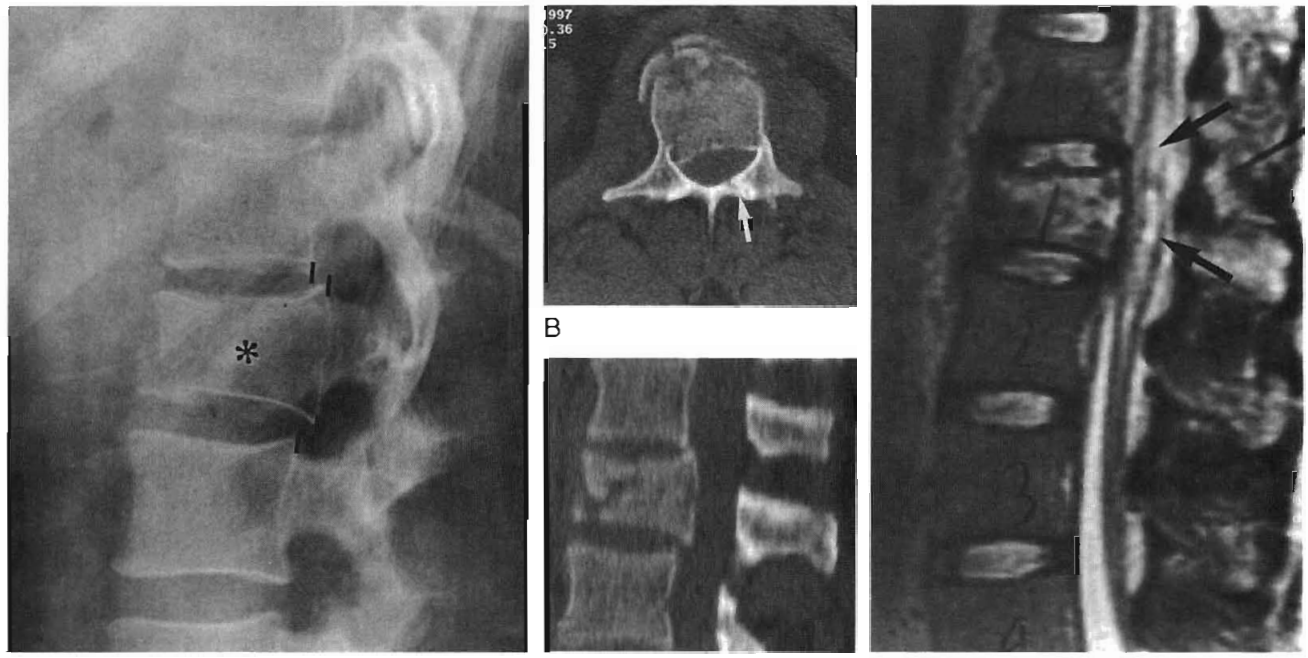


FIGURE 57–19. Post-traumatic vertebral body compression fracture. *A*, Lateral plain film of the thoracolumbar junction reveals a compression fracture involving the L1 vertebral body *(asterisk)*. The decreased height of the vertebral body and the inferior anterior corner fracture are well seen. The retropulsed body can also be seen when the outline of the adjacent vertebral bodies *(lines)* are compared. *B* and *C*, Axial *(B)* and sagittal reconstructed *(C)* CT scans of the same patient add substantial detail to the degree of canal narrowing secondary to the retropulsed fragment. A left laminar fracture *(arrow, B)* is also seen, which was not apparent on the plain film. *D*, Sagittal T2-weighted MRI demonstrates the compression fracture of L1 and the retropulsed posterior body, as well as contusion and swelling of the conus *(arrows)* as a direct result of the compression fracture.

MRI is also useful in detecting ligamentous injury by showing edematous changes or discontinuity in the ligaments. Although these findings are usually secondary, detection of isolated ligamentous injury may identify patients at risk for delayed instability. Epidural hematoma and the extent to which it is compressing the cord are also identified with MRI. Finally, although fractures are difficult to detect with MRI, the effect of bony fragment displacement and alignment abnormalities on the cord or nerve roots is elegantly seen with this modality (see Fig. 57-19*D*).

In summary, plain films are a useful screening tool to identify bony fractures and alignment abnormalities. CT further defines identified or suspected fractures and clarifies ambiguous areas on plain films. MRI is useful to identify intrinsic cord injuries and extrinsic soft tissue and bone abnormalities and their effect on the cord. Occasionally, all

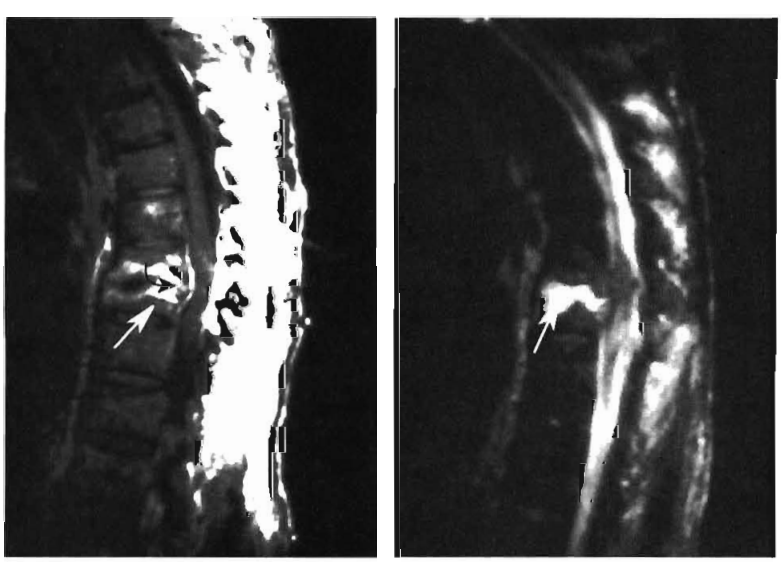


FIGURE 57–20. Discitis with epidural abscess. Sagittal post-contrast T1-weighted *(A)* and T2-weighted *(B)* MRI scans demonstrate features of discitis and adjacent osteomyelitis. The vertebral bodies and disc space are of low signal intensity on the T1-weighted image and bright signal intensity on the T2-weighted image (*straight arrows*). An epidural abscess surrounding and compressing the cord is also identified (*curved arrow*).

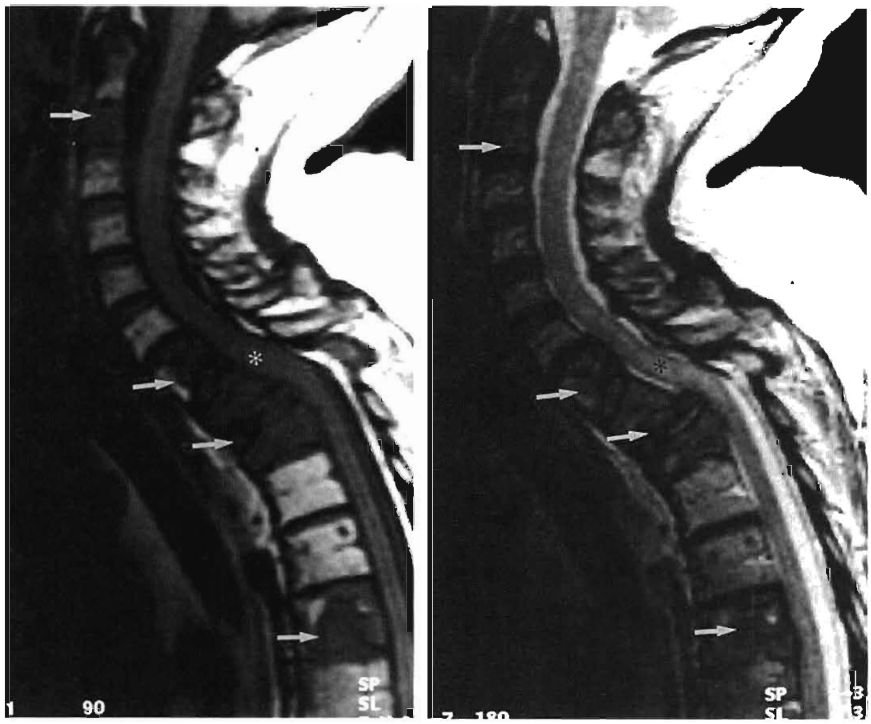


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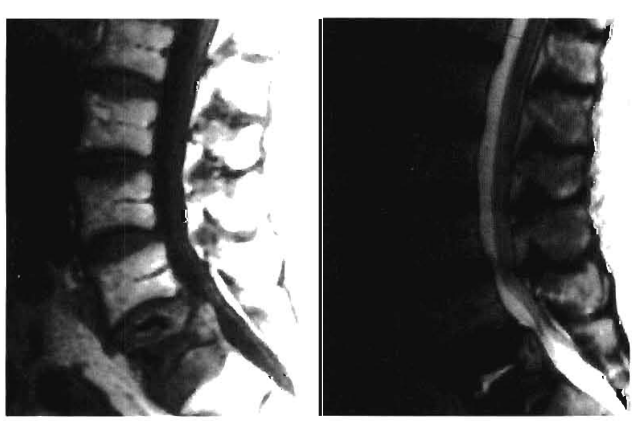
FIGURE 57–21. Metastatic disease. Sagittal T1-weighted *(A)* and T2-weighted *(B)* MRI scans of the spine show the metastatic lesions *(arrows)* as low intensity on the T1-weighted image, replacing the normal bright marrow. The high signal within the uninvolved vertebral bodies represents post-radiation changes. The hypointense lesions on the T2-weighted image (in contrast to the more typical hyperintensity) reflect the post-treatment appearance. Multiple compression fractures are identified within the upper thoracic spine, with collapse, retropulsed fragments, and cord compression. Edematous changes within the cord secondary to compression *(asterisk)* are also identified.

three modalities are necessary to establish the appropriate treatment plan.

Spinal Infection

Infections that involve the spine include discitis, epidural and subdural infections, myelitis, and cord abscess. In the management of spinal infections, delayed treatment can lead to increased morbidity and mortality,[44] making early diagnosis critical. MRI is the primary imaging modality in all types of spinal infection because of its higher sensitivity and its ability to detect changes earlier than plain films and CT. MRI findings with discitis are characteristic (Fig. 57-20). T1-weighted images show a narrowed disc space and hypointensity in the adjacent vertebral bodies. T2-weighted images show high signal in the affected disc space and vertebral bodies. Post-contrast studies show enhancement of the infected disc space and osteomyelitic bone. Paraspinal abscess, epidural extension, meningeal involvement, and cord compression are also readily seen with MRI.

Although MRI is sensitive in defining areas of myelitis, the findings are nonspecific and resemble those of other noninfectious and demyelinating disorders. Typically, focal or diffuse areas of hyperintensity are seen within the cord on T2-weighted images. Contrast enhancement is variable.



A B

FIGURE 57–22. Benign compression fracture. Sagittal T1-weighted *(A)* and T2-weighted *(B)* MRI scans demonstrate a compression fracture of L5. Compare the signal characteristics of the remaining bony elements and pedicles with the signal of the normal bony structures.

Neoplasm

Neoplasms involving the spinal axis typically present with progressive symptoms of myelopathy or cord compression. MRI is the primary modality for the evaluation of any suspected spinal tumor. It can demonstrate the location, extent, and nature of most tumors, regardless of the compartment of origin. Primary tumors of the bony elements and direct extension from paraspinal neoplasms are also easily identified with MRI.

In the evaluation of metastatic disease, MRI is more sensitive than bone scintigraphy.[45] Epidural and paraspinous soft tissue involvement and cord compression are also easily evaluated with MRI. Diffuse metastatic disease is recognized as heterogeneous or homogeneous hypointensity on T1-weighted images and hyperintensity on T2-weighted images (Fig. 57-21). MRI is valuable in identifying compression fractures and associated cord compression and is frequently able to distinguish between benign (osteoporotic) and pathologic (metastatic) fractures. Benign fractures have marrow intensity that is isointense with the marrow of uninvolved vertebral bodies on all sequences (Fig. 57-22), whereas pathologic fractures demonstrate the signal changes described earlier for metastatic disease.[46]

ANNOTATED REFERENCES

Askoy FG, Lev MH: Dynamic contrast-enhanced brain perfusion imaging: Technique and clinical applications. Neuroimaging Clin N Am 2001;11: 485-500.

Brain perfusion studies are the next step in neuroimaging for many forms of pathology and, more important, for the evaluation of head injury and stroke. This article provides an easily understood overview of the different MRI and CT perfusion techniques used. In addition, there is a detailed discussion of the clinical applications of perfusion imaging, with an emphasis on patients with stroke.

Beauchamp NJ, Bryan RN: Acute cerebral infarction: A pathophysiologic review and radiologic perspective. AJR Am J Roentgenol 1998;171:73-84.

The first part of this article reviews the progression from ischemia to stroke, the role of blood flow, and the biochemical ischemic cascade. The second part discusses the shortcomings of the current imaging approach for the diagnosis and treatment of stroke and the use of advanced techniques to overcome these shortcomings.

Cornelius RS, Leah JL: Imaging evaluation of cervical spine trauma. Neuroimaging Clin N Am 1995;5:451-463.

This article summarizes the most appropriate techniques in the evaluation of patients with suspected cervical spine injury. Although other modalities are covered, CT and MRI are emphasized. The issue of the role of imaging in low-risk patients is also covered.

Kleinman PK, Barnes PD: Head trauma. In Kleinman PK (ed): Diagnostic Imaging of Child Abuse. St Louis, Mosby, 1998, pp 285-342.

This chapter covers all aspects of head injury in children in a detailed and illustrative manner. Examples of the imaging characteristics of all forms of head injury in the pediatric population are clearly demonstrated and discussed.

Romaro JM, Schaefer PW, Grant PE, et al: Diffusion MR imaging of acute ischemic stroke. Neuroimaging Clin N Am 2002;12:35-53.

This article presents the theory and practice of diffusion-weighted imaging. Although the beginning of the article involves physics and biophysics, the remainder of the article contains practical information for the evaluation of ischemia and stroke. The article also discusses the use of diffusion-weighted images with stroke mimics, as well as other pathologic entities.

Chapter 58
INTENSIVE CARE AFTER NEUROSURGERY

Andrew I.R. Maas • Nino Stocchetti

KEY POINTS

1. Successful care for the neurosurgical patient requires excellent collaboration between neurosurgeon and intensivist. The result of a technically perfect operation can be ruined by inadequate postoperative care, and a complicated operative procedure will necessitate expert intensive care to correct abnormalities in homeostatic mechanisms and restore brain function.
2. The principal goal of postoperative neurosurgical intensive care is early detection and treatment of post-surgery complications. The second goal is to prevent secondary insults, which may initiate or exacerbate secondary damage in a vulnerable central nervous system.
3. Specific care and monitoring of the postoperative neurosurgical patient requires accurate knowledge of the preoperative situation and the intraoperative procedure, including the surgery, anesthesiology, and any surgical complications or difficulties.
4. The goal of cardiopulmonary and respiratory monitoring is to ensure accurate control of systemic hemodynamic and respiratory function, essential for optimization of cerebral oxygenation. Invasive arterial blood pressure monitoring is recommended with the reference point set at the same level as intracranial pressure measurement to allow accurate calculation of cerebral perfusion pressure.
5. The development of cerebral herniation (tentorial herniation/cerebellar tonsillar herniation) constitutes a neurosurgical emergency. A rapid intervention is required prior to further investigations to determine the cause.

Appropriate neurocritical care is fundamental to the success of neurosurgical operations to the brain and spinal cord. The great technical advances in operative procedures over the past decade have made lesions previously considered inoperable now treatable, and the advances in anesthesia have led to an increased number of operative procedures in both elderly and critically ill patients. Consequently, the number of patients requiring postoperative intensive care treatment has increased.

Successful care for the neurosurgical patient requires excellent collaboration between neurosurgeon and intensivist. The result of a technically perfect operation can be ruined by inadequate postoperative care, and a complicated operative procedure will necessitate expert intensive care to correct abnormalities in homeostatic mechanisms and restore brain function. Understanding of the complex interaction between the central nervous system and systemic functioning requires intimate knowledge of both general intensive care and cerebral and spinal pathophysiology. It can be safely concluded that the best care for neurosurgical patients can be provided by dedicated specialists with knowledge of both fields and a large amount of experience in treating such patients. We do not wish to challenge the concept of a closed format intensive care unit (ICU) but believe that concentration of care in units with sufficient volume, experience, and knowledge of neurocritical care is essential to the success of neurosurgery. The benefits of concentration of care have been well established in different fields of intensive care medicine, including trauma[1,2] and neonatology.[3,4] Treatment of patients with spontaneous intracerebral hemorrhage in a neuro-ICU is associated with reduced mortality, when compared with patients admitted to a general ICU[5,6] and the rate of mortality after aneurysmal subarachnoid hemorrhage is lower in centers with a higher case volume.[7] Protocol-driven approaches also improve results.[8-10]

The admission policy for postoperative neurosurgical care to ICUs varies widely between countries and centers and even within centers. In some centers, all patients are admitted for a 24-hour observation period after intracranial procedures; this is motivated by the observation that some patients, although fully alert and neurologically intact initially, develop complications such as a postoperative hematoma with rapid neurologic deterioration necessitating prompt intervention.

In other centers, patients are only admitted to the ICU after intracranial complications have been detected. Some hospitals have dedicated neuro-ICUs and in others, patients are admitted to general intensive care, sometimes even to different ICUs within one hospital. In general, the scarcity of intensive care beds has led to a more restrictive admission policy for postoperative neurosurgical care. The institution of high care units, sometimes termed "step down units" may permit more rational allocation of scarce intensive care resources, while at the same time affording sufficient guarantees for adequate postoperative monitoring. Here again, however, care should be provided by personnel well experienced in the care of neurosurgical patients, thus permitting early detection of possible deterioration and prevention of secondary complications.

PRIORITIES AND GOALS OF POSTOPERATIVE NEUROSURGICAL CARE

The principal goal of postoperative neuro-ICU is early detection and treatment of post-surgery complications.

TABLE 58–1. POSTOPERATIVE COMPLICATIONS

Systemic Complications	Neurosurgical Complications
Thromboembolic (DVT, pulmonary embolism, myocardial infarction)	Postoperative hematoma (subgaleal, epidural, subdural, intraparenchymal)
Infection (pneumonia, urinary tract infection, catheter sepsis)	Brain swelling (edema, vasodilation)
Hypovolemia (insufficient pre- and perioperative hydration, blood loss)	Cerebral ischemia (subarachnoid hemorrhage, vasospasm, vessel occlusion)
Coagulation disorders (blood loss, disseminated intravascular coagulation)	Infection (meningitis, subdural empyema, cerebral abscess)
Air embolism (sitting position, opening of large cerebral veins during surgery)	Seizures (infection, depressed compound skull fracture, cortical lesions)
Pulmonary (atelectasis, pneumothorax)	Hydrocephalus (obstruction/resorption)
Metabolic (hyperglycemia [steroid induced], diabetes insipidus, hyponatremia)	Tension pneumocephalus
Pressure sores and decubitus ulcers (intraoperative positioning, cervical traction, paraplegia)	CSF fistula
	Inverse cerebellar herniation
	Cranial nerve lesions

The second goal is to prevent secondary insults, which may initiate or exacerbate secondary damage in a vulnerable central nervous system.

Consequently, priorities are to ensure adequate monitoring facilities, which, in the sedated and ventilated patient, may require further invasive monitoring of the intracranial system, and to ensure adequate oxygenation and perfusion of the brain.

POSTOPERATIVE COMPLICATIONS AND SECONDARY INSULTS

Postoperative complications may be systemic or neurosurgical (Table 58-1).

PREVENTION AND MANAGEMENT OF SYSTEMIC COMPLICATIONS AFTER NEUROSURGERY

The prevention and management of systemic complications after neurosurgical procedures follows general principles of "intensive care" medicine. It is important to realize, however, that systemic complications and secondary insults may initiate or aggravate cerebral damage. Aggressive treatment aimed at preventing and limiting secondary insults is of paramount importance. The main secondary insults, their causes, and adverse effects on brain homeostasis and function are summarized in Table 58-2, further illustrating the complex interactions between systemic events and central nervous system (CNS) function.

TABLE 58–2. SYSTEMIC SECONDARY INSULTS

Event	Main Causes	Adverse Effect
Hypoxemia	Hypoventilation Aspiration atelectasis Pneumothorax Pneumonia Anemia	Decrease in oxygen delivery and increased risk of ischemic damage
Hypotension	Hypovolemia Cardiac failure Sepsis, spinal cord injury	Decreased CPP, decrease in CBF, increased risk of ischemia
Anemia	Blood loss	Decrease in oxygen delivery and increased risk of ischemic damage
Hypercapnia	Respiratory depression	Increased cerebral blood volume (CBV), raised ICP
Hypocapnia	Hyperventilation, spontaneous or induced	Cerebral vasoconstriction with increased risk of ischemic damage
Hyperthermia	Hypermetabolism, stress response, infection Central dysregulation	Metabolic requirements may exceed substrate delivery, resulting in energy depletion
Hypothermia	Exposure, central dysregulation	May be neuroprotective, but can cause significant coagulopathy and electrolyte disturbances
Hyperglycemia	Hypothermia, IV infusion of dextrose, steroids, stress response	Acidosis, electrolyte disturbances
Hypoglycemia	Inadequate nutrition, insulin overdose, pituitary insufficiency	Energy depletion, seizures
Hyponatremia	Insufficient intake (hypotonic fluids) Excessive sodium loss (cerebral salt wasting) Inappropriate ADH syndrome	Increased edema, seizures
Hypernatremia	Diabetes Insipidus Osmotic agents (mannitol, hypertonic saline)	Lethargy, coma

Conversely, CNS events may induce systemic derangement. For example, in response to raised intracranial pressure, mean arterial blood pressure may increase. In such situations, treatment of hypertension is contraindicated because it may exacerbate cerebral ischemia. In other situations, however, arterial hypertension may aggravate the occurrence of cerebral edema, and the clinical dilemma is then to balance a desire to limit edema formation with a desire to maintain adequate perfusion. Electrocardiographic abnormalities, and cardiac arrhythmias may be caused by subarachnoid hemorrhage, traumatic brain injury (TBI), or raised intracranial pressure (ICP). Many drugs routinely used in neurosurgical patients (e.g., steroids, antiepileptic agents) can cause complications or side effects. CNS damage may lead to disturbance in temperature control, causing hypo- or hyperthermia. Release of factors from damaged brain tissue may further initiate acute respiratory distress syndrome (neurogenic pulmonary edema) or induce coagulopathy. Various studies have confirmed a transient hypercoagulopathy syndrome both in the immediate postoperative phase after brain surgery[11] and in patients with TBI.[12-16] Deep venous thrombosis has been reported to occur in 18% to 50% of neurosurgical cases[17] and pulmonary embolism in 0% to 25%. The incidence of deep venous thrombosis and pulmonary embolism incidence is particularly high in patients with brain tumor.[18] Nevertheless, neurosurgeons tend to underestimate the risk of deep venous thrombosis and pulmonary embolism [19] and remain reluctant to routinely prescribe anticoagulant prophylaxis for fear of increasing the risk of postoperative bleeding.[20,21]

Existing evidence, however, does not clearly show an increased risk of clinically significant hemorrhagic complications with anticoagulant prophylaxis but does show a beneficial effect in reducing deep venous thrombosis and pulmonary embolism.[22-26] This supports the administration of antithrombotic prophylaxis prior to neurosurgical procedures in all patients,[27] including those with intracranial hemorrhagic lesions,[28] those with closed TBI,[29] and high-risk trauma patients.[30] In addition, early mobilization in the postoperative phase, whenever possible, is recommended. More consensus exists concerning routine administration of anticoagulant therapy in patients with spinal cord injuries.

PREVENTION AND MANAGEMENT OF NEUROSURGICAL POSTOPERATIVE COMPLICATIONS

SUPRATENTORIAL PROCEDURES

Postoperative Subgaleal Hematoma

Postoperative subgaleal hematoma can occur in up to 11% of procedures.[31,32] These hematomas generally result from either inadvertent damage to the superficial temporal artery with inadequate hemostasis or from hemorrhage from the temporal muscle. If the superficial temporal artery is damaged during the operation, ligation is preferred over coagulation. The occurrence of subgaleal hematomas can be minimized by routine use of postoperative wound drainage for 24 hours. Reoperation for subgaleal hematomas is seldom necessary unless there is a communication with the intracranial compartment resulting in secondary compression of the brain.[33]

Intracranial Hemorrhage

Intracranial postoperative hemorrhage occurs in approximately 1% of procedures and mainly concerns intraparenchymal hematomas (43-60%), epidural hematomas (28-33%), and subdural hematomas (5-7%).

After every supratentorial procedure, some blood may accumulate in the epidural space. Appropriate surgical technique aims to minimize this epidural space by circumferentially suturing the dura to the bone, periosteum, or galea. Inadequate hemostasis of meningeal arteries, blood loss from the temporal muscle, or blood loss from the bone may, however, induce a larger postoperative epidural hematoma. In cases of neurologic deterioration considered due to the postoperative epidural hematoma, surgical evacuation is indicated. Postoperative subdural hematomas occur less frequently and may result from delayed rupture of bridging veins after a large intracerebral decompression. On occasion, such subdural hematomas can occur distant from the primary site of operation.

Parenchymal hemorrhages are the most frequent cause of hematomas after supratentorial procedures and generally occur at the site of operation, particularly following partial tumor resection. An increase in systemic blood pressure at the end of surgery is another factor that may increase the risk of parenchymal hemorrhage. In rare cases, the hematoma may be located distant from the primary site of operation, and cerebellar hematomas have even been described after supratentorial surgery.[34] The possibility of a postoperative hematoma should be considered in all patients who are not fully alert after anesthesia as well as in those who exhibit secondary deterioration.

Postoperative Brain Swelling

Modern neuroanesthesiology techniques have diminished the incidence of peri- and postoperative brain swelling. Nevertheless, significant swelling may occur, causing surgical difficulties and possibly critical problems in the ICU. Predisposing factors are hypercapnia, arterial hypertension, and obstruction of venous drainage. In any patient with brain swelling during the surgical procedure, the possibility of a deep hematoma should be considered and urgent postoperative computed tomography (CT) should be performed. Brain swelling due to vasodilation can be corrected by hyperventilation and barbiturate administration. Brain swelling due to cerebral edema should be preferentially treated by osmotic agents and mild hyperventilation. Recently, a new syndrome has been described in which significant brain swelling after uneventful surgery was ascribed to intracranial hypotension caused by subgaleal suction.[35]

Tension Pneumocephalus

On postoperative CT scans, some air collection is generally observed.[36] In rare circumstances, the postoperative rewarming of air in the intracranial compartment or continuous air leakage, due to a cerebrospinal fluid fistula of the skull base, may lead to a tension pneumocephalus, with clinical symptomatology including a decreasing level of consciousness, signs of raised intracranial pressure, and occasionally seizures. Generally, postoperative air accumulations are self-limiting and do not require specific treatment.

Seizures

An epileptic seizure in the immediate postoperative period should be considered a serious complication that may cause significant deterioration due to vasodilation, increased cerebral oxygen consumption, and increased brain edema.

The benefits of prophylactic antiseizure medication should be balanced against risks. In some centers, routine prophylaxis is prescribed in all patients undergoing supratentorial brain surgery. In others, the indications are restricted to patients with a higher risk:

- Cerebrovascular surgery (arteriovenous malformation, aneurysm)
- Cerebral abscess and subdural empyema
- Convexity and parafalcial meningiomas
- Penetrating brain injury
- Compound depressed skull fracture

Opinions vary on the duration of prophylactic antiseizure therapy, with some centers recommending a treatment duration of 2 weeks and others continuing for at least 3 months.

INFRATENTORIAL SURGERY

The care for patients in the direct postoperative phase after infratentorial procedures poses specific problems: postoperative complications in the posterior fossa can lead to rapid deterioration due to the relatively small infratentorial reserve capacity and the immediate compression of the brainstem, resulting in respiratory insufficiency and acute herniation. Irritation of the brain stem may induce large swings in arterial blood pressure, increasing the risk of postoperative hemorrhage during hypertensive episodes. Cranial nerves are more susceptible to damage due to surgical manipulation than peripheral nerves.[37] Lesions of the lower cranial nerves may lead to a diminished gag reflex with increased risk of aspiration and pneumonia. After any infratentorial procedure, the risk of acute hydrocephalus due to obstruction at the level of the fourth ventricle is increased. Increased pressure in the infratentorial compartment may, in rare cases in which supratentorial cerebrospinal fluid drainage is performed, cause upward (inverse) herniation.

These aspects specific to the care of patients who have undergone posterior fossa surgery warrant the routine admission of all patients following such surgery for frequent monitoring in the ICU. Particular attention should be paid to the presence of the gag reflex before extubation and in the early stages after extubation, and even then frequent monitoring of the respiratory status is imperative.

After posterior fossa surgery, some patients develop a syndrome of aseptic meningitis.[38] This is characterized by meningeal symptoms, headaches, and an inflammatory response in the cerebrospinal fluid in the absence of evidence for infection. The origin of this syndrome has not been fully clarified, but symptoms may resolve sooner with intermittent cerebrospinal fluid drainage.

An infrequent transient complication observed after resection of large mid-line posterior fossa tumors is cerebellar mutism. The exact cause is poorly understood, but a vascular phenomenon has been hypothesized.[39-43] After surgery in the cerebellar pontine angle, specific attention should be paid to the function of the trigeminal and facial nerves, and prophylactic measures should be taken to prevent corneal damage.

For a discussion of aneurysmal subarachnoid hemorrhage, please see Chapter 52.

TABLE 58–3. POSTOPERATIVE INTAKE AFTER NEUROSURGICAL OPERATIONS

Preoperative situation	Neurologic deficit (level of consciousness, focal paresis, cranial nerve lesions, hormonal deficits)
	Preexisting disease (especially pulmonary and cardiac)
	Preoperative medication
	History of seizures
	Allergy
	Surgical position
Intraoperative details (anesthesia)	Narcotic agents and antagonists
	Blood loss and substitution
	Intraoperative laboratory values
	Intraoperative secondary insults, diabetes insipidus, etc.
	Indication, approach, and duration of surgery
Intraoperative course (surgical)	Surgical difficulties and complications (brain swelling, difficult hemostasis, temporary or definite vascular occlusion, opening of air sinus)
	Immobilization/positioning of patient.
Postoperative instructions (surgeon and anesthetist)	Postoperative medication (e.g., anticonvulsants, antibiotics, steroids, mannitol, antithrombosis prophylaxis)
	Instructions for postoperative care and monitoring
	Instructions for removal of drainage, tubes, and stitches
	Preferred duration of postoperative artificial ventilation.
	Instructions for follow-up computed tomography examination (if indicated)

ADMISSION EXAMINATION AND MONITORING IN THE INTENSIVE CARE UNIT

Specific care and monitoring of the postoperative neurosurgical patient requires accurate knowledge of the preoperative situation and the intraoperative procedure, including the surgery, anesthesiology, and any surgical complications or difficulties. Pertinent aspects are summarized in Table 58-3.

On admission, a full examination of the patient is required, including, whenever possible, assessment of level of consciousness and neurologic functioning. Medical care for the patient should be provided in joint collaboration between intensivist and neurosurgeon. Intensive care monitoring includes clinical surveillance, technical monitoring, and follow-up CT or magnetic resonance imaging (MRI). The various approaches to monitoring are summarized in Table 58-4. These are discussed in greater detail in Chapter 48.

CLINICAL SURVEILLANCE

Even in this era of sophisticated monitoring procedures, routine clinical examinations are essential. The clinical assessment has the purpose of disclosing major, life-threatening complications early after surgery, and of assessing neurologic deficits in the following hours to days that follow.

Early Evaluation

A simple check of consciousness, pupils, and the development of focal (mostly motor) deficits remains the most important

TABLE 58–4. POSTOPERATIVE MONITORING AFTER INTRACRANIAL PROCEDURES

Clinical surveillance	Level of consciousness (Glasgow Coma Scale), pupillary reactivity, focal deficits, cranial nerve lesions
Systemic monitoring	Electrocardiogram and heart rate, respiration, pulse oximetry, end tidal CO_2, blood pressure (invasive, noninvasive), temperature, central venous pressure
Brain specific monitoring	Intracranial pressure and cerebral perfusion pressure, jugular oximetry, brain oxygen tension monitoring, microdialysis, transcranial Doppler, electroencephalogram, evoked potentials
Accesses	Central or peripheral venous catheter, arterial catheter, urinary catheter, gastric tube
Laboratory examinations	Blood gases, hematology, electrolytes, on indication coagulation status
Imaging examinations	Chest radiograph (ventilated patients and after lung procedures)
	Computed tomography or magnetic resonance imaging follow-up (as required)

method for assessing patients in the neurosurgical ICU. Neurologic assessment should be repeated at regular intervals throughout the ICU course, as change in the examination findings is the most sensitive method for detecting neurologic deterioration.

The level of consciousness should be assessed by the Glasgow Coma Scale (GCS).[44] In this scale standardized assessment of three aspects of responsiveness is performed: the eye, motor, and verbal response (Table 58-5).

When administration of painful stimuli is required to assess the level of responsiveness, standardized administration is required: pressure on the nail bed and supraorbital pressure to test the localizing response of the motor scale (Fig. 58-1).

Accurate determination of the full GCS is not always possible because of sedation and paralysis, but, when possible, at least the best motor score should be recorded.

Some authors advocate separating the eye and verbal scores from the motor score in sedated and/or ventilated patients.[45] However, the motor score is the main predictor in unconscious patients and we would prefer an approach in which only the motor score is assessed when the level of sedation so permits. The development of pupillary abnormalities is a sensitive indicator for pressure on the midbrain (tentorial herniation). The pupillary reaction to light is mediated through parasympathetic fibers of the third cranial nerve (oculomotor nerve). Afferent light perception, conducted through the second cranial nerve (optic nerve) connects at the level of the internal eye muscle nuclei to the oculomotor

TABLE 58–5. GLASGOW COMA SCALE

Eyes	Motor	Verbal
1: none	1: none	1: none
2: to pain	2: abnormal extension	2: incomprehensible (groaning)
3: to speech	3: abnormal flexion	3: inappropriate
4: spontaneous	4: flexion (withdrawal)	4: disoriented, confused
	5: localizing	5: oriented
	6: obeying commands	

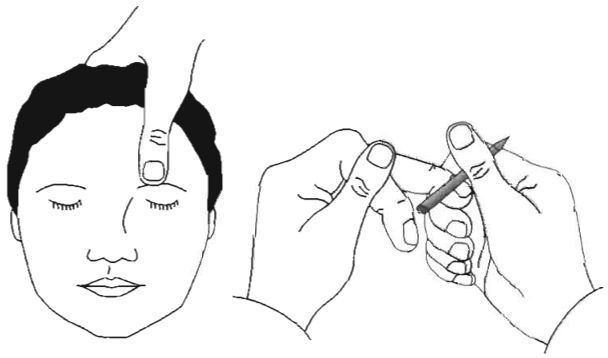


FIGURE 58–1. Supraorbital and nailbed pressure for assessment according to the Glasgow Coma Scale.

nerve supplying parasympathetic fibers to the sphincter pupillae muscle via the ciliary ganglia. Pressure on the oculomotor nerve leads to a loss of function of the parasympathetic fibers, causing a diminished pupillary response or absent pupillary reactivity, generally initially on the side of a lesion (Fig. 58-2). With progressive increases in pressure, both pupils become dilated and unresponsive to light. In patients with a lesion of the optic nerve, the consensual light reflex—that is, contraction of the pupil when a light is shone into the opposite eye—remains intact.

Further Evaluation

When major complications have been ruled out, it remains necessary to evaluate the persistence of previous deficits, their improvement after surgery, or the appearance of new signs attributable to surgery. It is expected, for example, that after the surgical removal of an eighth nerve neurinoma, some degree of damage of cranial nerve VII can occur. After surgical intervention on structures located in, or close to, the brainstem, deficits of the lower cranial nerves can occur as well. A careful, complete neurologic examination is required at this stage, since the simple check proposed in the previous section will not fully evaluate cranial nerve function. This evaluation is important because cranial nerve deficits can require immediate treatment, for example protection of the globe to prevent keratitis or avoidance of oral feeding if swallowing is impaired.

SYSTEMIC MONITORING: CARDIOPULMONARY, RESPIRATORY, AND TEMPERATURE

The goal of cardiopulmonary and respiratory monitoring is to ensure accurate control of systemic hemodynamic and respiratory function, essential for optimization of cerebral oxygenation. Invasive arterial blood pressure monitoring is recommended with the reference point set at the same level as ICP measurement to allow accurate calculation of cerebral perfusion pressure (CPP). Hypovolemic shock is common in the setting of multisystem injury or intraoperative blood loss with inadequate replacement. It is important to recognize that tachycardia and signs of peripheral vasoconstriction such as skin pallor and poor capillary refill can precede a drop in blood pressure. Treatment is rapid fluid resuscitation using isotonic crystalloid fluids, volume expanders, small volume resuscitation (hypertonic saline), and blood transfusions. Central venous pressure monitoring

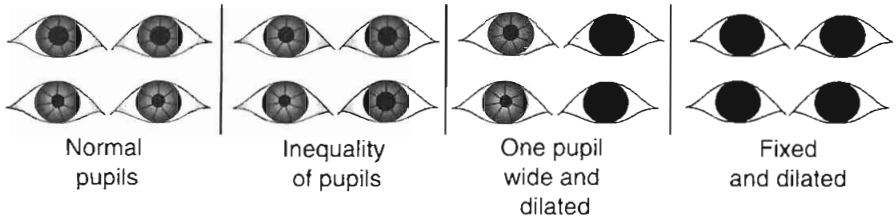


FIGURE 58–2. Pupillary reactivity and size.

can be used to guide volume resuscitation. After initial volume resuscitation, we suggest a hematocrit of approximately 30% to 33% as optimal in the acute postoperative period in patients in the neuro-ICU. After intracranial or spinal cord procedures we would advocate a more liberal use of blood transfusions than generally recommended in intensive care medicine, to promote adequate oxygenation of the central nervous system. This corresponds to the recommendations proposed by Goodnough and coworkers[46] in case of ischemia.

Cardiogenic shock due to primary loss of cardiac function is less common in neurosurgical patients but occurs in the elderly patient with either secondary cardiac ischemia or arrhythmias. These patients usually require the use of a pulmonary artery catheter to optimize volume status and cardiac output. Large pulmonary emboli, sepsis, or spinal paraplegia should also be considered in patients with systemic hypotension. In patients with spinal distributive shock, typically the hypotension is associated with bradycardia with a pulse 35 to 50. These patients should not be managed with excessive volume resuscitation but rather with vasopressors to restore alpha-adrenergic peripheral vasomotor tone. Central venous pressure monitoring or preferably pulmonary artery catheterization can guide the use of intravenous fluids and vasopressor therapy, with a goal of attaining a pulmonary artery wedge pressure of 12 to 14 mm Hg.

The combination of hypertension and bradycardia (Cushing response) should alert the physician to the potential of an expanding intracranial lesion and risk of brainstem herniation. In this situation, the use of antihypertensive agents is contraindicated and therapy should be aimed at the raised ICP.

Temperature monitoring is also important in the neuro-ICU, since hypothermia can depress neurologic function to the point of obtundation or coma. Conversely, fever, by increasing metabolic requirements, may exacerbate secondary injury. Core temperature should be kept lower than 38.0°C, using medications (e.g., acetaminophen, paracetamol, diclofenac) and external or intravascular cooling. Hypothermia may be due to adrenal or pituitary insufficiency, hypothalamic disorders, hypoglycemia, or intraoperative exposure. Deliberate hypothermia is sometimes used in complicated cerebrovascular procedures and as second tier therapy in patients with TBI to reduce ICP.

The possible benefits of hypothermia should be carefully balanced against potential risks (coagulation disorders, electrolyte shifts, fluid overload).

Brain specific monitoring, including the use of ICP monitoring, assessment of cerebral blood flow (CBF), cerebral oxygenation (using either a jugular venous bulb catheter or an oxygen-3 sensitive electrode), and electroencephalographic (EEG) monitoring can be helpful in postoperative patients in the neuro-ICU. These specific modalities are discussed in detail in Chapter 48.

Monitoring of ICP is indicated in trauma patients with severe brain injury (GCS score < 8), with abnormalities on the initial CT scan and further in patients with a normal admission CT scan if two or more of the following features are present: age greater than 40 years, unilateral or bilateral motor posturing, systolic blood pressure less than 90 mm Hg.

Routine ICP monitoring is not generally indicated in patients with mild or moderate head injury but may be considered when other severe extracranial injuries are present, necessitating anesthesia for surgery, or when the initial CT scan shows traumatic lesions with space-occupying effects. ICP monitoring is further indicated in poor grade patients with subarachnoid aneurysmal hemorrhage. Further, it may be considered in patients with other intracranial disorders, who are sedated and ventilated and in whom the risk of raised ICP is considered present (postoperative swelling, stroke, Reye syndrome). Relatively few data exist on routine ICP monitoring in the postoperative situation. In a series of 30 patients after severe head injury and elective craniectomy, 156 instances of ICP rise and/or drop in CPP were recorded.[47] These instances were only accompanied by clinical deterioration in 15 cases.

Telemetric ICP control has been proposed after posterior fossa surgery.[48] In a series of 514 patients after supra- and infratentorial surgery, Constantini and associates[49] described raised ICP in 13% to 18% of cases. Neurologic deterioration occurred in approximately half of the patients suffering ICP rise and was always preceded by the ICP increase. In a large series of 780 patients submitted to routine ICP monitoring after intracranial surgery, 47% required ICP-directed therapy.[50] In a report concerning 850 cases, Bullock and associates[51] concluded that ICP monitoring allows earlier identification of recurrent hematomas. These data would support a more routine application of ICP monitoring after intracranial surgery, particularly in more complex cases. In some institutions, ICP is routinely measured as part of the postoperative surveillance after major neurosurgical procedures, especially when there is the risk of postoperative bleeding. Figure 58-3 illustrates a case in which a substantial ICP rise was detected in the first postoperative hours. That was caused by an enlarging hemorrhage, which required re-intervention. Intracranial hemorrhages are a rare complication of ICP monitoring and are usually caused by multiple punctures in the presence of coagulopathies. This risk of infection is highest in the case of ventricular monitoring, and the rate of infection has been shown to be proportional to the duration of monitoring.

CEREBRAL BLOOD FLOW AND OXYGENATION

Intermittent measurements of CBF can be obtained with stable Xenon CT scanning or positron emission

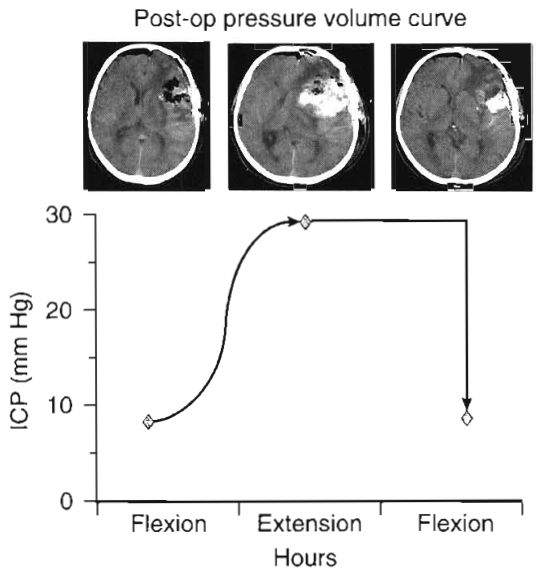


FIGURE 58–3. Raised intracranial pressure (ICP) as the first indication of a developing postoperative hematoma.

tomography studies. Techniques for continuously monitoring CBF at the bedside are currently being developed but are not routinely available. Transcranial Doppler echography provides a noninvasive assessment of blood flow velocity through the basal cerebral arteries. Transcranial Doppler echography is most useful for documenting the development of cerebral vasospasm. Global cerebral oxygenation can be assessed using jugular oximetry, which is discussed in Chapter 48. A decrease in jugular venous saturation of oxygen (Sjv_{O_2}) indicates that the brain is extracting more oxygen, suggesting that the oxygen supply is not adequate for metabolic demands. Interpretation of results of jugular oximetry require that systemic information, such as hemoglobin concentration and arterial saturation, and intracranial data, such as CPP, are combined. The technique has several limitations: first, continuous monitoring of Sjv_{O_2} with fiberoptic devices is prone to artifact; and second, under conditions of anemia or arteriovenous shunting, hypoxia may be present at the tissue level despite normal values of Sjv_{O_2}.

Regional monitoring of brain tissue oxygen tension is possible by inserting an oxygen-sensitive electrode in the cerebral cortex or white matter. By definition, this concerns a regional technique, and there is still considerable debate about whether this technique should be employed in relatively undamaged parts of the brain—and as such be considered representative of more global oxygenation and metabolism—or preferably be employed in the penumbral zone of lesions, the aim being to limit secondary damage in potential viable regions. Increased hyperventilation has further been shown to reduce cerebral tissue P_{O_2}. Experimental and clinical evidence suggests that CPP therapy may be targeted toward appropriate levels, based on results of tissue oxygen monitoring. Other techniques quantifying regional CBF by thermal diffusion or laser Doppler have been used mainly for research purposes but have not yet provided results on the basis of which therapeutic procedures can be targeted. Finally, the technique of microdialysis allows for the measurement of substrate and metabolites (glucose, lactate, pyruvate), amino acids (glutamate), and indicators of cerebral damage (glycerol) in the extracellular fluid of the brain. Dialysate fluid obtained after infusing saline through a semipermeable membrane reflects the composition of the extracellular fluids around the probe. Microdialysis is employed in various specialized neuro-ICUs, mainly for research purposes. Variable results and delays in obtaining real-time values have inhibited the application of results toward individualized targeted treatment.

ELECTRICAL MONITORING

Continuous EEG monitoring has the potential for detecting nonconvulsive status epilepticus in ICU patients. However, the value of this monitoring has been shown most often in the setting of stroke and TBI. As primary monitor of brain function, continuous EEG can be used to titrate continuous infusion of sedative agents, and the technique can further alert the physician to development of focal or global ischemia.[52,53] The sensitivity for detecting ischemia and hypoxia is high, but the specificity is low due to the effect of sedative medications. Continuous EEG may permit detection and treatment of such adverse events at an early stage, with a potential positive effect on outcome.[54] Measurement of evoked potentials,[55] assessing the integrity of sensor and motor pathways, may provide diagnostic and prognostic information but because of the complexity of the technique is not recommended for general use.

SPECIFIC THERAPEUTIC APPROACHES

TREATMENT OF CEREBRAL HERNIATION AND ELEVATED INTRACRANIAL PRESSURE

The development of cerebral herniation (tentorial herniation/cerebellar tonsillar herniation) constitutes a neurosurgical emergency. A rapid intervention is required prior to further investigations to determine the cause. According to the concept of the volume pressure curve (Fig. 58-4), a small reduction in intracranial volume will already significantly decrease raised intracranial pressure and reverse herniation. The emergency measures to be taken include the following:

- Ventricular cerebrospinal fluid drainage (if access is available)

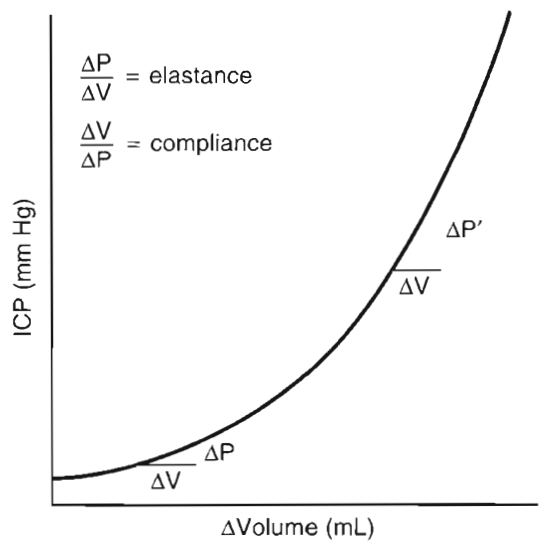


FIGURE 58–4. Intracranial pressure (ICP) volume curve.

- Administration of mannitol, 1 g/kg bodyweight
- Rapid sequence intubation with a neuroprotective strategy

Lumbar cerebrospinal fluid drainage should never be attempted, as this may increase herniation.

Following these emergency procedures, emergency head CT scan should be performed to detect the cause of raised ICP and permit targeted treatment, such as evacuation of a postoperative clot or further treatment of an acute obstructive hydrocephalus. In the absence of an acute cerebral herniation, elevated ICP is addressed first by ruling out treatable intracranial mass lesions and monitoring malfunction and remediable extracranial causes (Table 58-6).

The main intracranial causes of raised postoperative ICP are:

- Mass lesions (hematoma)
- Edema (vasogenic, cytotoxic, osmotic, hydrostatic)
- Increased cerebral blood volume (vasodilation)
- Disturbance of cerebrospinal fluid flow (hydrocephalus, benign intracranial hypertension)

Where appropriate, surgical intervention is indicated.

Conservative therapy of raised ICP includes:

- Sedation, analgesia, and mild to moderate hyperventilation ($PaCO_2$ 4-4.5 kPa [30-50 mm Hg])
- Osmotic therapy: preferably mannitol given repeatedly in bolus infusions (dose: 0.25-0.5 g/kg bodyweight, or as indicated by monitoring). Serum osmolarity should be maintained at less than 315 mOsm/L. If osmotherapy has insufficient effect, furosemide (Lasix) can also be administered.
- Cerebrospinal fluid drainage
- Volume expansion and inotropes or vasopressors when arterial blood pressure is insufficient to maintain CPP and CBF in a normovolemic patient

If these methods fail, second tier therapies for raised ICP include (1) more intensive hyperventilation (which should be used only with monitoring of cerebral oxygenation to detect cerebral ischemia); (2) administration of barbiturates; (3) mild or moderate hypothermia; and, alternatively, (4) decompressive surgery.

HEMODYNAMIC AND CEREBRAL PERFUSION MANAGEMENT

Neurogenic Pulmonary Edema

The development of neurogenic pulmonary edema has been described early in the postoperative period after a variety of neurosurgical procedures, including brain tumors (particularly those resected in the posterior fossa), cysts, hydrocephalus, intracranial hemorrhages, and brainstem lesions.[56-59] Although an infrequent event, this is a potentially life-threatening event that requires rapid evaluation and emergent therapy in the ICU. A 9% mortality rate directly attributable to neurogenic pulmonary edema has been reported in a recent review of this condition. Generally, this complication appears in the initial 4 hours after the neurologic event and is more common in women than in men, possibly related to the preponderance of cases in patients with subarachnoid hemorrhage.[59] The mechanism underlying this condition is generally believed to include central sympathetic discharge with pulmonary venoconstriction, although both low and high protein content have been reported in the edema fluid.[59,60] It is commonly associated with raised ICP, and, in addition to therapies directed at intracranial hypertension, therapeutic measures are mostly supportive. Supplemental oxygen is uniformly required and endotracheal intubation with mechanical ventilation and the application of positive end-expiratory pressure (PEEP) has been reported in about 75% of patients.[59] Most patients require vasoactive drugs.[60] Epinephrine has also been touted to have a direct beneficial effect on clearance of the alveolar fluid.[61] Remarkably, there do not appear to be any literature reports of the use of inhaled nitric oxide for this condition.

In some patients, the normal pressure autoregulatory mechanisms are disturbed and the risk exists that increased CPP may worsen cerebral edema. Careful observation of the change in ICP with respect to arterial blood pressure changes is required to determine whether the change in CBF in response to changes in blood pressure are consistent with disturbed or intact autoregulation. The general principles behind blood pressure manipulation in the injured brain are discussed in Chapter 47.

Vasopressor therapy may be needed in the postoperative care of patients in the neuro-ICU. Vasopressors are often required in the treatment of subarachnoid hemorrhage and severe traumatic brain injury (see Chapters 52 and 55). They may also be needed in the setting of the postoperative decompensation of a patient to maintain stability prior to reoperation and in the setting of neurogenic pulmonary edema. The vasopressors most frequently used in the care of the postoperative neurosurgical patient are listed in Table 58-7.

Neuroprotection

The original concept of neuroprotection depended on the initiation of treatment before the onset of an event leading to brain damage, and the methods employed aimed to minimize the intensity of an insult or its immediate effects upon the brain. Over the past two decades, the concept of neuroprotection has been extended to include treatment started

TABLE 58–6. REMEDIABLE EXTRACRANIAL CAUSES OF INTRACRANIAL HYPERTENSION

Calibration errors
Airway obstruction (kinked endotracheal tube, tongue, sputum retention, pneumothorax)
Hypoxia (FIO_2, lung disease/collapse)
Hypercapnia (hypoventilation)
Hypertension (pain, sedation, coughing/straining)
Hypotension (hypovolemia, sedation, cardiac)
Posture (Trendelenburg position, neck rotation)
Hyperpyrexia
Seizures
Hypo-osmolality (sodium, protein)

TABLE 58–7. VASOPRESSORS COMMONLY USED IN THE NEONATAL INTENSIVE CARE UNIT

Agent	Adrenergic Effect	Doses (μg/kg/min)
Dopamine	Primarily beta (low dose)	0.4-4
	Increasing alpha (higher dose)	5-8
Norepinephrine	Mainly alpha	0.04-0.1
Phenylephrine	Pure alpha	2-4

TABLE 58–8. MAIN APPROACHES IN NEUROPROTECTION

Strategies Aimed at Improving Metabolism and Micro-environment	Agents Acting on Specific Mechanisms	Pluripotent Agents Affecting Various Mechanisms	Strategies Promoting Cell Survival and Regeneration
Hypothermia	Alpha-adrenoceptor drugs	Barbiturates	Cellular replacement
Mannitol	Anti-inflammatory agents	Corticosteroids	Gene therapy
THAM	Apoptosis inhibitors, caspase inhibitors, and cyclosporine	Dexanabinol	Neurotrophic factors
	Arachidonic acid metabolism-modulators	Erythropoietin	
	Calcium channel antagonists	Magnesium	
	Calpain antagonists		
	Sex hormones		
	Ion channel modulators		
	Kappa opioid modulators		
	Kinin antagonists		
	Neurotransmitter-targeted agents		
	Nitric oxide modulators		
	Free radical scavengers and inhibitors of lipid peroxidation		

after the onset of an insult (i.e., resuscitation), reflecting our increased understanding of progressive pathophysiologic mechanisms causing and/or enhancing secondary brain damage. In neuroprotection, four main approaches can be discerned (Table 58-8). Although the agents used may have more utility in the specific settings of cardiopulmonary arrest, subarachnoid hemorrhage, TBI, and stroke (see Chapters 50, 51, 52, and 55), they may be useful in some post-operative neurosurgical patients, especially in cases with complications.

STRATEGIES AIMED AT IMPROVING METABOLISM AND MICROENVIRONMENT

Methods for improving metabolism and microenvironment include hypothermia to minimize the effects of energy failure, tris(hydroxymethyl)amino-methane (THAM) to correct brain acidosis, and mannitol to reduce ICP and improve CBF. Hypothermia decreases CBF by approximately 5.2% per degree of reduction in body temperature. The cerebral metabolic rate for oxygen ($CMRO_2$) and the arterial jugular venous oxygen difference ($AVDO_2$) fall after the institution of moderate hypothermia. This reflects a reduction in energy requirement and hence less energy loss in the injured brain. Stabilization of the cell membrane[62] and reduction of neurotransmitter turnover may also contribute to the benefit seen in models of ischemia.[63] Hypothermia has been associated with several complications, including cardiovascular instability (mainly arrhythmias), coagulopathy, electrolyte abnormalities,[64,65] and increased risk of infection and shivering. The use of hypothermia is therefore not without risks and requires high-level neuro-intensive care. Various approaches to cooling have been adopted, but the most frequently used employ surface cooling or gastric lavage with cold fluids. More recently, Marion[66] reported favorable results with the use of devices for intravascular cooling, and this technique can be expected to become standard for induction of hypothermia in the near future. Increased lactate acidosis in the cerebrospinal fluid was recognized in clinical investigations many years ago in the injured brain.[67,68] More recent studies, including magnetic resonance techniques and microdialysis, have confirmed earlier findings. The recognition of the occurrence of brain tissue and cerebrospinal fluid acidosis has stimulated studies to investigate the use of alkalizing agents such as THAM (tromethamine). THAM is a biologically inert amino alcohol that buffers carbon dioxide and acids in vitro and in vivo. Clinical studies have not shown conclusive evidence of benefit in the use of THAM, but nevertheless it is still used in some centers. It has been postulated that a possible beneficial effect of THAM could be to counteract ischemia produced by marked hypocapnia in patients treated with intensive hyperventilation.[69]

Mannitol is widely used in neurosurgery to treat raised ICP and to decrease brain bulk during intracranial operations and to treat cerebral ischemia. Mannitol is considered to exert beneficial effects by two mechanisms:

1. An immediate plasma expanding effect, reducing hematocrit and blood viscosity and consequently increasing CBF and cerebral oxygen delivery.
2. An osmotic effect, which is delayed for 15 to 30 minutes, while gradients are established between plasma and cells. Mannitol can be given in acute emergency situations such as cerebral herniation or as part of a conservative approach to treatment of raised ICP. Mannitol is thought to be more effective when given in small, frequent doses rather than by continuous infusion.[70] Given in high doses, mannitol may induce hypernatremia, decrease hematocrit, and increase osmolarity. A serious potential side effect is acute renal failure, which can occur if serum osmolarity increases above 320 mmol/L.

AGENTS ACTING ON SPECIFIC MECHANISMS

The increased understanding of the existence of progressive pathophysiologic mechanisms causing or enhancing secondary brain damage has led to the development of a large range of specifically targeted neuroprotective agents aimed at ameliorating such mechanisms, often showing marked beneficial effect in experimental studies. Unfortunately, in various fields of neuro-intensive care, promising experimental results have not translated into clinical efficacy. Calcium channel antagonists have proven benefit in the prevention and treatment of delayed ischemic deficits following aneurysmal subarachnoid

hemorrhage. By far the largest experience exists with the di-hydropyridine analogue nimodipine. In a meta-analysis performed by Barker and Ogilvy,[71] notable improvements in good and fair outcomes as well as reductions in death due to vasospasm and CT-detected infarcts were observed with nimodipine. Various studies on the use of calcium channel antagonists in the field of TBI have, however, yielded conflicting results, and current evidence does not support the use of these agents in patients with TBI, although the possibility of a small beneficial effect, particularly in patients with traumatic subarachnoid hemorrhage, cannot be definitely excluded.

PLURIPOTENT AGENTS AFFECTING VARIOUS MECHANISMS

The realization that various pathophysiologic mechanisms are frequently concurrently or sequentially active has increased interest in the use of agents with multiple mechanisms, and for such agents the term "dirty drugs" has been coined.[72]

Corticosteroids are widely used within neurosurgery to treat edema associated with brain tumors and to prevent brain edema associated with operative procedures. The presumed mechanisms of action include reduction of vascular permeability, reduction of cerebrospinal fluid production, attenuation of free radical production, inhibition of lipid peroxidation, reversal of intracellular calcium accumulation, and an anti-inflammatory effect. Despite the availability of many (small) studies, considerable uncertainty still remains concerning possible beneficial effects in patients with TBI.

Barbiturates are commonly used as second tier therapy for the treatment of raised ICP refractory to other treatment modalities. The main mechanisms by which barbiturates are neuroprotective has not been established.[73] The most important effects may relate to the coupling of CBF to regional metabolic demands, resulting in a decrease in CBF and related cerebral blood volume as a result of decreased metabolic requirements. Other possibilities include scavenging of oxygen free radicals and stabilization of cell membranes. The main complication of the use of barbiturates is arterial hypotension, which occurs in up to 58% of patients.[74] The decline in blood pressure may be greater than the reduction in ICP, risking a decrease in CPP, especially in patients with hypovolemia or cardiac disease. Other complications include hypoglycemia, hypernatremia, an increased risk of infection, liver and renal dysfunction, and cardiac failure.[74,75]

Dexanabinol, erythropoietin, and magnesium are agents with neuroprotective potential currently undergoing further clinical evaluation.

STRATEGIES PROMOTING CELL SURVIVAL AND REGENERATION

Strategies to promote cell survival and regeneration include cellular replacement, gene therapy, and administration of trophic factors. These futuristic approaches are aimed at promoting regeneration and neuroplasticity and may ultimately lead to improved functional recovery.[76,77] The potential of these novel therapies is strengthened by promising experimental and clinical results obtained in neurodegenerative diseases, including Parkinson disease, Huntington disease, and stroke.[77-80] This approach is currently the focus of large research efforts, which, it is hoped, will provide possibilities for further improving outcome in the subacute and chronic phases.

ANNOTATED REFERENCES

Constantini S, Cotev S, Rappaport ZH, et al: Intracranial pressure monitoring after elective intracranial surgery: A retrospective study of 514 consecutive patients. J Neurosurg 1988;69:540-544.

Study of 514 patients after supra- and infratentorial surgery demonstrating raised ICP (greater than 20 mmHg) in 18% of cases during the postoperative period. Of the 89 patients with elevated ICP, 47 (52.8%) had an associated clinical deterioration. It was concluded that ICP monitoring is advantageous in the immediate postoperative management after elective intracranial surgery and is almost risk-free. It should therefore be used liberally, especially when risk factors for ICP elevation can be identified prior to the end of surgery.

Constantini S, Kanner A, Friedman A, et al: Safety of perioperative minidose heparin in patients undergoing brain tumor surgery: A prospective, randomized, double-blind study. J Neurosurg 2001;94:918-921.

Prospective, randomized, double-blind trial that demonstrated the safety of the perioperative use of minidose heparin (5000 U) treatment in 103 patients undergoing craniotomy for supratentorial brain tumors. Treatment was started 2 hours before surgery and continued until full mobilization or for 7 days.

Diringer MN, Edwards DF: Admission to a neurologic/neurosurgical intensive care unit is associated with reduced mortality rate after intracerebral hemorrhage. Crit Care Med 2001;29:635-640.

Study using data prospectively collected from 36,986 patients listed in Project Impact demonstrating the benefits of focused neurointensive care in patients with spontaneous intracerebral hemorrhage when compared to care provided in a general ICU. Multivariate analysis of the data revealed that not being in a neuro-ICU was associated with an increase in hospital mortality rate (odds ratio, 3.4).

Fontes RB, Aguiar PH, Zanetti MV, et al: Acute neurogenic pulmonary edema: Case reports and literature review. J Neurosurg Anesthesiol 2003; 15:144-150.

This article provides a review of the literature of case reports of neurogenic pulmonary edema, an uncommon but important post-neurosurgical complication that requires emergency ICU assessment and therapy. The most frequent underlying factor was subarachnoid hemorrhage (42.9%). Symptom onset occurred less than 4 hours after the neurologic event in 71.4% of cases. One third of the patients presented with pink frothy sputum. Chest radiography showed bilateral diffuse infiltrates in 90.5% of cases. Supportive measures included oxygen support and vasoactive drugs. Recovery was usually very rapid: 52.4% of patients recovered in less than 72 hours. However, almost 10% of patients died of neurogenic pulmonary edema.

Livingston BM, Mackenzie SJ, MacKirdy FN, Howie JC: Should the pre-sedation Glasgow Coma Scale value be used when calculating Acute Physiology and Chronic Health Evaluation scores for sedated patients? Scottish Intensive Care Society Audit Group. Crit Care Med 2000;28:389-394.

Study in 13,291 consecutive admissions of the optimal application of the GCS score in the APACHE II and III scoring in the ICU. The GCS was found to be an important component of both APACHE II and APACHE III and should be assessed directly whenever possible. When patients are sedated, using the GCS score recorded before sedation was found to be preferable to the assumption of normality.

Mirski MA, Chang CW, Cowan R: Impact of a neuroscience intensive care unit on neurosurgical patient outcomes and cost of care: Evidence-based support for an intensivist-directed specialty ICU model of care. J Neurosurg Anesthesiol 2001;13:83-92.

Retrospective study that demonstrated reduced mortality rate, improved discharge disposition, and reduced length of hospital stay and cost when comparing similar cohorts of patients with intracranial hemorrhage treated in a neurosurgical ICU versus a general ICU.

Chapter 59

KEY ISSUES IN PEDIATRIC NEUROINTENSIVE CARE

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KEY POINTS

1. There are important **age-related differences** in both the CNS insults and the response to these insults in infants and children.
2. Neurointensive care for infants and children should focus on the **prevention of secondary extracerebral insults** and optimize brain-directed therapies. Optimization of cardiopulmonary physiology, maintenance of euglycemia, and prevention of hyperthermia and hyponatremia are important to optimize outcome.
3. Cardiopulmonary arrest in infants and children results from **asphyxia** in the majority of cases.
4. The **goals of treating status epilepticus** are to provide respiratory and cardiovascular support, terminate seizure activity, identify and treat the precipitating factors, and prevent systemic complications.
5. Congenital and acquired heart disease are the most important underlying causes of **embolic stroke** in infants and children.
6. The etiology and treatment of **bacterial meningitis** differ between neonates and older infants and children.
7. **Herpes simplex virus** is an important cause of severe encephalitis in children.
8. **Treatment of impending herniation** includes immediate airway control, mannitol or hypertonic saline administration, hyperventilation, cerebrospinal fluid drainage (if available), and emergent CT evaluation.

In this chapter we outline the epidemiology, presentation, course, and management of key disorders in pediatric neurointensive care. Critically ill infants and children with a compromised central nervous system (CNS) are complex patients and are often highly vulnerable to secondary brain injury. Minimizing physiologic derangements and optimizing therapy are essential from the scene through the pediatric ICU. In most cases, transport to a specialized pediatric facility is desirable. Trained specialists in pediatric critical care medicine, pediatric neurologic surgery, and child neurology should deliver the ICU care to these infants and children, with appropriate pediatric ancillary support. The information provided in this chapter is germane to practitioners involved in stabilization, emergency treatment, and transport and to pediatric subspecialists at the tertiary care centers. Recommendations in the areas of pediatric trauma (head and spinal cord injury), procedures, and monitoring are addressed in Chapters 47, 228, and 248. Neurointensive care issues relevant to the field of neonatology are outside the scope of this chapter and specialized textbooks and/or reviews in this area should be sought for information in that field.

ISSUES UNIQUE TO PEDIATRICS

Two key factors contribute to the unique nature of the practice of pediatric neurointensive care: differences in the specific insults to the CNS in infants and children versus adults and age-related differences in the response to these insults.

CNS INSULTS IN INFANTS AND CHILDREN

Unlike in adults, atherosclerotic vascular disease, resulting in stroke, intracerebral hemorrhage, and cardiopulmonary arrest plays little role in pediatric neurointensive care. For example, cardiopulmonary arrest in infants and children results primarily from asphyxia rather than myocardial infarction. Similarly, traumatic brain injury in infants younger than 2 years of age is largely the result of inflicted childhood neurotrauma (shaken baby syndrome, child abuse). Unique issues in victims of child abuse, such as chronic injury or delay in presentation, contribute to important differences in diagnosis, treatment, and outcome. The specific CNS insults relevant to pediatric neurointensive care include traumatic brain injury and spinal cord injury, cardiopulmonary arrest, status epilepticus, stroke, critical CNS infections, postoperative neurosurgical conditions, and several other less common disorders; traumatic brain and spinal cord injury are addressed in Chapters 55 and 56.

AGE-RELATED DIFFERENCES IN THE RESPONSE TO CNS INSULTS

Brain Water and Blood-Brain Barrier

Many biochemical, physiologic, and physical factors exhibit large fluctuations during brain development. Although the magnitude of these changes are most dramatic during prenatal development, they may contribute to age-related differences in response to critical CNS disorders.[1,2] Large decreases in brain water content occur during postnatal development into adult life.[3-5] These changes are global and correlate with the amount of myelination. The impact of these changes on edema formation after brain injury is unclear; however, the rapid and diffuse cerebral swelling phenomenon described in many CNS insults in infants and

children may be related to this high water content in the immature brain. This is suggested by studies showing that parenchymal injection of glutamate into the immature (but not adult) rat brain rapidly produces a large area of edema.[6] The rapidity of development and the great magnitude of edema may result, in part, from rapid diffusion of glutamate and other mediators through the immature brain. In contrast to the changes in brain water during development, there is little evidence to support similar changes in blood-brain barrier permeability.[7,8] However, studies in experimental models suggest that the immature blood-brain barrier is highly vulnerable to injury.[9-11] Blood-brain barrier permeability after CNS insults has received little study in pediatric patients.

Cerebral Blood Flow and Energy Metabolism

Postnatal changes in cerebral blood flow (CBF) and energy metabolism have been reported in numerous mammalian species including humans.[12-19] In all cases, CBF is quite low both before birth and during infancy, rapidly increases to a peak during childhood, and then decreases to a plateau with a gradual decline with increasing age during adulthood. In a study of 42 normal infants and children, cortical CBF in newborns was between 30 and 45 mL/100 g/min—lower than that reported in adults. In contrast, cortical flow in children between the ages of 5 and 6 years was between 50% and 85% higher than in adults. CBF decreased to adult values by about age 15 years (Fig. 59-1).[20,21] Increased CBF in children (vs. either adults or infants) corresponds to the period of maximal postnatal "brain growth," specifically, maximal increases in the number of synapses.[22-24] Similarly, cerebral metabolic rate for glucose is maximal in children between the ages of 3 and 9 years.[17] The impact of these factors in CNS injury is poorly understood. Hyperemia after injury has been implicated as an important facet of the pathophysiology of pediatric CNS injury. Because the level of CBF in the normal child is greater than in adults, the frequency of hyperemia in children is probably lower than has been suggested. Hyperemia in most gray matter structures, in children between the ages of 3 and 10 years, should probably be based on a flow value greater than about 70 mL/100 g/min[19-21,24] rather than the value of about 45 mL/100 g/min suggested for adults.[25] Alterations in metabolic demands after injury must also be considered.

Cerebral Perfusion Pressure

Cerebral perfusion pressure (CPP; mean arterial blood pressure–intracranial pressure [ICP]) is a critical determinant of CBF outside the limits of autoregulation or when autoregulation of blood pressure is disturbed. In adults, the normal range for CPP is generally accepted to be between 60 and 150 mm Hg.[26,27] Based on studies in normal immature animals, the lower limit for blood pressure autoregulation of CBF is directly related to age.[28-30] This is anticipated since CPP is a function of arterial blood pressure, which is dependent on age. Unfortunately, few data are available on normal values for CPP in infants and children. A mean value of 37.5 ± 4.9 mm Hg (± SD) was reported in normal preterm infants.[31] The lower limit of blood pressure autoregulation was not determined. This is well below the 60 mm Hg critical CPP value for the lower limit of CBF autoregulation in adults and highlights the problem in defining optimal CPP in pediatric neurointensive care—it is likely not a single number. There are also limited data available on the lower limit of blood pressure autoregulation of CBF in brain-injured infants and children. A study of 17 infants and children with meningitis and encephalitis showed a critical threshold for CPP of about 30 mm Hg.[32] However, survival, not CBF, was the outcome variable in that study. Muizelaar and coworkers[20,21] and Sharples and colleagues[33] examined CBF autoregulation after traumatic brain injury in children; however, normal values for blood pressure autoregulation of CBF for infants and children were not determined. Two recent studies suggest that the presence of mild hypertension after severe brain injury is associated with improved outcome in infants and children.[34,35] However, the impact of inducing mild hypertension in this setting on outcome remains to be studied.

Myelination

In humans, considerable myelination occurs during postnatal life.[23] The impact of this process on the age-related response in pediatric CNS injury is not known but has been suggested by many to contribute to enhanced plasticity in the pediatric brain.

Excitotoxicity

Increases in brain interstitial concentrations of excitatory amino acids such as glutamate are part of a fundamental

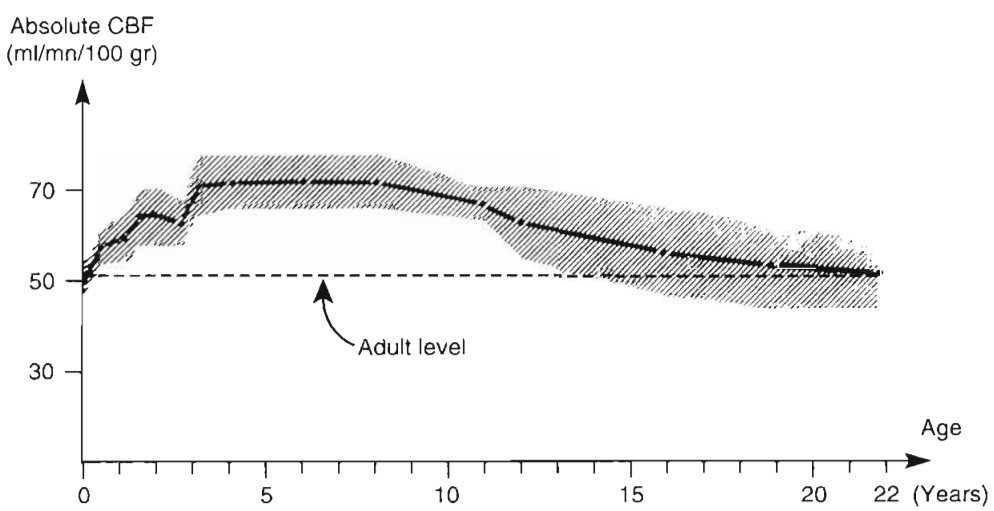

FIGURE 59–1. Mean *(the curve)* and ± 1 SD *(hatched area)* for normal cerebral blood flow in 42 children from 2 days to 19 years old compared with adult values *(dotted line)*. Compared with adult values, cerebral blood flow is lower in infancy, but thereafter values throughout childhood exceed those of adults.
(From Chiron C, Raynaud C, Maziere B, et al: Changes in regional cerebral blood flow during brain maturation in children and adolescents. J Nucl Med 1992;33:696-703. Reprinted by permission of the Society of Nuclear Medicine.)

response to CNS insults across all ages.[36-45] Excitotoxicity-mediated damage after brain injury has been reported in laboratory models in mature and immature animals and is suggested in clinical reports in children.[37,41-45] There are, however, important age-dependent facets of excitotoxicity. At several periods in development large numbers of excitatory amino acid receptors are produced, and these periods correlate temporally with increased synaptic plasticity.[38-41] Experimental data strongly suggest that the immature brain is at great risk for excitotoxicity.[37-39] In hypoxia-ischemia models, studies in immature animals (particularly those modeling the newborn) suggest that glutamate receptor antagonists, such as MK-801, are potent neuroprotectants.[38,39,41] The results of clinical trials in adults of agents targeting this receptor may not predict their effectiveness in infants or children with critical CNS insults. Further study in children is warranted.

Apoptosis

Experimental models and human data have made it increasingly clear that cells dying after CNS insults can be categorized on a morphologic continuum from necrosis to apoptosis.[46-48] The event involved in the cascades of neuronal death after CNS insults is discussed in detail in Chapter 38. The importance of balanced apoptosis (or programmed cell death) in embryogenesis and recent reports examining apoptosis in experimental traumatic brain injury suggest that there may be important age-related differences in the cell death cascades in response to traumatic or ischemic brain injury.[49] For example, neurons in developing animals appear to be more vulnerable to apoptosis than in mature animals.[46,49] There are also data supporting the concept that physiologic levels of excitatory amino acids are necessary for neuronal survival in the developing brain.[50] The implications on these data in experimental animals must be assessed with caution; however, they raise concern about the ability of therapies such as barbiturates or inhibitors of excitatory amino acid receptors to actually induce neuronal death during development. The fetal alcohol syndrome is the prototypical condition cited in this regard.[51] What remains unclear, however, is if this enhanced apoptotic response to CNS injury is limited to prenatal development or if it is important during treatment of infants and children in the pediatric ICU. Nevertheless, an important role for apoptosis in pediatric brain injury is suggested by the fact that analysis of cerebrospinal fluid (CSF) in infants and children with severe traumatic brain injury has provided some of the most compelling molecular data for the participation of these pathways in humans.[2] These data include participation of death effectors such as cytochrome-c and Fas receptor/ligand interactions and failure of anti-apoptotic pathways in infants and children with poor outcome after severe brain injury.[2,52-55] How these findings will influence our therapies remains to be determined, but they suggest that apoptotic neuronal death may represent a particularly important therapeutic target in pediatric neurointensive care.

Extracerebral Factors

Many "extracerebral" factors play a role in the age-related differences in the response to critical CNS disorders, including age-related differences in (1) the response to hypoxemia-ischemia and hypotension, (2) atherosclerosis and other risk factors for stroke, and (3) acute and chronic ethanol consumption. These are rarely discussed in this context.

Hypotension and hypoxemia are the two most important secondary insults in patients with critical CNS disorders. Hypotension is the most important extracerebral factor associated with poor outcome after severe traumatic brain injury.[56] This may contribute to the high mortality rate (62%) in this condition in children younger than age 4 years.[57] Nearly 50% of these children present with shock, versus only 30% of adults.[57] The limited blood volume of infants and young children make relatively small amounts of blood loss from scalp lacerations or other foci important. In contrast, the immature brain and cardiovascular systems are resistant to hypoxic-ischemic insults compared with mature individuals.[58] The duration of asphyxia resulting in cardiac arrest is inversely related to age.[59-62] Resistance to asphyxia-induced cardiac arrest in the immature individual, however, could have complex effects. For example, children may survive protracted episodes of hypoxemia and hypotension that would be lethal in adults. Resistance of the immature myocardium to asphyxia does not preclude the development of cerebral damage from hypoxemia, because between 25% and 56% of children who suffer asphyxia without cardiac arrest have poor neurologic outcome.[63] This might also explain some of the severe pathology seen in infants after inflicted childhood neurotrauma, in which apnea, seizures, and agonal states occur.[64]

Unlike adults, atherosclerotic vascular changes are largely absent in children. This influences pathophysiology. Although normal aging produces a gradual decline in CBF, this decline is accentuated in adults by the presence of risk factors for stroke (e.g., diabetes, cigarette smoking, hypertension), which enhance incipient cerebrovascular disease.[65] Atherosclerosis also limits the ability of cerebral circulation to respond to a metabolic challenge.[66-69] Some adults may even have maximally dilated cerebral vessels in the resting state. The potential of these factors to unfavorably affect outcome in adults (vs. children) is obvious. Ethanol consumption is associated with severe traumatic brain injury in adults, with as high as 50% of patients having positive blood alcohol levels.[70-73] Chronic and acute alcohol consumption can have either detrimental or beneficial effects on brain injury.[73] Ethanol use or intoxication is uncommon in pediatric traumatic brain injury, particularly in infants and young children.

SPECIFIC DISEASES OR CONDITIONS

CARDIOPULMONARY ARREST

Cardiopulmonary arrest in adults is addressed in detail in Chapter 50. Although some of that chapter is germane to pediatric patients, the importance of asphyxia as the etiology in children mandates a separate discussion.

Epidemiology

The causes of cardiopulmonary arrest in childhood are heterogeneous. Causes of arrest in the prehospital setting include trauma, sudden infant death syndrome, poisoning, and respiratory distress secondary to drowning, choking, severe asthma, or pneumonia.[74] Traumatic arrest secondary to exsanguination, massive head injury, or airway compromise is the leading cause of death in childhood and young adulthood. Nontraumatic arrest typically occurs as a consequence of hypoxemia and hypercarbia, leading to respiratory arrest, bradycardia, and, ultimately, asystole or pulseless

electrical activity.[74-76] Ventricular tachycardia or fibrillation occurs less commonly in children than adults, but it is not rare. Five to 15 percent of children with prehospital arrest have these rhythms.[77-79] The majority of arrests in the prehospital setting occur in previously healthy patients, whereas most in-hospital arrests occur in children with preexisting medical conditions.[80] Children with special health care needs are especially vulnerable to acute deterioration.

Outcome

The rate of survival from pediatric cardiopulmonary arrest is about 13%, with survival from in-hospital arrest greater than that from prehospital arrest (24% vs. 9%).[76] Asystolic patients have the lowest rate of survival (~5%) whereas patients with ventricular fibrillation or ventricular tachycardia have higher rates of survival (~30%). Patients presenting with isolated respiratory arrest have the highest rate of survival (~75%).[81,82] Witnessed arrest and bystander cardiopulmonary resuscitation (CPR) are associated with survival, whereas CPR of greater than 30 minutes and administration of more than two doses of epinephrine are associated with poor outcome.[74,77,83,84] About 60% of survivors will have good neurologic outcome, with the remainder showing severe disabilities. Intermediate outcomes are uncommon. Reported mortality rates for children remaining comatose after brain injury range between 34% and 73% dependent on whether traumatic brain injury is included.[85-90] Accurate prediction of poor outcome in this group can enable withdrawal of support and decrease the possibility of "rescuing" children to survival in a neurologically devastated state.[91,92] Predictors of poor outcome in children include remaining comatose at 24 hours, a Glasgow Coma Scale (GCS) score of less than 5, absence of spontaneous respirations, absence of pupillary reflex, and specific abnormalities found on electroencephalography (EEG) or after testing of somatosensory-evoked potentials. Predictors of poor outcome should be applied with caution to children suffering cardiopulmonary arrest caused by drug overdose or hypothermic exposure (ice cold water drowning) in which good outcomes have been reported in some cases after even prolonged durations of arrest.

Treatment

The optimal treatment of pediatric cardiopulmonary arrest is prevention. The use of child restraints in motor vehicles, bicycle helmets, pool fences, and fire alarms has contributed to important reductions in morbidity and mortality. Also, the number of cases of sudden infant death syndrome has decreased in the United States from 4900 infants in 1992 to 2600 infants in 1999 in association with the recognition that placing infants on their backs during sleep lowers the risk of this condition. For health care providers, the key to prevention is recognizing and treating *early* signs of cardiopulmonary compromise (tachycardia and increased work of breathing).

If cardiopulmonary arrest occurs, the most important first step is to provide immediate CPR. Many infants and children, especially in the prehospital setting, will be rescued solely by the administration of CPR.[74] The technique for children is similar to that used in adults except for delivery of chest compressions. Only one hand is used to deliver chest compressions to children younger than age 8 years. Two methods are approved for delivering chest compressions to infants. When two or more rescuers are available, one rescuer provides chest compressions by encircling the chest with two hands and depressing the sternum with both thumbs while

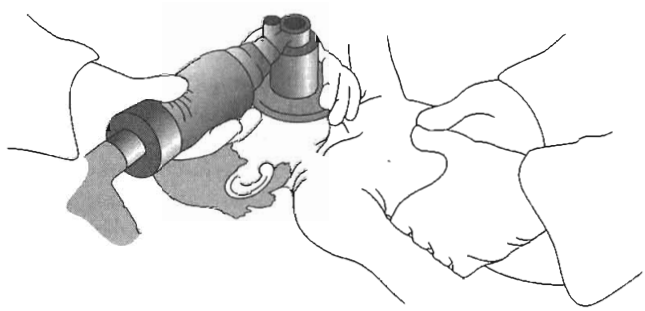

FIGURE 59–2. Two-person technique for cardiopulmonary resuscitation in infants and young children. (Reprinted from Pediatric Basic Life Support. Guidelines 2000 for Cardiopulmonary and Emergency Cardiovascular Care: International Consensus on Science. Circulation 2000;102(8)(Suppl):I253-I290.)

the other rescuer provides ventilation (Fig. 59-2). When only one rescuer is present, two fingers from one hand are used to provide chest compressions and the other hand is used to maintain the head-tilt. Providing adequate ventilation is especially important for children because most pediatric arrests are secondary to airway compromise. In contrast, adults frequently suffer from cardiac causes of arrest and require intensified efforts at providing chest compressions and early defibrillation. Thus, the recommended ratio of chest compressions to ventilations for young children is 5:1, compared with a ratio of 15:2 for older children and adults. Once the patient is intubated, ventilations should be asynchronous. Although ventricular fibrillation and ventricular tachycardia are uncommon in children, survival with this rhythm is high (about 30%) and thus cardiac rhythm should be ascertained as early as possible.[76] Automated external defibrillators that can deliver a 50-J dose are now available and are appropriate for use in children aged 1 to 8 years.[93]

Intubation of pediatric patients is a difficult task for inexperienced providers. Furthermore, the short length of the trachea combined with patient movement during transport and patient care can easily result in displacement of the endotracheal tube.[94] Thus, secondary confirmation of endotracheal tube placement is critical. End-tidal CO_2 detection is the method most commonly utilized for secondary confirmation of endotracheal tube placement in children. However, a false-negative reading can occur when circulatory collapse is so severe that CO_2 is not delivered to the alveolar space. If CO_2 is not detected during CPR, tube placement can be confirmed by visualizing the airway with a laryngoscope. Although no single confirmation technique is 100% reliable in all circumstances, some effort of secondary confirmation of tube placement should be performed after intubation of *all* children.

Patients are initially resuscitated using 100% oxygen. The rationale is that hypoxia often causes or contributes to the development of cardiac arrest, and an oxygen debt accumulates during cardiac arrest. However, there is increasing awareness that oxygen might contribute to reperfusion injury, and thus *prolonged* delivery of *unnecessarily* high concentrations of oxygen should be avoided.[95]

Adults resuscitated from cardiac arrest demonstrate intact cerebrovascular reactivity with evidence of hyperventilation-associated ischemia.[96] Although there is evidence that injured brain has diminished metabolism, which may offset the decrease in blood flow, it seems prudent to avoid decreasing CBF to injured brain. Therefore, hyperventilation should be reserved for patients with signs of cerebral herniation syndrome or suspected pulmonary hypertension. In addition to

avoiding purposeful hyperventilation, it is prudent to guard against inadvertent hyperventilation during patient transport.[97] Increased use of quantitative continuous CO_2 monitors throughout the health care system would decrease the occurrence of inadvertent hyperventilation.

Establishing vascular access in children can be challenging. Fortunately, intraosseous access can be achieved within 30 to 60 seconds and provides a route for drug and fluid administration when intravascular access cannot be readily achieved. Drugs, including lidocaine, epinephrine, atropine, and naloxone (mnemonic "LEAN") can be administered through the endotracheal tube. Optimal doses for drugs given via the endotracheal tube are not established, but the recommended dose of epinephrine is 0.1 mg/kg (10 times the intravenous dose). A bedside glucose measurement should be obtained; and if hypoglycemia is present, it should be treated with 0.5 to 1.0 g/kg of glucose given intravenously. There is experimental evidence that hyperglycemia exacerbates ischemic injury in mature brain and hypoglycemia exacerbates ischemic injury in immature brain. Thus, euglycemia is desirable. Initial resuscitation fluids should be limited to isotonic crystalloid solutions, such as normal saline or lactated Ringer's solution.

The most commonly used drugs in pediatric resuscitation are epinephrine, atropine, and sodium bicarbonate (Table 59-1). Magnesium and calcium are reserved for specific indications such as torsades de pointes, hypocalcemia, and calcium channel blockade. Amiodarone has recently been added to the American Heart Association (AHA) pediatric algorithms based on extrapolation from adult experience.[98] Adults with ventricular fibrillation or ventricular tachycardia in the prehospital setting are more likely to be successfully defibrillated after intravenous administration of amiodarone compared with lidocaine.[99] Accordingly, amiodarone (5 mg/kg bolus) is a therapeutic option for children with pulseless arrest. Amiodarone (5 mg/kg infused over 20 to 60 min) is also an option for ventricular tachycardia with a pulse but should be used with extreme caution because of the risk for profound hypotension. Vasopressin has been added to the AHA adult algorithms as an alternative to epinephrine on the basis of its improved myocardial and CBF effects. However, subsequent clinical data in adults have not consistently yielded positive results and pediatric data are limited to small case series.[100,101] The optimal vasopressor for hemodynamic support after return of circulation in children is not known.

Extracorporeal membrane oxygenation (ECMO) has been used to successfully resuscitate children from selected causes of in-hospital cardiac arrest.[102-106] ECMO-CPR provides greater cerebral and myocardial blood flow than either closed- or open-chest CPR and facilitates titration of temperature, blood flow, and oxygen-carrying capacity. Good outcomes have been documented with the use of ECMO even when initiated after durations of conventional CPR typically associated with poor outcome. It is best reserved for patients with reversible conditions or as a bridge to cardiac transplantation.

Post-Resuscitative Care

Temperature control is a priority for patients who remain comatose after cardiac arrest. Adults cooled to 32°C to 34°C for 12 to 24 hours after resuscitation from ventricular fibrillation demonstrate improved survival and neurologic outcome.[107,108] In contrast, fever worsens outcome in experimental models of brain injury and has been associated with worse clinical outcome in adults with ischemic brain injury. Children resuscitated from cardiac arrest often develop mild hypothermia followed by delayed fever.[109] There is a consensus that initial hypothermia, if tolerated, should be permitted to continue and fever should be vigilantly avoided. The practice of inducing hypothermia in normothermic children is more controversial. Experimental models using either pediatric mechanisms of injury (asphyxia, hypovolemic shock) or examining the immature brain suggest a beneficial effect of induced hypothermia. However, clinical data are limited and there is a concern about hypothermia-impaired immune function and risk of pneumonia/sepsis. Clinical trials of induced hypothermia for neonatal asphyxia are ongoing.

During recovery from global ischemia there is a period of prolonged, multifocal, decreased CBF. Hypotension and hypoxia should be avoided during this period to prevent development of a secondary brain injury. As previously mentioned, the optimal regimen of oxygen and pressor therapy is not known and requires further study.

Sustained elevation of ICP may be more common after asphyxial arrests versus arrests of cardiac origin[110] and is a poor prognostic sign in children with drowning. ICP monitoring fell out of favor in the 1980s when it was found to not influence outcome in small case series.[111] However, studies using contemporary ICP-directed therapy (perhaps including induced hypothermia) deserve reevaluation.

TABLE 59–1. DRUGS COMMONLY USED IN ARREST OR PERI-ARREST CONDITIONS

Drug	Dose	Maximum Single Dose	Route
Adenosine*	0.1 mg/kg Repeat dose: 0.2 mg/kg	12 mg	i.v. (rapid push)
Atropine	0.2 mg/kg (0.1 mg/min)	Children: 0.5 mg Adolescents: 1 mg	i.v., i.o., e.t.
Amiodarone	5 mg/kg	300 mg	i.v., i.o. (bolus in pulseless arrest, otherwise give slowly)
Calcium chloride (10%)	20 mg/kg	500 mg	i.v., i.o. (slowly)
Dextrose	0.5-1 mg/kg	N/A	i.v., i.o.
Epinephrine	0.01 mg/kg (0.1 mg/kg if given e.t.)	5 mg	i.v., i.o., e.t.
Lidocaine	1 mg/kg	100 mg	i.v., i.o., e.t.
Narcan	0.1 mg/kg	2 mg	i.v., i.o., e.t.
Magnesium	25-50 mg/kg	2 g	i.v., i.o.
Sodium bicarbonate (8.4%)	1 mEq/kg	N/A	i.v./i.o.

i.v., intravenous; i.o., interosseous; e.t., endotracheal.
*For supraventricular tachycardia.

Miscellaneous

Most pediatric victims of cardiopulmonary arrest will not be successfully resuscitated. The difficulty of accepting this reality often results in prolonged attempts at resuscitation. The AHA 2000 Guidelines state, "In the absence of recurring or refractory ventricular fibrillation or ventricular tachycardia, history of a toxic drug exposure, or a primary hypothermic insult, resuscitative efforts may be discontinued if there is no return of spontaneous circulation despite advanced life support. In general, this requires no more than 30 minutes."[98] This acknowledges the futility of prolonged resuscitative efforts and empowers clinicians to feel *permitted to stop* resuscitative efforts. The guideline does not mandate stopping at a specific duration of CPR, but clinicians should recognize that the chance of survival with lifelong severe disabilities correlates with the duration of CPR.

Surveys indicate that most family members would like to be present during resuscitation attempts of a loved one.[112-115] Presence during resuscitation can help family members adjust to the death of a loved one.[116,117] Although allowing family presence during resuscitation requires planning and additional resources, when done properly it is worth the effort. Perhaps one of the most disheartening statistics in resuscitation research is the high divorce rate (up to 90%) of parents after the death of a child. Thus, pastoral and social services can be integral components of care during both the acute resuscitation event and long-term follow-up.

STATUS EPILEPTICUS

Status epilepticus is a pediatric emergency traditionally defined as either a continuous seizure of at least 30 minutes or more than two discrete seizures without complete recovery of consciousness. Refractory status epilepticus is defined as failure of two first-line antiepileptic medications to treat this condition for greater than 60 minutes. Many children with refractory status epilepticus have new or established CNS lesions.[118]

Epidemiology and Etiology

The incidence of pediatric status epilepticus from a prospective study is 40 cases/100,000 per year. Infants younger than 1 year of age have the highest incidence at 150 cases/100,000 per year.[119] More than 90% of cases are convulsive status epilepticus. The first episode of status epilepticus occurs at a mean age of 4.2 years.[120] There is a slight male predominance in status epilepticus.[119,121]

There are five etiologic categories of status epilepticus that have bearing on treatment and prognosis. A child with *idiopathic or cryptogenic* status epilepticus has no prior history of seizures and no known risk factors. *Atypical febrile* status epilepticus occurs during fever in children with no prior history of seizures without fever. Children with *acute symptomatic* status epilepticus have new CNS lesions such as encephalitis, trauma, tumor, stroke, or anoxia. Children with *remote symptomatic* status epilepticus have pre-existing CNS lesions and therefore a lowered seizure threshold. In these children status epilepticus can occur without provocation, sometimes even years after the initial insult. Finally some children have status epilepticus resulting from *progressive encephalopathy,* including neurodegenerative diseases, malignancies, and neurocutaneous syndromes (Table 59-2).[119,121,122]

In one study, status epilepticus accounted for 1.6% of total pediatric ICU admissions and etiology varied with age.

TABLE 59-2. ETIOLOGY OF STATUS EPILEPTICUS

Idiopathic/cryptogenic (24%)
Atypical febrile (24%)
Previously normal
Previously abnormal
Acute symptomatic (23%)
CNS infection
Anoxia
Trauma
Stroke/hemorrhage
Intoxication
Metabolic
Anticonvulsant withdrawal
Remote symptomatic (23%)
Progressive encephalopathy (6%)
Neurocutaneous syndrome
Neoplasm
Genetic/metabolic

In children younger than 2 years of age, *acute symptomatic* status epilepticus from meningitis and encephalitis accounted for 51% of cases whereas *remote symptomatic* status epilepticus in children with a prior diagnosis of epilepsy was seen in 16% of children. Older children were more likely than younger children to have a history of epilepsy.[121] Mortality rates for status epilepticus in children are between 3% and 6%.[119,122] Mortality is dependent on etiology, age, and duration of status epilepticus. Mortality rates of 0% and 12.5% were seen when patients were divided into either unprovoked/febrile status epilepticus or acute CNS insult/progressive encephalopathy groups, respectively.[121] Morbidity risk varies from between 11% and 25%. Infants are at great risk for morbidity because the etiology in this group is commonly *acute symptomatic* status epilepticus. Neurologic sequelae of status epilepticus include epilepsy, recurrence, mental retardation, and motor disorders. However, many of the morbidities can be attributed to the underlying disease and not status epilepticus per se. Risk of recurrence in the category of *idiopathic* status epilepticus is less than 5%. In contrast, recurrence of status epilepticus in children in the *acute symptomatic* groups can be as high as 60%.[119,123] Systemic complications occur, with increasing frequency, in proportion to the duration of status epilepticus, the most important being respiratory failure and cardiovascular compromise and autonomic and metabolic disturbances.[124]

Diagnosis

Status epilepticus can be convulsive or nonconvulsive, when comparing clinical events with electrographic information. Convulsive seizures either begin as generalized seizures or progress from partial seizures. Nonconvulsive seizures are characterized as having subtle clinical signs such as nystagmus, irregular clonic twitches along with decreased consciousness, and/or ictal discharges on EEG. Included under the subheading of nonconvulsive seizures are complex and simple partial and absence seizures.[125]

Treatment

The goals in treating status epilepticus are to provide respiratory and cardiovascular support, terminate clinical and electrical seizure activity, identify and treat precipitating factors, and prevent systemic complications.[125] Recognizing that a prolonged duration of seizure increases the risk of morbidity and mortality, the Epilepsy Foundation of America

published a consensus view to initiate antiepileptic drugs for treatment 10 minutes after the onset of an episode of status epilepticus.[126] A timetable for treatment of status epilepticus in children is provided in Table 59-3.

History of present and past illness may be useful in determining the cause of status epilepticus and in choosing therapy, but it should not delay resuscitation efforts. Initial treatment includes basic life support—airway, breathing, and circulation (ABCs). The prevention of hypoxemia and hypotension, which exacerbate neuronal injury, is important. The airway should be kept open with simple maneuvers and 100% oxygen applied to the patient with a non-rebreathing mask. The airway should also be kept clear of airway secretions. Efficacy of oxygenation efforts should be monitored by pulse oximeter. Ventilation efforts are assessed clinically or by arterial blood gas determinations. If the patient is unable to maintain adequate oxygenation or ventilation, endotracheal intubation using rapid sequence intubation technique is indicated. Circulation is monitored by assessment of ECG, blood pressure, and perfusion. Ideally, a large-bore peripheral intravenous catheter should be placed for fluid and drug administration. A bedside blood glucose determination should be obtained. Serum electrolyte levels, renal and liver functions, and anticonvulsant levels should be assessed. Serum and urine toxicology screen should be obtained. Fever and hypoglycemia should be treated as quickly as possible to prevent CNS injury. The neurologic examination follows, focusing on GCS score, signs of raised ICP, focal deficits, and pupil size. In patients receiving neuromuscular blockade, electrical seizure activity should be monitored with continuous EEG. The ABCs should be reassessed throughout the resuscitation.

First-line antiepileptic drugs for pediatric status epilepticus include benzodiazepines, phenytoin or fosphenytoin, and phenobarbital. Drug choice depends on the route available (intravenous is preferred), the patient's maintenance anticonvulsants (a different class is recommended), and patient characteristics. Evidence-based studies of anticonvulsants in children are rare. Recommendations are extrapolated from studies in adult. The optimal first-line treatment of status epilepticus in children is controversial.

Phenytoin/Fosphenytoin. In a study in adults comparing lorazepam, phenytoin, phenobarbital, and diazepam, phenytoin had the highest success rate in stopping status epilepticus.[127] Phenytoin is not commonly associated with respiratory depression and has less of an effect on the impairment of consciousness than either benzodiazepines or barbiturates. Fosphenytoin has the advantage of having a faster infusion rate, shorter onset of action, and less cardiovascular side effects than phenytoin but is more expensive.

Lorazepam. In the same study in adults, lorazepam had the second highest success rate in stopping status epilepticus.[127] Lorazepam can be administered rapidly, has a long duration of effect, and is effective even when administered rectally. Lorazepam produced less respiratory failure requiring intubation than diazepam in retrospective[128] and prospective studies.[129] Incidence of respiratory depression in these studies varied widely—between 3% and 76%.

Diazepam. Although the onset of action of diazepam is rapid (between 1 and 3 minutes after intravenous administration), it has a large volume of distribution; therefore, its duration of action is only 15 to 30 minutes. Thus, concomitant maintenance antiepileptic drugs are generally needed. Rectal diazepam has gained attention recently through its use as a first-line outpatient drug for use by parents or emergency services.

Phenobarbital. Phenobarbital is a very effective anticonvulsant, but it is often not the first choice in the treatment of status epilepticus because of side effects of respiratory depression and cardiovascular disorders, especially when it is used in combination with benzodiazepines. Infants metabolize phenobarbital more rapidly than older children and often require higher doses adjusted for body weight. Nevertheless, the pharmacokinetics of phenobarbital are more predictable than those of phenytoin in infants.

TABLE 59–3. SUGGESTED TIMETABLE FOR THE EMERGENCY DIAGNOSIS AND TREATMENT OF STATUS EPILEPTICUS

Time	Exam/Intervention	Testing
Initial presentation: *0 min*	Airway, breathing, circulation IV access, monitoring	Glucose, oxygenation via pulse oximetry ± blood gas analysis
Primary survey: *5 min*	Neurologic exam Administer antiepileptic drugs Lorazepam, 0.1 mg/kg i.v. Phenobarbital, 20 mg/kg i.v. Normal saline maintenance i.v. Reduce fever	Electrolytes, renal and liver function, ammonia, anticonvulsant levels, toxicology, complete blood cell count, urinalysis
Secondary survey: *15-30 min*	Evaluate treatment results Second line antiepileptic drug if seizure persists Phosphenytoin, 20 mg/kg i.v. or phenytoin, 20 mg/kg i.v.	Patient-specific: cranial imaging (CT vs. MRI), lumbar puncture, EEG, ECG
Status epilepticus: *>30 min*	Intubation and mechanical ventilation	
Refractory status epilepticus: *>60 min*	Titrate anti-epileptic drug to burst suppression. Pentobarbital, 10 mg/kg i.v. given over 30 min, then 5 mg/kg every hour for 3 doses, then 1 mg/kg/h; titrate to effect Midazolam, 0.15 mg/kg i.v. then 1-2 μg/kg/min titrate to effect Phenobarbital, 5-10 mg/kg i.v. every 20 minutes to achieve burst suppression, then every 12 hours Evaluate need for vasopressors.	Continuous EEG Neurologic consultation Consider anesthesia consultation for treatment with inhaled gas.

Additional Diagnostic Workup

Lumbar puncture is best performed early after presentation, but not in unstable patients or those who may have increased ICP. The decision to perform lumbar puncture should be guided by head CT. Otherwise, the type of neuroimaging used in infants and children with status epilepticus should be individualized, depending on history and physical findings. Both electrocardiography and EEG are useful to investigate cause of status epilepticus (i.e., long QT syndrome or identifiable EEG patterns). EEG is also useful in titrating therapy (see later).[125]

Drug Treatment for Refractory Status Epilepticus

Initiation of treatment for refractory status epilepticus should occur by 60 minutes, usually with neurologic consultation and with appropriate monitoring in a pediatric ICU or intermediate unit. These patients are mechanically ventilated, and seizures are typically treated with a variety of therapies, generally to induce burst suppression on continuous EEG. Most commonly, pentobarbital is used as a continuous infusion to treat refractory status epilepticus. Pentobarbital is given initially as a slow intravenous loading dose of 5 to 15 mg/kg, followed by an infusion rate of 1 mg/kg/hr titrated to effect. There are differing opinions on when to begin to wean therapy, but it is generally recommended that about 12 hours of seizure cessation be attained before weaning the infusion.[130] In children, placement of either a central venous pressure or pulmonary artery catheter is indicated to titrate fluid, inotropic, and/or pressor support. Pentobarbital use often requires the addition of inotropes or pressors. As an alternative to continuous barbiturate infusion, phenobarbital can be administered every 20 minutes (5 to 10 mg/kg i.v.) to achieve burst suppression, and then as a chronic therapy every 12 hours. A midazolam infusion has also been shown to be effective in refractory status epilepticus in some children (0.15 mg/kg IV bolus followed by infusion of 1 to 2 mg/kg/min). The infusion can be increased every 15 minutes if seizures are still present on continuous EEG or if burst suppression is not achieved. With this approach, in one series, inotropic support was not required.[131]

STROKE

Epidemiology

Stroke in children is becoming increasingly recognized and now exceeds an incidence of 8 cases per 100,000 children per

TABLE 59–4. MOST COMMON RISK FACTORS FOR CHILDHOOD ISCHEMIC STROKE

Vascular

Arteriopathies
Transient cerebral arteriopathy of childhood
Postvaricella angiopathy
Fibromuscular dysplasia
Moyamoya syndrome
Postradition vasculopathy

Vasospastic Disorders
Migraine
Ergot poisoning
Vasospasm with systemic arterial hypertension

Vasculitis
Meningitis
Systemic lupus erythematosus
Polyarteritis nodosa
Granulomatous angiitis
Takayasu's arteritis
Dermatomyositis
Inflammatory bowel disease
Drug abuse (cocaine, amphetamines)

Systemic Vascular Disease
Early atherosclerosis
Diabetes
Ehlers-Danlos syndrome
Pseudoxanthoma elasticum
Homocystinuria
Fabry's disease

Trauma
Brain herniation and arterial compression
Posttraumatic dissection
Intra-oral traumatic brain injury
Carotid ligation (e.g., extracorporeal membrane oxygenation)
Arteriography

Intravascular

Hematologic Disorders
Hemoglobinopathies (sickle cell anemia)
Thrombocytosis
Polycythemia
Leukemia or other hematologic neoplasms

Acquired Prothrombotic States
Prothrombotic medications
Pregnancy and the postpartum period
Lupus anticoagulant
Anticardiolipin antibodies
Lipoprotein abnormalities
Hyperhomocysteinemia

Congenital Prothrombotic States
Antithrombin deficiency
Protein S deficiency
Protein C deficiency
Plasminogen deficiency
Factor V Leiden
Prothrombin gene mutation
Methylenetetrahydrofolate reductase

Metabolic Disorders
Hyperhomocysteinemia
Hyperlipidemia

Embolic

Congenital Heart Disease
Complex congenital heart defect
Ventricular/atrial septal defect
Coarctation of the aorta
Patent foramen ovale
Patent ductus arteriosus

Acquired Heart Disease
Rheumatic heart disease
Prosthetic heart valve
Bacterial endocarditis
Cardiomyopathy and myocarditis
Atrial myxoma
Cardiac rhabdomyoma
Cardiac arrhythmia

Trauma
Amniotic fluid or placental embolism
Fat or air embolism
Foreign body embolism
Cardiac catheterization

TABLE 59–5. DIAGNOSTIC WORKUP IN PEDIATRIC STROKE

There are no published consensus guidelines on the evaluation of stroke in children, but several systematic approaches have been recommended. The evaluation should include:

1. History of head trauma, neck trauma, recent infection, illness, unexplained fever or malaise, drug ingestion, developmental delay, family history of bleeding problems, and associated headache
2. Family history, with special attention to premature vascular disease, hematologic disease, and mental retardation
3. Physical examination including head circumference, skin abnormalities, cardiac evaluation, and carotid artery examination
4. MRI and MRA (CT if MR unavailable)

If the MRI and MRA reveal an infarct, with vascular distribution, then consider:

1. Echocardiogram, electrocardiogram
2. Blood studies including complete blood cell count, erythrocyte sedimentation rate, hemoglobin electrophoresis, protein S, protein C, antithrombin III, factor V Leiden, anticardiolipin antibodies, lupus anticoagulant, homocysteine, cholesterol, and varicella titer
3. Lumbar puncture
4. Transcranial Doppler with bubble study
5. Radiograph of cervical spine (posterior infarctions)

If the MRI and MRA reveal an infarct, with nonvascular distribution, then consider:

1. Cerebrospinal fluid lactate levels
2. Plasma ammonia and amino acids
3. Urine organic acids

If the MRI and MRA reveal a hemorrhage, then consider:

1. Coagulation studies
2. Conventional angiography

If the MRA is normal, then consider conventional angiography.

*Adapted from the Children's Hemiplegia and Stroke Association. Website: http://www.chasa.org/diagnosis.htm.

year.[132] Substantial advances in our knowledge of this condition in children have resulted from the work of the Canadian Pediatric Ischemic Stroke Registry. Neonates account for about 25% of these cases. The increasing incidence is believed to result from improvements in diagnostic tools (MRI, CT, MRA) applied to the pediatric population and to increasing survival rates in infants and children with stroke risk factors (e.g., complex congenital heart disease, malignancies).

Etiology

As discussed, atherosclerosis is a key risk factor for stroke in adults. In pediatric and neonatal stroke, extracerebral risk factors contribute to about 75% of cases; however, the spectrum of risk factors differs from those seen in adults. DeVeber[132] grouped the most common risk factors for childhood ischemic stroke into vascular, intravascular, and embolic categories (Table 59-4). The most common vascular risk factor has been reported to be transient cerebral arteriopathy.[133] Post-varicella arteriopathy, migraine, traumatic carotid dissection, and vasculitis, such as moyamoya, are also important examples in this category. In the intravascular category, sickle cell anemia, sinus thrombosis, leukemias, and both acquired and congenital prothrombotic states are important examples. Dehydration and intravascular volume depletion increase stroke risk in these settings, which are of special importance in the pediatric ICU. Recent data revealed an 84% incidence of an acute systemic illness and a 30% incidence of dehydration in cerebral sinovenous thrombosis in infants and children.[134] Congenital and acquired heart disease in infants and children are the most important underlying causes of embolic stroke.[132] The risk of stroke in children after surgery for congenital heart disease is about 1 in 250 cases.[135]

Diagnosis

The clinical presentation of stroke in infants and children is age related. Infants present typically with seizures and lethargy whereas older children may present with acute focal neurologic deficits or diffuse symptoms (headache, lethargy, or seizures).[132,136] In some cases, the duration of neurologic deficits in pediatric stroke may be shorter than the 24-hour deficits classically required to differentiate stroke from transient ischemic attack in adults.[137] It is often difficult to differentiate migraine, Todd's paralysis, and stroke in children. Complicating this problem, CT may be normal within the initial 12 hours.[132] MRI is a more sensitive technique for diagnosing stroke, and advanced MRI modalities such as perfusion, diffusion, and MRA are important adjuncts to making the diagnosis. These methods are discussed in Chapter 48. Because of the impact of making specific vascular diagnoses on the management strategy, angiography is often recommended in children with idiopathic stroke.[132]

In addition to the importance of echocardiography in the diagnostic work of stroke after cardiac surgery or catheterization, endocarditis, cardiomyopathy, and other occult cardiac abnormalities are also important risk factors for embolic stroke, thus recognizing the importance of echocardiography and the general diagnostic workup for stroke in children.[138,139] A general diagnostic approach to pediatric stroke is presented in Table 59-5.

Treatment

In the acute setting, antithrombotic therapy has been used increasingly in the therapy for pediatric stroke. Strater and colleagues[140] compared treatment with low-molecular-weight heparin versus aspirin in 135 children across a variety of causes (including idiopathic, cardiac, vascular, and infectious) and suggested safety when used to prevent stroke recurrence. This is a controversial area for which there is a lack of systematic study.[141] DeVeber[132] recommends that neonates do not require antithrombotic treatment because of negligible recurrence risk, whereas older children require aspirin (2 to 3 mg/kg/day).[142] In dissection, high-grade stenosis, or severe prothrombotic state, low-molecular-weight heparin or warfarin (Coumadin) is recommended for several months. In endocarditis, anticoagulation is not recommended because of the risk of rupture of occult mycotic aneurysms. Thrombolytic therapy has been subjected to very limited study in children. Cases describing the use of tissue plasminogen activator and cerebral balloon angioplasty in acute stroke in children with dramatic results are being reported.[143]

Supportive Care in the Pediatric ICU

An evidence-based approach for care in the pediatric ICU of children with stroke is lacking. Nevertheless, intensive care for the child with stroke must be at a level that is commensurate with that provided for other critical pediatric neurologic disorders, such as severe traumatic brain injury[144] and ruptured arteriovenous malformation.[145]

Careful attention to the ABCs with a neurointensive care approach is essential. If the GCS score is 8 or less and/or the airway or ventilation is compromised, intubation is indicated

and should be performed using a neuroprotective rapid-sequence approach. Normal values for both $PaCO_2$ and PaO_2 should be ensured.

Arterial blood pressure must be adequate to optimize cerebral perfusion. The management of systemic hypertension in the setting of pediatric stroke can be complicated by the variety of underlying disorders (i.e., status post cardiac surgery, underlying hypertension) and the presence or absence of hemorrhage. In adults with thrombotic or hemorrhagic stroke and systemic hypertension, it is generally recommended that mean arterial blood pressure not be aggressively reduced below 130 mm Hg.[146] Age-appropriate guidelines for this question are not available for children. In the pediatric ICU, for acute stroke, it is a reasonable first approach to extrapolate from the adult recommendations.

In infants and children with severe stroke with infarction and cerebral swelling, signs and symptoms of raised ICP can develop. Standard protocols for monitoring ICP and treatment of raised ICP in stroke in infants and children have not been developed. Nevertheless, intracranial hypertension can develop; and even in the absence of controlled trials on the beneficial effects of ICP-directed therapy in severe pediatric stroke, ICP monitoring and ICP-directed therapy should be considered if signs and symptoms of intracranial hypertension develop. Anecdotal reports of successful treatment with a variety of therapies including mild hypothermia and decompressive craniectomy have been reported.[147,148] Plasticity in the pediatric brain, particularly in the recovery from focal lesions, should prompt the consideration of an aggressive approach.[149-151] However, long-term morbidity remains substantial after stroke in childhood.[152]

Other aspects of contemporary pediatric neurointensive care should include maintenance of euglycemia and careful fluid management to maintain both a euvolemic state and avoid hyponatremia. In children, normal saline or 5% dextrose in normal saline should be used in the initial 24 hours, carefully following blood glucose concentration, followed by the addition of dextrose or initiation of hyperalimentation after 24 hours. In infants, either 5% or 10% dextrose in normal saline should be used, with insulin titrated to treat hyperglycemia. The specific glucose level associated with the exacerbation of secondary damage in infants and children has not been determined. A value of 200 mg/dL is a reasonable threshold in the absence of clear-cut evidence. Appropriate nutritional support should also be instituted as soon as possible. Rehabilitation services should be consulted during the pediatric ICU admission.

CRITICAL CNS INFECTIONS

Any microbe may cause CNS infections; age and immune status of the host and epidemiology of the pathogen give evidence to the specific pathogens. Regardless of the etiology, most children with CNS infection present with nonspecific symptoms including fever, headache, nausea, vomiting, anorexia, and irritability. Photophobia, neck pain and rigidity, seizures, mental status change, and focal neurologic deficits are common signs that are determined by the specific pathogen and area of CNS infected.

Bacterial Meningitis

Epidemiology

The etiology of bacterial meningitis and its treatment differ in neonates (0 to 28 days of life) versus older infants and children. During the first 2 months of life, the bacteria that cause meningitis in normal infants reflect the maternal flora and the environment to which the infant is exposed. The most common pathogens include groups B and D streptococci, gram-negative enteric bacilli, and *Listeria monocytogenes*. Occasionally, *Haemophilus influenzae* (both type B and non-encapsulated strains) and other pathogens—more typically found in older patients—can be the etiologic agent. Bacterial meningitis in children between 2 months and 12 years of age is usually caused by *Streptococcus pneumoniae, Neisseria meningitides,* or *H. influenzae* type b. After the implementation of immunization against *H. influenzae,* the incidence of *H. influenzae* meningitis decreased rapidly. Subsequent to the universal recommendation for the use of conjugated pneumococcal vaccine at 2 months of age in 2000, the incidence of meningitis caused by this pathogen is also decreasing. Anatomical abnormalities, surgical procedures, neurotrauma, or immune deficiency often underlie meningitis caused by other agents.[153]

Bacterial meningitis most commonly results from hematogenous dissemination of microorganisms from a distant site of infection; bacteremia usually precedes meningitis or occurs concomitantly. Colonization of the nasopharynx with a pathogenic microorganism is the usual source of bacteremia. Bacteria gain entry to the CSF through the choroid plexus of the lateral ventricles and the meninges and then circulate to the extracerebral CSF and the subarachnoid space. Bacterial cell wall lipopolysaccharide of gram-negative bacteria and pneumococcal cell wall components stimulate a marked inflammatory response, with local production of tumor necrosis factor-alpha, interleukin-1β, prostaglandin E, and other mediators, leading to neutrophil infiltration, increased vascular permeability, and thrombosis. Inflammation of spinal nerves and roots produces meningeal signs, and inflammation of the cranial nerves produces optic, oculomotor, facial, and auditory neuropathies. Intracranial hypertension can produce oculomotor and abducens nerve palsy. Intracranial hypertension in meningitis is believed to result from a combination of cell death (cytotoxic cerebral edema), cytokine-induced increased capillary vascular permeability (vasogenic edema), and increased hydrostatic pressure after obstruction of CSF reabsorption and/or flow. Rarely, meningitis may follow bacterial invasion from a contiguous focus of infection such as paranasal sinusitis, otitis media, mastoiditis, orbital cellulites, or cranial or vertebral osteomyelitis or may occur after introduction of bacteria via penetrating head trauma or meningomyelocele.[154]

Diagnosis

The clinical presentation may be as fulminant as rapidly progressing shock, purpura, disseminated intravascular coagulation, and altered consciousness, frequently resulting in death within 24 hours. More often, however, children present with several days of fever with upper respiratory tract or gastrointestinal symptoms, followed by nonspecific signs of CNS infection such as lethargy and irritability. The presence of headache, emesis, bulging fontanelle, widening of the sutures, oculomotor or abducens nerve paralysis, hypertension with bradycardia, apnea, or hyperventilation suggests intracranial hypertension. Papilledema is uncommon in uncomplicated meningitis and suggests a more chronic process, such as intracranial abscess, sinus thrombosis, or subdural empyema. Seizures can result from cerebritis, infarction, or electrolyte abnormalities and occur in between 20% and 30% of children with meningitis. Seizures that occur at presentation or

within first 4 days of onset are usually of no prognostic significance. Seizures that persist beyond the fourth day of illness and those that are difficult to treat are associated with poor prognosis.[155]

The diagnosis of acute bacterial meningitis is confirmed by analysis of CSF. Contraindications for an immediate lumbar puncture are (1) evidence of increased ICP (other than bulging fontanelle), (2) presence of severe cardiopulmonary compromise or likelihood that positioning for the procedure would significantly compromise cardiopulmonary function, (3) infection of the skin overlying the needle insertion site, and (4) coagulopathy. If lumbar puncture is delayed, then empirical antibiotic treatment should be started after a blood culture is obtained. Blood culture reveals the susceptible bacteria in 80% to 90% of cases of meningitis. The need for a cranial CT scan, for signs and symptoms of increased ICP or brain abscess, should not delay therapy. Table 59-6 summarizes the CSF findings in CNS infections. Pleocytosis with lymphocyte predominance may be seen early in bacterial meningitis; conversely, neutrophilic pleocytosis may be present in patients during the early stages of acute viral meningitis. The shift to lymphocytic-monocytic predominance in viral meningitis invariably occurs within 8 to 24 hours. A traumatic lumbar puncture complicates the diagnosis of meningitis. If the CSF is bloody, it should be collected in three or more tubes. If the CSF clears in successive tubes, it suggests a traumatic lumbar puncture. Blood that does not clear is more suggestive of intracranial bleeding. The CSF leukocyte to erythrocyte ratio in CSF from a traumatic lumbar puncture is generally similar to that in a concurrently obtained peripheral blood sample (usually 1:500 to 1:1000).[156]

The mortality rate of bacterial meningitis after the neonatal period is less than 10% secondary to appropriate recognition, prompt antibiotic treatment, and supportive care. Severe neurodevelopmental sequelae occur in between 10% and 20% of pediatric patients. The most common sequelae include hearing loss, mental retardation, epilepsy, delay in language acquisition, visual impairment, and behavioral problems. Sensorineural hearing loss occurs in 30%, 10%, and 5% to 10% of patients with pneumococcal, meningococcal, and *H. influenzae* type b meningitis, respectively.[157]

Treatment

The initial (empirical) choice of antibiotic treatment in immunocompetent infants and children is primarily determined by the antibiotic susceptibilities of *S.pneumoniae.* In the United States, between 25% and 50% of strains of *S. pneumoniae* are currently resistant to penicillin, and up to 25% of isolates are resistant to cefotaxime or ceftriaxone. Based on this, empirical therapy is with vancomycin (60 mg/kg/24 hr, divided q 6h) and cefotaxime (200 mg/kg/24 hr, divided q 6h) or ceftriaxone (100 mg/kg/24 hr, given either as a single daily dose or divided q 12h). Patients allergic to beta-lactam antibiotics can be treated with chloramphenicol (100 mg/kg/24 hr, divided q 6h). If *L. monocytogenes* infection is suspected, as in infants between 1 and 2 months of age or patients with T-lymphocyte deficiency, ampicillin (200 mg/kg/24 hr, divided q 6h) should be administered with either cefotaxime or ceftriaxone. If a patient is immunocompromised and gram-negative bacterial meningitis is suspected, ceftazidime and an aminoglycoside may be used as initial therapy. The duration of treatment should be either 10 or 14 days depending on the bacteria; gram-negative bacillary meningitis should be treated for 3 weeks or for at least 2 weeks after sterilization of CSF. Repeat lumbar puncture may be indicated in some neonates and in children with gram-negative or beta-lactam–resistant meningitis caused by *S. pneumoniae.* Of the adjunctive treatments that might limit CNS inflammation, only corticosteroids have been properly assessed in clinical trials. Adjuvant corticosteroid use was associated with lower case fatality and lower rates of both severe hearing loss and long-term neurologic sequelae in acute bacterial meningitis. Corticosteroids administered either before or with the first dose of antibiotic reduced severe hearing loss in bacterial meningitis caused by *H. influenzae* as well as in meningitis caused by *S. pneumoniae.*[159] The recommended dose of dexamethasone is 0.6 mg/kg/24 hr divided every 6 hours

TABLE 59–6. CEREBROSPINAL FLUID FINDINGS IN CNS INFECTIONS

Type of Infection	Pressure (cm H_2O)	Leukocytes (mm^3)	Protein (mg/dL)	Glucose (mg/dL)
Normal	5-8	< 5, ≥ 75% lymphocytes < 30 for neonates	20-45 Up to 180 for neonates	>50 (or 75% serum glucose)
Acute bacterial	↑ (10-30)	300-2000 PMNs predominate	100-500	↓ (<40 or <50% serum glucose)
Partially treated bacterial meningitis	nl or ↑	5-10,000 Usually PMNs	100-500	nl or ↓
Viral meningitis or meningoencephalitis	nl or slightly ↑ (8-15)	Rarely >1000 PMNs early, then mononuclear cells	50-200	nl (decreased in some mumps cases)
Tuberculous meningitis	↑	10-500 PMNs early, lymphocytes predominate through most of the course	100-3000	<50
Fungal meningitis	↑	5-500 PMNs early, lymphocytes predominate through most of the course	25-500	<50
Syphilis	↑	50-500 Lymphocytes predominate	50-200	nl
Amebic *(Naegleria)* meningoencephalitis	↑	1000-10,000 or more PMNs predominate	50-500	nl or slightly ↓

for 4 days.[154] There are no data about the role of corticosteroids in newborns or in patients with nosocomial or CSF shunt–associated meningitis.

The patients who manifest signs of poor perfusion, cutaneous manifestations of disseminated intravascular coagulation (purpura, petechiae), irregular respiratory pattern, altered mental status, cranial nerve involvement, and other signs potentially indicative of raised ICP and the patients who have rapid clinical presentation, significant metabolic acidosis, hypoxemia, hypercapnia, neutropenia, hyponatremia, anemia, and abnormal liver or renal function should be admitted to the pediatric ICU—at least until (1) the course of illness can be determined, (2) the first several doses of antibiotics are administered, and (3) a tentative bacteriologic diagnosis is made. Early recognition of complications such as shock or raised ICP and initiation of treatments in a timely fashion may improve outcome in cases of fulminate meningitis.

Acute CNS complications during the treatment of meningitis include seizures, intracranial hypertension, cranial nerve palsies, stroke, herniation, and thrombosis of the dural venous sinuses (Fig. 59-3).[160] Subdural effusions develop in between 10% and 30% of pediatric patients and are more common in infants. They are asymptomatic in between 85% and 90% of the cases. Aspiration of subdural effusions is indicated in the presence of raised ICP; fever alone is not an indication for aspiration. SIADH with hyponatremia and reduced serum osmolality occurs in between 30% and 50% of children. Cerebral salt wasting can also be seen. Attention as to maintaining a normal serum sodium concentration using either normal saline or judicious titration of hypertonic saline is important to preventing exacerbation of brain edema. Prolonged fever (>10 days) occurs in 10% of the patients. It is usually due to intercurrent viral infection, secondary or nosocomial bacterial infection, thrombophlebitis, drug reaction, pericarditis, or arthritis. Thrombocytosis, eosinophilia, or anemia may also develop during treatment.[155]

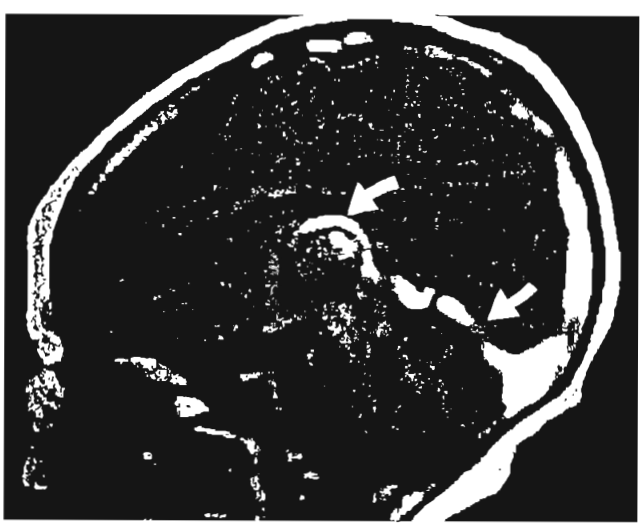

FIGURE 59–3. Sagittal T1-weighted MR image revealing thrombosis of the sagittal sinus *(high signal over the convexity of the hemisphere)*, straight sinus *(arrow)*, and internal cerebral veins *(curved arrow)* as a complication of bacterial meningitis in an infant. (From Connor SEJ, Jarosz JM: Magnetic resonance imaging of the cerebral venous sinus thrombosis. Clin Radiol 2002;57:449-461.)

Supportive Care in the Pediatric ICU

The issues in ICU care for infants and children with bacterial meningitis are similar to ones mentioned under encephalitis. The reader is referred to the following section for details.

Viral Encephalitis

Epidemiology

Enteroviruses are the most common etiologic agent for encephalitis in children. The severity of the disease ranges from mild illness to severe encephalitis with death or long-term morbidity. Enterovirus infections spread directly from person to person, with an incubation period of between 4 and 6 days. Most cases occur in summer and fall in temperate climates. Arboviruses are responsible for some cases of encephalitis in children. The most common arboviruses responsible for CNS infection in the United States are St. Louis and California encephalitis and the West Nile virus.[161]

Several members of the herpesvirus family can cause encephalitis. Herpes simplex virus type 1 is an important cause of severe encephalitis in children and adults. The cerebral cortex, especially the temporal lobe, is often severely affected by herpes simplex virus. Neonatal herpes infections are usually caused by herpes simplex virus-2 contracted at delivery via vertical transmission. Three forms of the disease develop in neonates: (1) skin, eye, mouth disease (seen in 45% of cases), (2) encephalitis (seen in 35% of cases), and (3) disseminated intravascular coagulation (seen in 20% of cases). The transmission rate from mother to infant is between 30% and 40% when genital infection is primary and 3% for reactivated herpes infection. The mean age at onset of cutaneous or systemic disease is 6 days after birth. In contrast, the mean age at onset of encephalitis is 11 days after birth. The diagnosis of herpes simplex virus infection in neonates can be difficult to make unless skin lesions are present. Cultures of conjunctiva, nasopharynx, and rectum at between 48 hours and 72 hours of age may identify early infection. In neonates, the mortality rates are approximately 50% and 14% for herpes simplex virus disseminated disease and encephalitis, respectively.[161]

A number of other viral causes are important in pediatric encephalitis. Varicella-zoster may cause CNS infection in close proximity to chickenpox. The most common manifestation of CNS infection by varicella-zoster is cerebellar ataxia. Cytomegalovirus infection of the CNS may be either part of congenital infection or disseminated disease in an immunocompromised host. CNS diseases caused by Epstein-Barr virus may present as perceptual distortions of sizes, shapes, and spatial relationships known as "Alice in Wonderland syndrome." There may be meningitis, seizures, ataxia, facial palsy, transverse myelitis, and encephalitis.[161]

Infectious agents can enter the brain via a hematogenous route or by neuronal tracts. Many hematogenous pathogens cause direct endothelial damage to arteries, arterioles, and capillaries, resulting in vasculitis, hemorrhage, and thrombosis. Postinfectious encephalitis is an autoimmune process characterized by a perivenulitis with demyelination. It is uncommon in children younger than 1 year of age.[162] The mortality rate in untreated cases of herpes simplex virus encephalitis is 70%, and fewer than 3% return to normal function. Early treatment with acyclovir reduces the mortality rate to 20% to 30%, but there is still substantial morbidity.[163]

Diagnosis

The onset of illness is generally acute and often preceded by a nonspecific febrile illness of few days' duration. The manifestations of viral encephalitis in older children are headache and hyperesthesia, whereas in infants, irritability and lethargy predominate. Adolescents frequently complain of retrobulbar pain. Fever, nausea, vomiting, photophobia, and pain in the legs, back, and neck are common. Exanthems often precede or accompany the CNS signs. Seizures occur in 60% of the cases during the course of herpes simplex virus encephalitis. The diagnosis of viral encephalitis is usually made on the basis of clinical presentation of nonspecific prodrome followed by progressive CNS symptoms. The CSF usually shows a mild mononuclear predominance. In the diagnostic workup, the CSF should be cultured for viruses, bacteria, fungi, and mycobacteria.[164] Detection of viral DNA or RNA by polymerase chain reaction is useful for diagnosis of herpes simplex virus, varicella-zoster, cytomegalovirus, Epstein-Barr virus, and enteroviral meningoencephalitis. Polymerase chain reaction of CSF is 100% specific and more than 90% sensitive for herpes simplex virus.[165] About 50% of patients with herpes simplex virus encephalitis have focal abnormalities on nonenhanced CT. MRI is the imaging modality of choice and should ideally be the first step after initial clinical examination. The EEG is abnormal in almost all cases of herpes simplex virus encephalitis and may show periodic lateralized epileptiform discharges (Fig. 59-4).[166]

Treatment

Antiviral therapy with acyclovir is indicated for herpes simplex virus encephalitis. Acyclovir has a relatively short half-life in plasma, and more than 80% is excreted unchanged in the urine; thus, renal impairment can exacerbate toxicity. The standard dose of acyclovir for herpes simplex virus encephalitis is 30 mg/kg/24 hr divided every 8 hours for 14 days. The dose in neonates is 60 mg/kg/day. The duration of treatment is 21 days for immunocompromised patients. Acyclovir is effective in encephalitis due to herpes simplex virus types 1 and 2 and varicella-zoster. The dose of acyclovir for varicella-zoster encephalitis is similar to that for herpes simplex encephalitis.[164]

Supportive Care in the Pediatric ICU

A substantial body of data supporting an evidence-based approach to care in the pediatric ICU of children with meningitis and encephalitis is lacking. Careful attention to the ABCs with a neurointensive care approach is essential. If the GCS score is less than 8 and/or the airway or ventilation is compromised, intubation is indicated and should be performed using a neuroprotective rapid-sequence approach. Normal values for both $PaCO_2$ and PaO_2 should be ensured. Bacterial meningitis and encephalitis can be associated with severe septic shock that should be approached and treated according to published guidelines.[167] Arterial blood pressure must be adequate to optimize cerebral perfusion.

In infants and children with meningitis and encephalitis, increased ICP may develop. The most important morbidity and mortality of CNS infections is herniation of brain tissue secondary to intracranial hypertension. No randomized controlled trial has been conducted to evaluate the effect ICP monitoring has on outcome in meningitis or encephalitis in children or adults. However, evidence supports the association of intracranial hypertension and poor neurologic outcome in infants and children.[168-170] In addition, ICP monitoring and

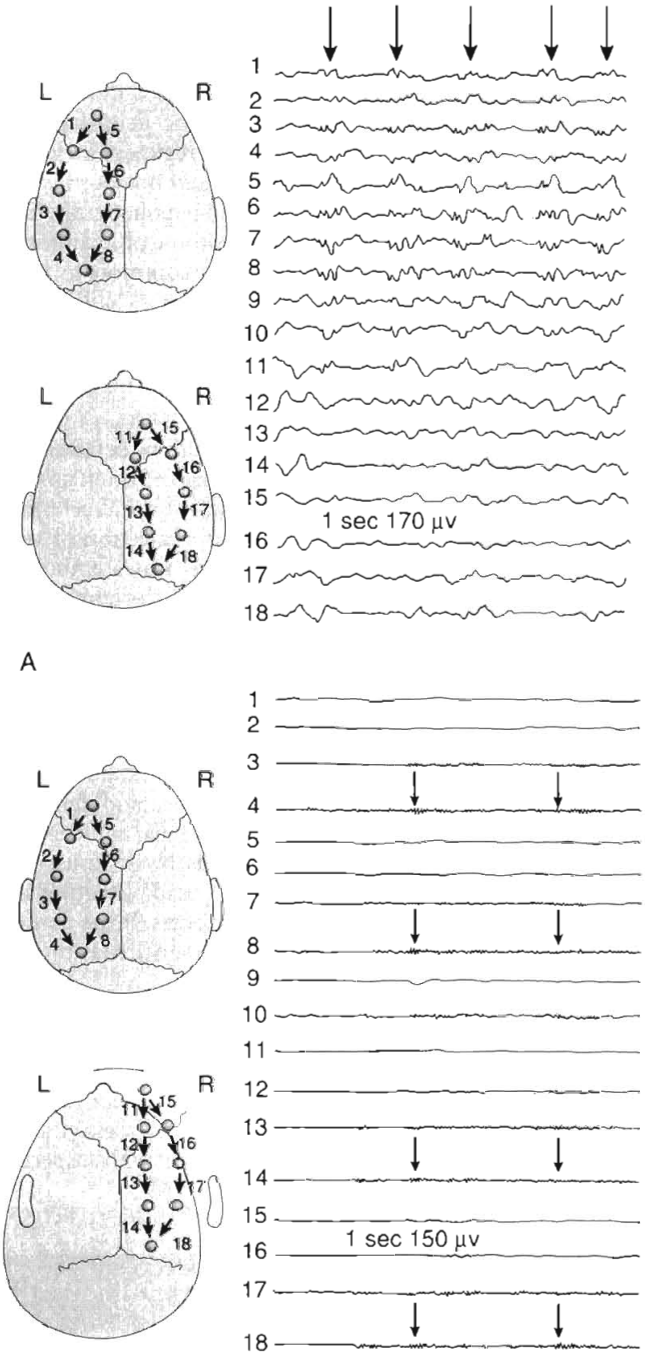

FIGURE 59–4. A, Electroencephalogram showing periodic lateralized epileptiform discharges (PLEDS) in a child with herpes simplex encephalitis. The discharges are seen diffusely in the left hemisphere (leads 1 to 10) occurring at intervals at about 2.5 seconds *(arrows)*. B, Normal background activity in an awake subject for comparison. *Arrows* show normal alpha rhythm in posterior leads bilaterally. (From Watenberg N, Morton LD: Images in Clinical medicine: Periodic lateralized epileptiform discharges. N Engl J Med 1996;334(10):634.)

aggressive treatment of intracranial hypertension showed reductions in the expected mortality rate in pediatric and adult patients with meningitis and encephalitis.[171-174] ICP monitoring and ICP-directed therapy should be considered if signs and symptoms of intracranial hypertension develop in children with meningitis and encephalitis. ICP monitoring in patients with known or suspected CNS infection

with a GCS score less than 8 may be considered at the discretion of the physician. An external ventricular drain is the preferred route of ICP monitoring if there is hydrocephalus or CSF is required for therapeutic or diagnostic drainage.

Other aspects of contemporary pediatric neurointensive care should be included in the treatment regimen, including maintenance of euglycemia and careful fluid management to maintain both a euvolemic state and avoid hyponatremia. This is particularly important because the syndrome of inappropriate secretion of antidiuretic hormone is common in these conditions. Appropriate nutritional support as outlined in Chapter 113 should also be instituted as soon as possible.

Brain Abscess

Epidemiology and Diagnosis

Brain abscesses are most common in children between the ages of 4 and 8 years. The underlying causes of brain abscess include chronic otitis media and sinusitis, orbital cellulitis, dental infections, penetrating head injury, infection of ventriculoperitoneal shunts, immunodeficiency states, embolization due to congenital heart disease with left-to-right shunts, and meningitis. About 80% of brain abscesses in children occur in frontotemporal and parietal lobes, and 30% have multiple sites of involvement. Table 59-7 summarizes the relationships between predisposing conditions and site of brain abscess, likely pathogens, and suggested initial empirical treatment. In the early stages, the clinical presentation of brain abscess includes low-grade fever, headache, and lethargy. Vomiting, papilledema, focal neurologic signs, and seizures may develop as the inflammation proceeds. Nystagmus, ipsilateral ataxia and dysmetria, headache, and vomiting are characteristic signs of cerebellar brain abscess. If the abscess ruptures into the ventricular cavity, severe shock may rapidly develop and death may result.[175]

Contrast medium–enhanced head CT and MRI are the most reliable methods of identifying brain abscess. An abscess cavity shows a ring-enhancing lesion with enhanced CT. MRI with gadolinium administration may reveal a capsule. Blood cultures are positive in roughly 10% of cases. Lumbar puncture should not be undertaken in a patient with suspected brain abscess because examination of CSF is seldom useful and this procedure may precipitate herniation.

Treatment

Treatment is initiated with an antibiotic regimen that is based on the probable pathogenesis and most likely organism. An encapsulated abscess should be treated by antibiotics and aspiration, which is also the most likely diagnostic approach. Surgery is indicated when the abscess (1) is larger than 2.5 cm in diameter, (2) contains gas, (3) is multiloculated, (4) is located in the posterior fossa, or (5) when fungus is identified. The duration of treatment depends on the organism and response but usually ranges between 4 and 6 weeks. Other aspects of neurointensive care in the pediatric ICU for infants and children with brain abscess should mirror those presented previously for meningitis and encephalitis.[176]

POSTOPERATIVE NEUROSURGICAL CASES

Epidemiology

Neurosurgical procedures for children vary widely in all aspects and include elective and emergent operations in all ages of children for a variety of illnesses, most commonly brain tumors, hydrocephalus, and arteriovenous malformations.

Diagnosis

The need for admission to a pediatric ICU is largely determined by the potential complications associated with the specific surgery involved. The most common complications that require intensive monitoring after neurosurgical procedures include hydrocephalus, airway compromise, bleeding, vascular complications, fluid and electrolyte abnormalities, and seizures. Hydrocephalus is an obvious concern in patients undergoing procedures for the treatment of hydrocephalus, either with shunting, ventriculostomy, or a decompressive procedure. Patients with congenital hydrocephalus require ICU monitoring, depending largely on their preoperative status. A child with slowly progressive hydrocephalus with few clinical symptoms may not require admission to the pediatric ICU, whereas preoperative symptoms that raise a

TABLE 59–7. PREDISPOSING CONDITIONS, ETIOLOGIC AGENTS, AND EMPIRICAL TREATMENT IN BRAIN ABSCESS

Predisposing Condition	Site of Abscess	Etiologic Agents	Treatment
Sinusitis Orbital cellulites Dental infection	Frontal lobe	Streptococci *Bacteroides* Enterobacteriaceae *Staphylococcus aureus* *Haemophilus* species	Vancomycin + third-generation cephalosporin + metronidazole
Otitis media Mastoiditis	Temporal lobe/cerebellum	Streptococci *Bacteroides* Enterobacteriaceae *S. aureus* *Haemophilus* species *Pseudomonas aeruginosa*	Vancomycin + third-generation cephalosporin + metronidazole
Head trauma Postsurgical infection	Site of the injury or surgery	*S. aureus* Streptococci Enterobacteriaceae *Clostridium*	Vancomycin + third-generation cephalosporin + metronidazole
Congenital cyanotic heart disease	Middle cerebral artery distribution	*Streptococcus viridans* Anaerobic and microphilic streptococci	Penicillin + metronidazole
Ventriculoperitoneal shunt	Site of the shunt	*P. aeruginosa* Streptococci Enterobacteriaceae	Vancomycin + ceftazidime

concern of potential herniation will require close observation and monitoring. Patients with Chiari malformations, tumors impinging on CSF drainage, or ventricular hemorrhages all carry a significant risk of developing postoperative hydrocephalus.

Airway compromise is a potentially life-threatening complication that is of particular concern after neurosurgical procedures involving the brainstem, because vocal cord paralysis or cranial nerve damage is possible. Patients with congenital facial abnormalities are also at risk for respiratory compromise. A third scenario that predisposes neurosurgical patients to airway problems is a procedure requiring prone positioning during surgery, because significant facial swelling can result.

Although the potential for bleeding is always a concern after surgical procedures, there are certain diseases that carry more than the typical risk for hemorrhage. In particular, surgical resection of a vascular malformation is of concern for bleeding if complete resection is incomplete or impossible. However, all procedures carry a risk for postoperative bleeding, including procedures that do not involve a craniotomy.

Surgical procedures near major arteries can cause vasospasm with resultant cerebral ischemia or infarct. Subarachnoid hemorrhage from aneurysmal or vascular malformation rupture is another well-known cause of vasospasm.

Electrolyte abnormalities can result from three disturbances in normal regulatory mechanisms: diabetes insipidus, the syndrome of inappropriate secretion of antidiuretic hormone, and cerebral salt wasting (see later for management). Other complications from neurosurgical procedures include CSF leak, aseptic meningitis, and pseudomeningocele.

Physical Examination

The immediate examination should include an evaluation of the ABCs. Specific to neurosurgical patients, however, a rapid neurologic examination is important to evaluate for baseline deficits after surgery. This is essential for evaluation of changes in neurologic status. For example, unequal pupillary size may be a result of surgical intervention and would be present immediately after the surgery. However, development of unequal pupils in a patient who previously had equal pupillary size may be the first sign of impending herniation. The initial neurologic examination should include a gross evaluation of mental status. Patients routinely have a depressed level of consciousness after anesthesia, but repeated examinations are necessary to ensure that mental status continues to improve. Measurement of the GCS score is one means of objectively quantifying a child's level of consciousness. Cranial nerve examination is limited by the child's ability to cooperate but should include pupillary response (cranial nerve II), observation of extraocular movements (cranial nerves III, IV, and VI), jaw deviation during sucking in an infant (cranial nerve V), facial asymmetry while crying or laughing (cranial nerve VII), gag reflex (cranial nerves IX and X), and shoulder droop (cranial nerve XI). The motor examination relies heavily on careful observation of movements, because few patients will be able to cooperate with a formal examination early after surgery. Similarly, the sensory examination involves observing gross responses to stimuli. A full evaluation of deep tendon reflexes is usually possible. Neurologic evaluation should be repeated frequently during the first 24 hours, evaluating for new or progressing neurologic deficits.

Treatment

All patients in the pediatric ICU should have cardiorespiratory monitoring. Respiratory monitoring should be designed to warn of impending airway compromise, including measurement of respiratory rate, pulse oximetry, and repeated examinations evaluating work of breathing, air entry, and evidence of stridor. Hemodynamic monitoring is useful for evaluating both hemodynamic and neurologic status. Increases in heart rate and blood pressure can be an indication of pain or of seizure activity. Increased blood pressure with a low heart rate is worrisome for raised ICP and impending herniation, although herniation is not always signaled by Cushing's triad in children. Tachycardia with prolonged capillary refill or hypotension may indicate excessive fluid losses, either from bleeding, third space losses, or excessive urine output. Tachycardia and hypotension can also result from loss of vasomotor tone, either from infection, medications, or loss of neurologic regulation after spinal surgery. Invasive blood pressure monitoring is necessary when patients are at high risk for any of the complications listed earlier. Strict measurement of fluid intake and output is essential to monitor fluid balance and interpret disturbances in fluid and electrolyte regulation. When the surgical procedure carries a high risk of a complicating fluid regulation abnormality, as in craniopharyngioma resections, serum and urine electrolytes should be tested every 4 to 6 hours, along with continuous urine measurement and central venous pressure monitoring.

Temperature control is important after neurosurgical procedures and should therefore be monitored closely. Aggressive measures to prevent hyperthermia are warranted because neurologic injury is exacerbated by high brain temperature.

Fluid management for the postoperative neurosurgical patient differs from other postoperative patients in a few key ways. Although maintenance of circulating volume is important, it is important to avoid excessive hydration to prevent exacerbating cerebral edema. In general, neurosurgical procedures do not result in the large third-space losses seen with other surgeries. Once adequate volume status is achieved to maintain perfusion, fluid requirements will usually be met with a maintenance fluid rate.

Euglycemia is important after neurologic surgery, because both hypoglycemia and hyperglycemia can exacerbate neurologic injury. Based on recommendations in adults, initial intravenous fluids in older children should generally be normal saline or 5% dextrose in normal saline and serum glucose levels should be monitored closely. The duration for the dextrose restriction in older children is controversial because ketosis develops even with euglycemia. Generally this is maintained for the initial 24 hours. Hyperglycemia, however, should probably be avoided throughout the entire acute period after CNS insults. Infants, on the other hand, do not have the same capacity for maintaining serum glucose levels if maintained with no source of carbohydrate intake. Initial dextrose concentration in the infant with a CNS insult should probably be 5% (in normal saline). When higher dextrose concentrations are used, such as with hyperalimentation, hyperglycemia should be carefully managed with insulin infusion. It must be recognized that the risk of exacerbation of brain injury by hyperglycemia in infants and children is likely but somewhat theoretical. In contrast, it is clear that hypoglycemia can be harmful to the injured brain and should be avoided.

Hyponatremia is of particular concern in neurosurgical patients because the osmotic effects can result in increasing

cerebral edema. Normal saline is the preferred intravenous fluid to avoid this complication. When hyponatremia occurs in conjunction with a decreasing urine output, a high specific gravity, and a high sodium concentration in the urine, it is likely a result of the syndrome of inappropriate secretion of antidiuretic hormone. In this case, fluid restriction is indicated. Neurosurgical patients also have two unique possible sources for excessive sodium loss: CSF losses from extraventricular drainage and urine losses from cerebral salt wasting. Both require correction of sodium losses.

Mild hypernatremia is generally not detrimental and is usually a result of excessive intake or osmotic diuresis. A progressively increasing serum sodium concentration in the presence of increasing volume of hypo-osmolar urine, however, suggests diabetes insipidus. This complication is unusual except with surgeries that have the potential for pituitary injury. Management of diabetes insipidus requires careful titration of fluids, with a maintenance rate to cover insensible losses (300 mL/m^2/day) plus total replacement of urine output with a fluid that matches the urine electrolyte concentrations. Vasopressin or desmopressin therapy may be required to control the free water loss.

A few medications should be considered for every neurosurgical patient. First, antiemetics are important to prevent postanesthesia nausea and vomiting, because vomiting can cause a dramatic increase in intracranial pressure. Ondansetron and droperidol are good choices for antiemetic therapy because they are minimally sedating.[177] Postoperative seizures can have serious consequences. Antiepileptics should be considered in all patients at risk for postoperative seizures. Typically, phenytoin is the least sedating drug for seizure prophylaxis. Patients on chronic anticonvulsants should have their usual regimen started as soon as possible after the surgery. Dexamethasone is used to reduce edema formation around brain tumors and reduce tumor size.[178] The use of corticosteroids is controversial in most other settings. However, patients who received corticosteroids preoperatively may require stress-dose corticosteroids during the postoperative period. Prophylaxis with H_2 blockers may reduce gastrointestinal hemorrhage in critically ill patients[179] but may also increase the risk of nosocomial infections.[180] Gastrointestinal bleeding is more common after resection of a posterior fossa tumor, and use of prophylaxis has been advocated in these patients.[181]

Emergency Intervention

The postoperative problem of most concern, and sometimes the most difficult to evaluate in a child, is an altered mental status. Although anesthetics or narcotics can produce an altered sensorium, emergent evaluation is indicated if reversal of these medications does not yield a reassuring examination. If the patient's GCS score is less than 8, intubation should be performed before any transport or testing. If an extraventricular drain is in place, it should be opened and low enough to allow CSF drainage. Mannitol should be given if signs of impending herniation exist and transient hyperventilation begun until a definitive surgical intervention is carried out. An emergent head CT should then be performed. Further action will be guided by the CT findings.

OTHER CRITICAL CNS DISORDERS IN INFANTS AND CHILDREN

There are other critical CNS disorders in infants and children including hepatic encephalopathy, hypertensive encephalopathy, and Reye's syndrome. Discussion of these less common disorders is beyond the scope of this chapter, and the reader is referred to the appropriate primary references or other textbooks focused on pediatric critical care medicine. Reye's syndrome was once a key disorder in the field of pediatric neurointensive care—reaching a peak of 555 cases in the United States in 1980. In the past decade fewer than 2 cases per year have been reported.[182]

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Section IV

RESPIRATORY DISORDERS

Chapter 60

BEDSIDE MONITORING OF PULMONARY FUNCTION

Richard H. Kallet • Julin F. Tang

KEY POINTS

PULSE OXIMETRY

1. Because **pulse oximeters cannot be calibrated**, their accuracy is highly variable and dependent on both the calibration curve programmed into the monitor and the quality of signal processing.
2. **Carboxyhemoglobin** and oxyhemoglobin absorb equivalent amounts of red light, so that **carbon monoxide poisoning** results in a falsely elevated oxygen saturation as measured by pulse oximeter (SpO_2).
3. **Motion artifact and low perfusion** are the most common sources of SpO_2 inaccuracies.
4. **Falsely low SpO_2 readings** occur when even minor gaps exist between the probe and skin.
5. **Pulse oximeters** have greater bias and less precision in patients with dark pigmentation.

CAPNOMETRY

1. In **normal subjects**, the gradient of partial pressure of carbon dioxide in arterial blood to partial pressure of carbon dioxide in end-tidal exhaled gas ($PaCO_2$-$PETCO_2$ gradient) is 4 to 5 mm Hg, whereas in **critically ill patients**, the $PaCO_2$-$PETCO_2$ gradient can be markedly elevated, particularly in those with obstructive lung diseases (7 to 16 mm Hg).
2. **The $PaCO_2$-$PETCO_2$ gradient** is affected by changes in respiratory rate, tidal volume, CO_2 production, and mixed venous CO_2 content.
3. **At frequencies above 30**, capnometers tend to underreport the true $PETCO_2$.
4. **In some patients with acute respiratory distress syndrome**, the $PaCO_2$-$PETCO_2$ gradient may be an effective way to titrate positive end-expiratory pressure (PEEP).
5. **During precordial compressions**, $PETCO_2$ can distinguish between successful and unsuccessful resuscitation, with values greater than 10 mm Hg associated with successful resuscitation.

ASSESSMENT OF PULMONARY MECHANICS

1. **Distinguishing the resistive from the elastic recoil-related pressures** requires the introduction of an end-inspiratory circuit occlusion after tidal volume delivery.
2. In clinical practice, the **pause-time used for an end-inspiratory circuit occlusion** is set at 0.5 to 1 second, to limit any potential artifact from spontaneous breathing efforts that may falsely raise or lower the end-inspiratory plateau pressure.
3. The **driving pressure necessary to overcome resistance** increases disproportionately to changes in gas flow, so that resistance can be determined accurately only with a constant inspiratory flow (square wave) pattern.
4. **Intrinsic PEEP is measured** by occluding both limbs of the ventilator circuit for 3 to 5 seconds at end-expiration, thus allowing alveolar pressure to equilibrate with airway pressure. This pressure represents the average intrinsic PEEP throughout the lungs.
5. When using the **pressure-volume curve of the respiratory system** for lung-protective ventilation in patients with acute respiratory distress syndrome, PEEP is set 2 cm H_2O above the lower inflection point to ensure optimal lung recruitment, and tidal volume is set below the upper inflection point to prevent lung injury from excessive stretch.

ASSESSMENT OF BREATHING PATTERN, STRENGTH, AND CENTRAL DRIVE

1. A **threshold value of less than 105** for the respiratory rate–tidal volume ratio has both a high positive predictive value (0.78) and a negative

predictive value (0.95) for the ability to maintain unassisted breathing.

2. **In patients recovering from respiratory failure,** successful weaning is generally associated with a maximal inspiratory pressure greater than –30 cm H_2O.
3. During brief trials of unassisted breathing, an inspiratory occlusion pressure 100 msec after the onset of effort (P0.1) greater than 7 cm H_2O tends to describe patients requiring total ventilatory support and has been reported as a cutoff level in patients who ultimately fail a trial of extubation.

The safe and effective management of patients with acute respiratory failure requires accurate bedside monitoring of pulmonary function. This chapter focuses on the more common noninvasive techniques for monitoring pulmonary gas exchange, respiratory system mechanics, and breathing pattern.

PULSE OXIMETRY

Pulse oximetry is a microprocessor-based instrument that incorporates both oximetry and plethysmography to provide continuous noninvasive monitoring of the oxygen saturation of arterial blood (SaO_2). It is considered one of the most important technologic advances for monitoring patients during anesthesia and critical care.[1] Oximetry uses spectrophotography to determine SaO_2. According to the Beer-Lambert law, the concentration of a substance can be determined by its ability to transmit light.[2] Oxygenated hemoglobin (HbO_2) and deoxygenated or "reduced" hemoglobin (HbR) species absorb light differently, so that the ratio of their absorbencies can be used to calculate saturation. In addition, there are two minor hemoglobin species: carboxyhemoglobin (COHb) and methemoglobin (MetHb). Fractional SaO_2 is the proportion of oxygenated hemoglobin relative to the four hemoglobin species:

$$\frac{HbO_2}{HbO_2 + HbR + COHb + MetHb} \times 100$$

Measuring fractional hemoglobin requires a co-oximeter that incorporates four wavelengths to distinguish each species. In contrast, oxygen saturation as determined by pulse oximeter (SpO_2) uses two wavelengths, so that it measures functional SaO_2:

$$\frac{HbO_2}{HbO_2 + HbR} \times 100$$

The pulse oximeter probe is embedded into either a clip or an adhesive wrap and consists of two light-emitting diodes on one side, with a light-detecting photodiode on the opposite side. Either a finger or an earlobe serves as the sample "cuvette." The tissue bed is transilluminated, and the forward-scattered light is measured. Pulse oximetry targets the signal arising from the arterial bed as light absorbance fluctuates with changing blood volume. Arterial blood flow causes signal changes in light absorption (the pulsatile, or alternating current, component) that can be distinguished from venous and capillary blood in the surrounding tissues (the baseline, or direct current, component) (Fig. 60-1).[2] The ratio of absorbencies is calibrated empirically against SaO_2 measured by co-oximetry in normal volunteers subjected to various levels of oxygenation. Pulse oximeters are calibrated against measured SaO_2 down to 70% (saturations below this level are determined by extrapolation).[3] The resulting calibration curve is stored in the monitor's microprocessor to calculate SpO_2.[4]

ACCURACY AND PRECISION

Because pulse oximeters themselves cannot be calibrated, their accuracy is highly variable and dependent on both the calibration curve programmed into the monitor and the quality of signal processing.[3,4] The accuracy of the calibration curve depends on laboratory testing conditions (co-oximeter used, range of oxygenation studied, and characteristics of sample subjects). Most manufacturers report an accuracy of ±2% at an SaO_2 greater than 70% and ±3% when the SaO_2 is 50% to 70%.[2] In normal subjects tested at an SaO_2 between 99% and 83%, pulse oximetry has a bias and precision that are within 3% of co-oximetry.[5] However, under hypoxic conditions (SaO_2 78% to 55%), when the monitor must rely on extrapolated values, bias increases (8%) and precision deteriorates (5%).[5] Likewise, in critically ill patients, pulse oximeters historically perform well when the SaO_2 is greater than 90% (bias of 1.7%; precision of ±1.2%), but accuracy diminishes at an SaO_2 below 90% (bias of 5.1%; precision of ±2.7%).[6] Technologic advances over the past decade have apparently improved this performance; a recent study comparing pulse oximetry to co-oximetry reported a bias of 0.19% and a precision of

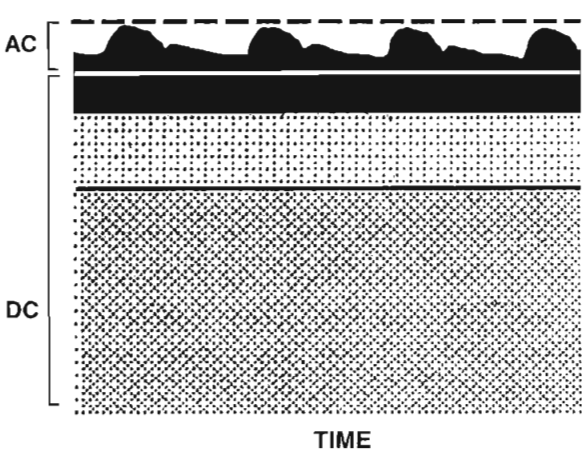

FIGURE 60–1. Schematic depiction of the pulse oximeter light absorption signal, whereby the signal change caused by arterial blood flow (pulsatile, or alternating current, component) can be distinguished from that of the tissue and surrounding venous blood (baseline, or direct current, component). (Adapted with permission from Datex-Ohmeda Inc., Madison, Wis.)

±2.22% over an SaO_2 range of 60% to 100%.[7] The most significant sources of inaccuracy were finger thickness, hemoglobin level, skin color, and peripheral temperature.

DYNAMIC RESPONSE

Because pulse oximeters detect very small optical signals (and must reject a variety of artifacts), data must be averaged over several seconds, thus affecting response time.[3] Pulse oximeters may register a near-normal SpO_2 when the actual SaO_2 is less than 70%.[3] A prolonged lag time is more common with finger probes than ear probes[3,8,9] and is attributed to hypoxia-related peripheral vasoconstriction.[3] Bradycardia also is associated with a prolonged response time.[9]

SOURCES OF ERROR

Dyshemoglobins and Vascular Dyes. Significant amounts of carboxyhemoglobin or methemoglobin can cause errors in SpO_2. Carboxyhemoglobin and oxyhemoglobin absorb equivalent amounts of red light, so that carbon monoxide poisoning results in a falsely elevated SpO_2. In contrast, methemoglobin causes substantial absorption of both red and infrared light, so that the ratio approaches 1 (estimated SpO_2 of 85%).[2] Significant methemoglobin causes falsely low SpO_2 values when the actual SaO_2 is greater than 85% and falsely high values when the SaO_2 is less than 85%.[2] Administration of methylene blue or indocyanine green dyes for diagnostic tests causes a false, transient (1- to 2-minute) drop in SpO_2 to as low as 65%.[10,11]

Motion Artifact and Low Perfusion. Motion artifact and low perfusion are the most common sources of SpO_2 inaccuracies, because the photoplethysmographic pulse signal is very low compared with the total absorption signal.[12,13] The combination of motion artifact and low perfusion substantially lowers SpO_2 accuracy compared with either artifact alone.[14] Causes of motion artifact include shivering, twitching, agitation, intra-aortic balloon pump assistance, and patient transport.[15,16] Signs of motion artifact include a false or erratic pulse rate reading or an abnormal plethysmographic waveform. Peripheral hypoperfusion from hypothermia, low cardiac output, or vasoconstrictive drugs may increase bias, reduce precision, and prolong the detection time for a hypoxic event.[16]

Venous Pulsation and Cardiac Arrhythmia. Venous congestion and arteriovenous anastomoses cause the cutaneous veins to pulsate, resulting in a falsely low SpO_2.[17] Similar artifacts may occur during hypovolemia and high airway pressure ventilation.[18] Cardiac arrhythmias apparently do not affect SpO_2 accuracy.[19]

Nail Polish and Skin Pigmentation. Both dark skin pigmentation and dark nail polish interfere with the absorption of the wavelengths used by pulse oximetry. Pulse oximeters thus have greater bias and less precision in black patients.[6] Whereas an SpO_2 of 92% is sufficient to predict adequate oxygenation in white patients, a saturation of 95% is required in black patients.[6] Dark nail polish falsely lowers SpO_2, whereas red polish does not affect accuracy.[20] When nail polish cannot be removed, mounting the oximeter probe sideways on the finger produces an accurate reading.[21]

Ambient Light, Anemia, and Hyperbilirubinemia. Although pulse oximeters compensate for the presence of ambient light, the sensor should be shielded from intense light sources with an opaque material. Falsely low SpO_2 readings occur when even minor gaps exist between the probe and skin, allowing reflected light off the skin surface to "shunt" directly to the photodiode.[22] Xenon surgical lamps and fluorescent lighting can cause a falsely low SpO_2.[23] Under conditions of anemia (Hb 8 g/dL) and severe hypoxia (SaO_2 54%), SpO_2 bias is markedly increased (−14%).[24] Hyperbilirubinemia does not affect SpO_2 directly.[25] However, carbon monoxide is a byproduct of heme metabolism, and icteric patients tend to have higher levels of carboxyhemoglobin,[25] so that SpO_2 may be falsely elevated.

REFLECTANCE PULSE OXIMETRY

Reflectance pulse oximetry was designed to counter signal detection problems associated with finger probes during hypoperfusion. Whereas traditional probes work by transilluminating a tissue bed and measuring the forward-scattered light on the opposite side of the finger or earlobe, reflectance probes are constructed with the light-emitting diodes and the photodetector located on the same side. The photodetector measures the back-scattered light from the skin.[26] Reflectance pulse oximetry probes are usually placed on the forehead, which is less susceptible to vasoconstriction.[26] In addition, the more liberal placement sites for reflectance pulse oximetry has allowed fetal monitoring during labor.[27] Intraesophageal SpO_2 monitoring is currently under investigation.[28] Anasarca, excessive head movement, and difficulty in securing the probe site are some of the problems encountered with reflectance pulse oximetry.[29] Light "shunting" from poor skin contact and direct sensor placement over a superficial artery are associated with artifacts.[30] Reflectance pulse oximetry is also limited by poor signal-to-noise ratio and variability among sites in the arrangement of blood vessels and tissue blood volume.[30]

TECHNOLOGIC ADVANCES

Recent advances in signal analysis and processing have markedly improved SpO_2 accuracy during low perfusion and have reduced the problem of motion artifact.[14,31] According to recent independent testing, these advances have been made by several manufacturers.[32] Durban and Rostow reported that new pulse oximeter technology can accurately detect SaO_2 in 92% of the cases in which traditional SpO_2 monitoring failed due to low perfusion and motion artifact.[33]

CAPNOMETRY

Capnometry consists of the measurement and numeric display of expired carbon dioxide (CO_2) at the patient's airway opening.[34] When a waveform plotting CO_2 against time or volume is also displayed, it is referred to as capnography, and the waveform is referred to as a capnogram.[34] Capnometry is most commonly measured by infrared light absorption. CO_2 absorbs infrared light at a peak wavelength of approximately 4.27 μm.[34,35] Because this is close to the peak absorbency wavelength for nitrous oxide (which can interfere with the partial pressure of CO_2 [PCO_2] signal),[34] capnometers can be adjusted for monitoring during general anesthesia. Capnometry works by passing infrared light through a sample chamber to a detector on the opposite side. More infrared light passing through the sample chamber (i.e., less CO_2) causes a larger signal in the detector relative to the infrared light passing through a reference cell. Either the sample chamber is attached directly to the Y-adapter of the ventilator circuit (mainstream), or a sampling line at the Y-adapter continuously aspirates gas into a sampling chamber located inside the monitor (sidestream).

CLINICAL APPLICATIONS

Capnometric determination of the partial pressure of CO_2 in end-tidal exhaled gas ($P_{ET}CO_2$) is used as a surrogate for the partial pressure of CO_2 in arterial blood ($PaCO_2$) during mechanical ventilation.[36,37] Capnometry is used for diverse purposes, such as the diagnosis of pulmonary embolism,[38] determination of lung recruitment response to positive end-expiratory pressure (PEEP),[39,40] detection of intrinsic PEEP,[41] evaluation of weaning,[42,43] indirect marker of elevated deadspace ventilation,[44,45] assessment of cardiopulmonary resuscitation,[46] indirect determination of cardiac output through partial CO_2 rebreathing,[47] verification of endotracheal cannulation,[48] detection of airway accidents,[49] and even verification of feeding tube placement.[50]

$PaCO_2$-$P_{ET}CO_2$ GRADIENT

Normal subjects have a $PaCO_2$-$P_{ET}CO_2$ gradient of 4 to 5 mm Hg,[36,38,42,51-55] In critically ill patients, the $PaCO_2$-$P_{ET}CO_2$ gradient can be markedly elevated, with a tendency toward wider gradients in obstructive lung diseases (7 to 16 mm Hg)[41,42,52] than in acute lung injury or cardiogenic pulmonary edema (4 to 12 mm Hg).[41,42,56-58] A strong correlation between $\Delta P_{ET}CO_2$ and $\Delta PaCO_2$ ($r = 0.82$), along with minor bias and reasonable precision between $P_{ET}CO_2$ and $PaCO_2$, suggests that arterial blood gas monitoring may not be needed to assess ventilation unless the $\Delta P_{ET}CO_2$ exceeds 5 mm Hg.[43] Yet several studies found that the $\Delta P_{ET}CO_2$ often falsely predicts the degree and direction of $\Delta PaCO_2$.[53-55,58] Therefore, despite $P_{ET}CO_2$ monitoring, routine arterial blood gas analysis is still required in critically ill patients.

Several factors determine the $PaCO_2$-$P_{ET}CO_2$ gradient. Whereas $PaCO_2$ reflects the mean partial pressure of CO_2 in alveolar gas (P_ACO_2), $P_{ET}CO_2$ approximates the peak P_ACO_2.[59] During expiration, lung regions with high ventilation-to-perfusion ratios dilute the mixed CO_2 concentration so that $P_{ET}CO_2$ is usually lower than $PaCO_2$.[60] However, when CO_2 production is elevated (or expiration is prolonged), $P_{ET}CO_2$ more closely resembles mixed venous PCO_2, as a higher amount of CO_2 diffuses into a progressively smaller lung volume.[59] Thus, the $PaCO_2$-$P_{ET}CO_2$ gradient can be affected by changes in respiratory rate and tidal volume (V_T), owing to alterations in expiratory time, and by CO_2 production and mixed venous CO_2 content.[59] In fact, it is not uncommon for $P_{ET}CO_2$ to exceed $PaCO_2$.[60] Inotropic or vasoactive drugs may affect the $PaCO_2$-$P_{ET}CO_2$ gradient in an unpredictable manner, either by increasing cardiac output and pulmonary perfusion (thereby reducing alveolar deadspace) or by reducing pulmonary vascular resistance and magnifying intrapulmonary shunt by countering hypoxic pulmonary vasoconstriction.[53]

In addition, mechanical factors can cause either inconsistencies or inaccuracies in $P_{ET}CO_2$. The sample tubing length and aspirating flow rates used in sidestream capnometers affect the time required to measure changes in tidal CO_2 concentration.[61] At frequencies above 30, capnometers tend to underreport the true $P_{ET}CO_2$.[62] This may occur because of gas mixing between adjacent breaths during transport down the sampling line and in the analysis chamber.[62] This problem can be avoided with mainstream analyzers, which provide near-instantaneous CO_2 measurement (<250 msec).[63]

$PaCO_2$-$P_{ET}CO_2$ GRADIENT, POSITIVE END-EXPIRATORY PRESSURE, AND LUNG RECRUITMENT

PEEP recruits collapsed alveoli, improves ventilation-perfusion matching, and reduces alveolar deadspace, although excessive levels cause overdistention and increased alveolar deadspace.[64] Because the $PaCO_2$-$P_{ET}CO_2$ gradient correlates strongly with the physiologic deadspace–to–tidal volume ratio (V_D/V_T),[44,45] it may be useful in titrating PEEP in acute respiratory distress syndrome (ARDS). An animal model of ARDS found that the stepwise application of PEEP progressively reduced the $PaCO_2$-$P_{ET}CO_2$ gradient and coincided with maximal or near-maximal improvements in oxygenation.[56] However, PEEP applied beyond the lowest $PaCO_2$-$P_{ET}CO_2$ gradient caused a secondary rise in the gradient, along with decreased cardiac output. Although a subsequent trial was unable to reproduce these findings in humans,[57] another study found that the $PaCO_2$-$P_{ET}CO_2$ gradient narrowed (14 to 8 mm Hg) and oxygenation improved when PEEP was set at the lower inflection point of the pressure-volume curve.[40] When PEEP was set 5 cm H_2O above the lower inflection point, the $PaCO_2$-$P_{ET}CO_2$ gradient rose to 11 mm Hg, and cardiac output trended downward. In patients without a lower inflection point, the $PaCO_2$-$P_{ET}CO_2$ gradient did not change in response to PEEP. Thus, in a subset of ARDS patients, the $PaCO_2$-$P_{ET}CO_2$ gradient may be an effective way to titrate PEEP.

$P_{ET}CO_2$ MONITORING DURING CARDIOPULMONARY RESUSCITATION

Monitoring end-tidal CO_2 concentration is a reliable method for evaluating the effectiveness of cardiopulmonary resuscitation.[65] In animal models, $P_{ET}CO_2$ is strongly correlated with coronary perfusion pressure and successful resuscitation,[66] whereas in humans, changes in $P_{ET}CO_2$ are directly proportional to changes in cardiac output.[67] $P_{ET}CO_2$ during precordial compressions can distinguish successful from unsuccessful resuscitation, with values greater than 10 mm Hg[68] or greater than 16 mm Hg[69] associated with successful resuscitation.

MEASUREMENT OF DEADSPACE VENTILATION

Ventilation-perfusion abnormalities are the primary physiologic disturbance in nearly all pulmonary diseases and the principal mechanism for elevated $PaCO_2$.[70] Deadspace ventilation (V_D), the portion of V_T that does not encounter perfused alveoli, directly impacts CO_2 excretion and is used as an indirect measure of ventilation-perfusion abnormalities. Physiologic V_D represents the summation of anatomic- (conducting airway) and nonperfused alveolar components. Clinically, physiologic V_D/V_T is used to assess the severity of pulmonary disease and the efficacy of ventilator manipulations.

Physiologic V_D/V_T typically is measured during a 3- to 5-minute exhaled gas collection into a 30- to 60-L Douglas bag. An arterial blood gas reading is obtained during the midpoint of the collection. V_D/V_T is calculated using the Enghoff modification of the Bohr equation, whereby the difference between $PaCO_2$ (a surrogate for the mean P_ACO_2)

and mean expired CO_2 tension (P_ECO_2) is divided by $PaCO_2$:

$$\frac{V_D}{V_T} = \frac{(PaCO_2 - P_ECO_2)}{PaCO_2}$$

The deadspace volume per breath or per minute can be determined by multiplying V_D/V_T by the simultaneously measured average V_T or minute ventilation ($\dot{V}_E$)[71]:

$$V_D = \frac{(PaCO_2 - P_ECO_2)}{PaCO_2} \times V_T \text{ or } \dot{V}_D = \frac{(PaCO_2 - P_ECO_2)}{PaCO_2} \times \dot{V}_E$$

By subtracting the physiologic V_D per minute from the $\dot{V}_E$, the alveolar minute ventilation ($\dot{V}_A$) is obtained ($\dot{V}_A = \dot{V}_E - \dot{V}_D$). $\dot{V}_A$ also can be calculated as the volume production of CO_2 per minute ($\dot{V}CO_2$) divided by the $PaCO_2$[71]:

$$\dot{V}_A = \frac{\dot{V}CO_2}{PaCO_2} \times 0.863$$

Expired gas collection with a Douglas bag is the classic method for measuring V_D/V_T. However, the gas collection system requires additional valving and connectors, making the procedure time-consuming and awkward. Metabolic monitors produce equally accurate, reliable results and are less cumbersome.[72,73] In addition, newer monitors incorporating capnography and pneumotachygraphy now provide accurate single-breath determinations of V_D/V_T.[74]

A significant source of measurement error is the contamination of expired gas with circuit compression volume.[75] During positive-pressure ventilation, part of the V_T is compressed in the circuit, and during expiration, this gas mixes with CO_2-laden gas from the lungs. The dilution of the expired CO_2 results in a falsely elevated V_D/V_T that is directly proportional to the peak inspiratory pressure and circuit compliance. Clinically, correcting V_D/V_T for compression volume is done by multiplying the measured P_ECO_2 by the ratio of the ventilator-set V_T to the V_T delivered to the patient.[76] This requires determination of the ventilator circuit compliance.

Clinically, V_D/V_T may assist in the management of pulmonary disease in terms of both ventilator adjustments and diagnostic testing. Suter and colleagues found that V_D/V_T decreased as the lung was recruited but increased with lung overdistention during PEEP titration in ARDS.[64] Fletcher and Jonson used V_D/V_T to optimize V_T and inspiratory time settings during general anesthesia.[77] Measuring V_D/V_T may assist in identifying patients who can be removed from mechanical ventilation. Hubble and coworkers found that values less than 0.50 predicted successful extubation, and values greater than 0.65 identified patients at risk for postextubation respiratory failure.[74]

One of the main clinical uses of V_D/V_T is to aid in the diagnosis of acute pulmonary embolism. V_D/V_T is comparable to radioisotopic lung scanning in detecting acute pulmonary embolism, with a value less than 0.40 suggesting that a significant embolus is improbable.[78] Single-breath estimates of alveolar V_D are also capable of identifying patients with pulmonary embolus.[79] Recently, increased physiologic V_D/V_T (>0.60) was found to be significantly associated with mortality in patients with ARDS[80] and in neonates with congenital diaphragmatic hernia.[81] In particular, the findings that V_D/V_T is elevated early in the course of ARDS and is associated with increased mortality may be particularly useful. The efficacy of new therapies for ARDS may be judged, in part, by their ability to reduce V_D/V_T.

ASSESSMENT OF PULMONARY MECHANICS

Assessment of pulmonary mechanics is crucial to monitoring pulmonary function during artificial ventilation. It requires the measurement of V_T, peak inspiratory flow rate, and four pressures: peak airway pressure, end-inspiratory plateau pressure, end-expiratory pressure in the circuit, and any occult end-expiratory pressure measured during an end-expiratory pause maneuver. From these variables, the compliance and resistance of the respiratory system are determined.

COMPLIANCE

Under conditions of passive mechanical ventilation, peak airway pressure denotes the total force necessary to overcome the resistive and elastic recoil properties of the respiratory system (i.e., both lungs and chest wall). Distinguishing the resistive from the elastic recoil–related pressures requires introduction of an end-inspiratory circuit occlusion after V_T delivery (Fig. 60-2).[82] During the end-inspiratory pause, peak airway pressure dissipates down to a stable plateau pressure. After a 3-second pause-hold, "quasi-static" conditions usually exist, so that the corresponding plateau pressure represents the elastic recoil pressure. Dividing the V_T by the plateau pressure (Pplat) minus the PEEP yields the "quasi-static" compliance of the respiratory system (Crs-stat).[83] Even at moderate levels of $\dot{V}_E$ (>10 L/min), dynamic gas trapping frequently occurs,[84] so that Crs-stat should be based on the total PEEP (PEEPtot) measured during an end-expiratory pause rather than the PEEP applied at the airway:

$$\text{Crs-stat} = \frac{V_T}{\text{Pplat} - \text{PEEPtot}}$$

During patient-triggered ventilation, the assessment of pulmonary mechanics becomes uncertain. Clinically, the pause time is decreased to 0.5 to 1 second, to limit any potential artifact from spontaneous breathing efforts that may falsely raise or lower the plateau pressure.

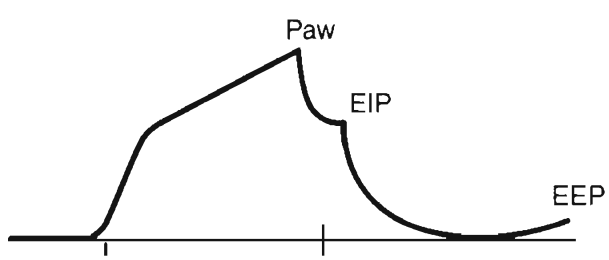

FIGURE 60–2. Depiction of a scalar (time) waveform of peak airway pressure (Paw) during constant volume mechanical ventilation with a square wave of inspiratory flow. As inspiration commences, the abrupt increase in flow against the resistance of the patient-ventilator circuit results in an immediate pressure step that is proportional to both the flow rate and the resistance. The slope in the pressure-time curve reflects the rate rise in alveolar pressure and provides qualitative information about the dynamic compliance of the respiratory system (lungs and chest wall). The introduction of an end-inspiratory pause-hold results in dissipation of Paw down to a stable end-inspiratory plateau pressure (EIP), which reflects the elastic recoil pressure of the respiratory system. Release of the pause-hold expels the tidal volume (V_T), and pressure is released down to the baseline end-expiratory pressure (EEP). Dividing V_T by EIP – EEP yields the quasi-static compliance of the respiratory system, whereas dividing the inspiratory flow rate by Paw – EIP yields the resistance of the respiratory system.

RESISTANCE

Respiratory system resistance (Rrs) is the ratio of driving pressure to flow[85] and is calculated as the difference between the peak airway pressure (Paw) and the end-inspiratory plateau pressure (Pplat) divided by the preocclusion peak inspiratory flow rate ($\dot{V}_I$) and expressed as cm H_2O/L per second[86]:

$$Rrs = \frac{Paw - Pplat}{\dot{V}_I}$$

Resistance is flow dependent, because the driving pressure necessary to overcome resistance increases disproportionately to changes in $\dot{V}_I$ (due to increased turbulence).[87] Therefore, respiratory system resistance can be accurately determined only with a constant inspiratory flow (square wave) pattern.[86] Because resistance is expressed as cm H_2O/L per second, a $\dot{V}_I$ of 60 L/min (1 L/sec) is a convenient setting to measure resistance, and it also happens to be a standard setting for patient comfort.

COMPLIANCE AND RESISTANCE IN NORMAL AND PATHOLOGIC CONDITIONS

In mechanically ventilated, normal patients, compliance is 57 to 85 mL/cm H_2O, and resistance is 1 to 8 cm H_2O/L per second.[88-90] Abnormalities in compliance and resistance in patients with acute respiratory failure are dependent on both the cause and the severity of the disease. Patients with ARDS or cardiogenic pulmonary edema tend to have a low compliance (35 or 44 mL/cm H_2O, respectively) and an elevated resistance (12 or 15 cm H_2O/L per second, respectively).[91] In contrast, patients with chronic airway obstruction tend to have both a higher compliance (66 mL/cm H_2O) and a higher resistance (26 cm H_2O/L per second).[91]

DYNAMIC GAS TRAPPING AND INTRINSIC POSITIVE END-EXPIRATORY PRESSURE

Dynamic gas trapping occurs whenever the expiratory time is less than 3.5 time constants (an exponential function defining the time required for volume or pressure equilibration across the respiratory system).[92] At end-expiration, if the respiratory system remains above its relaxed position, the elastic recoil pressure in the lung is positive. This is referred to as intrinsic PEEP.[93] Intrinsic PEEP is measured by an end-expiratory circuit occlusion whereby, after a normal expiratory time elapses, both the inspiratory and expiratory ventilator valves close for 3 to 5 seconds, allowing alveolar pressure to equilibrate with airway pressure (Fig. 60-3).[94,95] This pressure represents an average intrinsic PEEP throughout the lungs[94,96] and underestimates the peak end-expiratory alveolar pressure, because some volume egresses into the circuit.[94] Intrinsic PEEP is common in mechanically ventilated patients with various lung diseases. Patients with ARDS or cardiogenic pulmonary edema tend to have markedly lower levels of intrinsic PEEP (3 to 4 cm H_2O) compared with patients with chronic obstructive lung diseases (14 cm H_2O).[91]

Different degrees of intrinsic PEEP may coexist in the lungs because of regional variations in time constants.[95,96] Comparing dynamic measurements of intrinsic PEEP with static measurements provides a gross indication of time

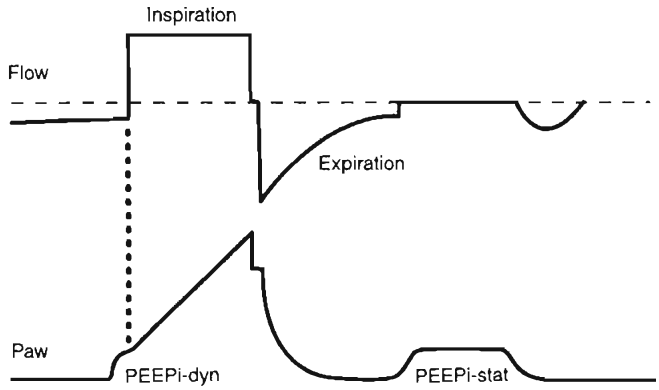

FIGURE 60–3. Simultaneous scalar waveforms of flow and peak airway pressure (Paw) illustrate the clinical measurement and separation of dynamic from static measurements of intrinsic positive end-expiratory pressure (PEEPi). Dynamic measurements reflect the lowest level of PEEPi in the respiratory system and are measured as the positive Paw just before inspiratory flow begins. The maximal level of PEEPi is the pressure plateau measured during an end-expiratory pause-hold.

constant inhomogeneity and intrinsic PEEP variation within the lungs.[95] Dynamic measurements are based on the fact that inspiratory flow does not begin until airway pressure exceeds total PEEP.[93,95] By using waveform graphics, the airway pressure above applied PEEP (just before inspiratory flow begins) represents the minimal level of total PEEP in the respiratory system (see Fig. 60-3).[95]

PRESSURE-VOLUME CURVES

The static pressure-volume relationship is used to analyze the elastic properties of the respiratory system and to guide mechanical ventilation in ARDS.[97] Pressure-volume (P-V) curves usually have a sigmoidal shape (Fig. 60-4). When inflation begins below functional residual capacity (FRC), there is relatively little volume change as transpulmonary pressure increases. This is referred to as the "starting compliance" and corresponds to the first 250 mL of volume change.[98] It reflects either the relatively high pressure required to overcome small airway closure in the dependent lung zones[99] or the relatively small area of aerated lung tissue as

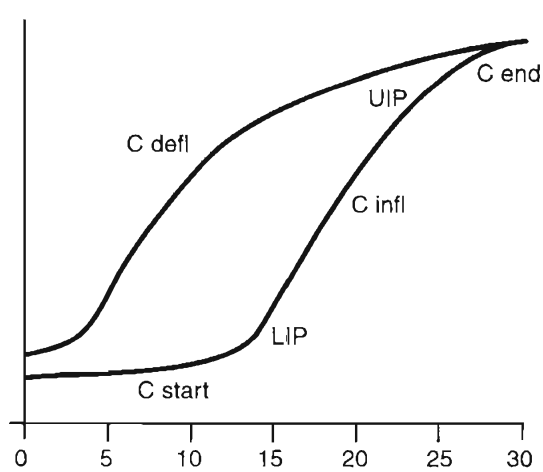

FIGURE 60–4. Static pressure-volume relationship (curve) of the respiratory system depicted from below functional residual capacity to total lung capacity. Cdefl, deflation compliance; Cend, end compliance; Cinfl, inflation compliance; Cstart, starting compliance; LIP, lower inflection point; UIP, upper inflection point.

inflation commences.[98] Typically, this low compliance segment in the P-V curve is followed by an abrupt slope change with a concave appearance that is termed the lower inflection point,[100] or "Pflex."[101] A common interpretation of the lower inflection point is that it signifies an abrupt reopening of collapsed peripheral airways and alveoli.[97,99-101] Above the lower inflection point, the P-V curve becomes linear and is referred to as the "inflation compliance."[102] As the total lung capacity is approached, compliance decreases and the P-V curve becomes convex (bow shaped). This is referred to as "end compliance"[102] and is thought to signify the loss of distensibility at maximal inflation.[99] The zone at which inflation compliance transforms to end compliance is referredto as the upper inflection point.[102] As the lung is deflated, the linear portion of the curve is referred to as the "deflation compliance," or "true physiologic compliance," as it represents the elastic properties of the lung after full recruitment.[103] As lung deflation proceeds below FRC, an inflection point often occurs that represents small airway closure.[103] On the deflation limb, airway closure occurs at a lower pressure because the minimal force necessary to maintain patent airways is less than the pressure needed to recruit collapsed ones.[104]

Pressure-Volume Curve Construction

There are two general approaches for measuring the P-V curve: the step method[102] and the pulse method.[105] In the step method, the chest is passively inflated (and then deflated) in small-volume steps with a calibrated supersyringe over a volume range of 1.5 to 2 L. P-V curve measurements require a short-acting neuromuscular blocking agent and sedation to ensure complete passive ventilation. Generally, the patient's lung volume history is standardized with several deep inflations. Afterward, the patient is disconnected from the ventilator for 5 seconds to ensure that the relaxed elastic recoil volume is reached. Then the patient is connected to a calibrated supersyringe filled with 100% oxygen and connected to a pressure manometer. Volume steps of 100 mL are used to inflate the chest, and the system pressure is measured after a 2- to 3-second pause, to allow for resistive pressure dissipation.[104] Inflation continues until either a volume of 1.5 to 2 L is delivered or a maximum pressure of 40 to 50 cm H_2O is reached.[102] Deflation of the chest is accomplished in the same stepwise fashion back to its relaxed volume. The entire procedure usually requires 60 to 90 seconds.[100] Volume steps are plotted against the corresponding static pressure points on graph paper to obtain the curve. Respiratory system compliance is the slope of the inflation and deflation curves between volumes of 0.5 and 1 L.[100]

The pulse method is based on the principle that when a low, constant flow of gas is injected into the lungs, volume change is proportional to time, so that direct volume measurement is unnecessary.[106] The technique requires either a calibrated oxygen flowmeter with sufficient pressure or ventilator manipulation. However, the inspiratory flow rate must be low enough (≤10 L/min) to minimize resistive pressures.[107] This may be problematic when a ventilator is used, because the rate, V_T, and inspiratory time adjustments required to achieve a flow of 10 L/min or less will be limited by the lowest preset rate and the longest inspiratory duty cycle.

Determination of Lower and Upper Inflection Points

In clinical practice, the lower inflection point of the inflation limb is usually determined by the graphic technique (Fig. 60-5).[97] First a tangent is drawn extending the slope of the starting compliance. Another tangent is drawn extending the slope of the inflation compliance down toward the horizontal axis. Where the two tangents intersect, a third tangent is drawn down to the horizontal axis, and this point is considered the lower inflection point. The same technique can be used to determine the upper inflection point on the inflation limb, as well as the deflation limb's lower inflection point. Typically, PEEP is set 2 cm H_2O above the lower inflection point to ensure optimal lung recruitment,[97] and V_T is set below the upper inflection point to prevent lung injury from excessive stretch.[108]

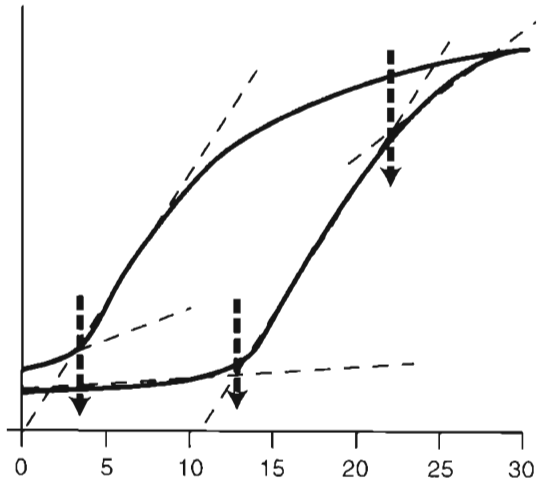

FIGURE 60–5. Graphic technique for determining the lower and upper inflection points of the pressure-volume curve. Tangents are drawn, extending the slopes of the various compliance segments of the curve. Where the tangents intersect, a third tangent is dropped down to the horizontal axis *(arrows)*.

ASSESSMENT OF BREATHING PATTERN, STRENGTH, AND CENTRAL DRIVE

RATE AND TIDAL VOLUME

Basic assessment of the respiratory pattern includes the measurement of respiratory rate and V_T. A normal respiratory rate is 12 to 24 breaths/min, and mechanical ventilation is generally indicated when it exceeds 35.[109] A V_T of 5 mL/kg is considered sufficient to maintain unassisted breathing.[110] Tachypnea is often the earliest sign of impending respiratory failure, even when arterial blood gases remain within normal limits.[111] This may reflect the fact that muscle fatigue (which results from a mechanical workload that exceeds the power capacity of the ventilatory muscles) occurs before overt ventilatory pump failure.[112] Experimentally, adaptation of a rapid-shallow breathing pattern follows the onset of fatigue.[113]

Of particular interest is the utility of breathing pattern in assessing the feasibility of weaning from mechanical ventilation. Typically, patients who fail to wean are more tachypneic (respiratory rate >32) and have an abnormally low V_T (<200 mL).[114] The respiratory rate–V_T ratio is an elegant method to evaluate weaning. Using a threshold of less than 105, this ratio has both a high positive predictive value (0.78) and a negative predictive value (0.95) for the ability to maintain unassisted breathing.[115] Although the utility of the respiratory rate–V_T ratio has been confirmed by other studies,[116,117] the original negative predictive value, at a cutoff

greater than 105, appears to be too low.[117,118] The respiratory rate–V_T ratio also correlates strongly with work of breathing and breathing effort.[119,120] In fact, the respiratory rate–V_T ratio and the tension-time index of the ventilatory muscles are considered the major pathophysiologic determinants of the successful transition from ventilator dependence to unassisted breathing. This suggests that, in general, sophisticated bedside work-of-breathing measurements are unnecessary for evaluating the feasibility of weaning. In fact, the efficacy of the respiratory rate–V_T ratio may obviate the need to routinely measure other weaning variables.

MAXIMAL INSPIRATORY PRESSURE

Maximal inspiratory pressure (MIP) reflects the force reserve of the inspiratory muscles. Normal subjects making voluntary inspiratory efforts against an occluded airway can generate a MIP of approximately –90 cm H_2O.[121] In patients recovering from respiratory failure, successful weaning has generally been associated with a MIP greater than –30 cm H_2O.[122] Although MIP is not as useful as the respiratory rate–V_T ratio in predicting weaning success (positive predictive value of 0.58), a value more positive than –20 cm H_2O has a negative predictive value of 1.[115] MIP is useful in determining whether a patient's inability to tolerate weaning trials can be explained by weakness. In particular, patients with suspected dynamic hyperinflation should have MIP measured over approximately 10 efforts (or 20 seconds) with directional values in place, so that each effort takes place from a lung volume at or below normal FRC.[123] This should improve the force-length relationship of the inspiratory muscles and help determine whether weakness can be attributed to a geometric disadvantage of muscles (secondary to hyperinflation) or whether there is a biochemical or histologic component. In particular, the clinician should observe whether the MIP can be sustained for several seconds or the pressure rapidly decays. We have observed that regardless of the value obtained, a MIP that quickly dissipates is common among ventilator-dependent patients and may be indicative of inadequate energy reserves.

CENTRAL VENTILATORY DRIVE

An important aspect of monitoring breathing pattern is the assessment of central ventilatory drive. Heightened drive increases the work of breathing during mechanical ventilation.[123] Next to respiratory rate, the most important clinical measure of central ventilatory drive is the inspiratory occlusion pressure 100 msec after the onset of effort ($P_{0.1}$). Briefly occluding the airway at the onset of inspiratory effort results in isometric contraction of the inspiratory muscles, so that $P_{0.1}$ is independent of respiratory system mechanics.[124] Measuring airway pressure at 100 msec indirectly reflects efferent motor neuron output. An increasing stimulus to the inspiratory muscles causes a more forceful contraction, with a proportional increase in pressure development. The selection of 100 msec is based on the fact that conscious or nonconscious perception of (and response to) sudden load changes requires approximately 250 msec.[125] It is convenient that during mechanical ventilation, the lag associated with the trigger phase provides sufficient time to measure $P_{0.1}$.[126] Some ventilators[127] and pulmonary mechanics monitors[128] now measure $P_{0.1}$. Experimentally, $P_{0.1}$ has been used for closed-loop control of pressure support levels during weaning from mechanical ventilation.[129]

At rest, $P_{0.1}$ is normally 0.8 cm H_2O and varies directly with $\dot{V}_E$,[130] whereas in patients with respiratory failure, it ranges from 2 to 6 cm H_2O, depending on the level of ventilatory support.[126,128,131-133] $P_{0.1}$ correlates highly with patient work of breathing, and changes in $P_{0.1}$ (which occur with ventilator adjustments) show a high degree of sensitivity and specificity for corresponding changes in patient work.[134,135] $P_{0.1}$ has been used to predict weaning and extubation success in patients recovering from acute respiratory failure. Levels exceeding 6 cm H_2O may predict weaning failure in chronic obstructive lung disease,[136] whereas a $P_{0.1}$ greater than 4 cm H_2O may presage failure in ARDS.[137] During brief trials of unassisted breathing, a $P_{0.1}$ greater than 7 cm H_2O tends to describe patients requiring total ventilatory support and has been reported as a cutoff level in patients who ultimately fail a trial of extubation.[138] $P_{0.1}$ values between 4 and 7 cm H_2O may indicate patients who can be managed with partial ventilatory support, whereas a value less than 4 cm H_2O may indicate patients no longer in need of mechanical assistance.[137]

A limitation of $P_{0.1}$ is that it dissociates from ventilatory drive when muscle weakness is present or hyperinflation alters the force-length relationship of the inspiratory muscles. In these situations, relating $P_{0.1}$ to MIP may provide a more accurate assessment of a patient's ability to sustain unassisted breathing. Evidence suggests that $P_{0.1}$/MIP ratios exceeding 0.15 describe patients requiring ventilatory support.[137,138]

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Alberti A, Gallo F, Fongaro A, et al: P0.1 is a useful parameter in setting the level of pressure support ventilation. Intensive Care Med 1995;21:547-553.

This paper describes the potential use of P0.1, an indirect measurement of central respiratory drive and inspiratory effort, as a simple method for both titrating the level of mechanical ventilatory support and assessing weaning tolerance.

Falk JL, Rackow EC, Weil MH: End-tidal carbon dioxide concentration during cardiopulmonary resuscitation. N Engl J Med 1988;318:607-611.

This landmark paper introduced one of most important clinical applications of capnography: the monitoring of spontaneous circulation and the effectiveness of precordial compressions in the setting of cardiac arrest. A sudden rise in end-tidal CO_2 concentration from approximately 1% to 3% (7 to 20 mm Hg) coincides with the return of spontaneous circulation.

Nuckton TJ, Alonso JA, Kallet RH, et al: Pulmonary dead-space fraction as a risk factor for death in acute respiratory distress syndrome. N Engl J Med 2002;346:1281-1286.

This study provides the first evidence that a pulmonary-specific variable can independently predict the risk of death in patients with ARDS. Deadspace fraction may prove to be a useful measurement by which to judge the efficacy of future therapies for ARDS.

Pepe PE, Marini JJ: Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction. Am Rev Respir Dis 1982;126:166-170.

This case series report introduced one of the most crucial concepts and monitoring imperatives of invasive mechanical ventilation. This description of the mechanics and clinical implications of dynamic hyperinflation remains one of the most lucid in the critical care and pulmonary literature.

Tremper KK, Barker SJ: Pulse oximetry. Anesthesiology 1989;70:98-108.

This paper remains one of the best written on the subject of pulse oximetry. It provides clinicians with an elegant discussion of the history, physics, engineering, and clinical aspects of this technology.

Chapter 61
PRINCIPLES OF GAS EXCHANGE

John J. Marini

KEY POINTS

1. The **quantity of oxygen loaded onto the arterial bloodstream** per unit time (O_2 delivery, D_{O_2}) is the product of the cardiac output and the oxygen contained within each milliliter of blood. Thus, a deficiency of either cofactor can be partially offset by a compensatory increase of the other.
2. **Hypoxemia** due to a relatively small number of lung units with very low $\dot{V}/\dot{Q}$ characteristics may not respond noticeably to oxygen therapy unless a very high F_IO_2 is employed; however, it is possible to convert very poorly ventilated lung units into airless, unventilated units with inspired gas having a very high F_IO_2, owing to replacement of unabsorbable nitrogen with absorbable oxygen (absorption atelectasis). **In the presence of shunt or very low $\dot{V}/\dot{Q}$ units,** however, the influence of mixed venous oxygen content may be profound, owing to its admixture with well-oxygenated pulmonary venous blood.
3. Because of the **hyperbolic relationship of $PaCO_2$ to alveolar ventilation,** relatively small changes of effective ventilation can profoundly influence $PaCO_2$ and pH when alveolar ventilation is low and $PaCO_2$ is high. Once $PaCO_2$ has climbed to approximately double its normal value, fluctuations of pH and $PaCO_2$, with their attendant adverse effects on hemodynamics and pulmonary artery pressure, place the critically ill patient at risk of blunted ventilatory drive.
4. The **expiratory capnogram** offers data of considerable clinical value when P_{CO_2} is plotted along a volume axis: it provides estimates for the "anatomic" (Fowler) deadspace, as well as for the mixed expired CO_2 concentration used in calculations of deadspace fraction and CO_2 production.

The primary purpose of the lung is to allow the respiratory gases, oxygen (O_2) and carbon dioxide (CO_2), to exchange freely between gas and blood. Unless otherwise compensated by adjustments of blood flow and cardiac output, failure to maintain arterial values of O_2 and CO_2 within tolerated physiologic limits interferes with effective cellular energy production, upsets the body's chemical balance, and, when severe, may be the proximate cause of lasting disability or death. The objective of this chapter is to review the principles of respiratory gas exchange across the lungs, with special reference to the setting of critical illness.

OXYGEN EXCHANGE

Most O_2 carried in the blood is bound reversibly to hemoglobin, with only a small quantity dissolved in plasma. Whereas O_2 binding by hemoglobin is essentially complete at a partial pressure (PaO_2) less than 150 mm Hg, depending on pH, temperature, and innate hemoglobin affinity, the dissolved fraction continues to rise linearly with increasing PaO_2. The equation relating blood O_2 content, expressed as milliliters per deciliter, to hemoglobin concentration ([Hgb], in g/dL), to O_2 saturation (a decimal fraction), and to PaO_2 is:

$$CaO_2 = 1.31 \bullet [Hgb]\, SaO_2 + 0.0031 \bullet PaO_2.$$

Except in extreme conditions under which hemoglobin is unable to bind O_2 (e.g., carbon monoxide intoxication, methemoglobinemia) or under which very severe anemia limits the hemoglobin bound O_2 fraction, dissolved O_2 accounts for a very small percentage of the total.[1] In fact, hemoglobin is such an effective carrier for O_2 that the quest to develop an effective blood substitute for clinical use has been only partially successful. Intravascularly delivered products based on stroma-free hemoglobin (an avid O_2 binder) and perfluorocarbon (an efficient dissolver of O_2) are potentially effective but have encountered problems with stability, toxicity, and cost.[2] For the present, blood substitutes must be considered impractical for the clinical setting.

OXYGEN DELIVERY

Metabolizing tissues require an adequate supply of O_2 to efficiently produce the energy needed for cellular function. The quantity of O_2 loaded onto the arterial bloodstream per unit time (O_2 delivery, DO_2) is the product of the cardiac output and the O_2 contained within each milliliter of blood. Therefore, a deficiency of either cofactor can be partially offset by a compensatory increase of the other. Conversely, sluggish blood flow, whether caused by low cardiac output or high resistance through the tissues, can limit the O_2 actually delivered to the cell. Increased blood viscosity impedes the transit of erythrocytes through the capillary bed, thereby acting to limit oxygen consumption (V_{O_2}).[3] For this reason, paraproteinemia, extreme leukocytosis, and polycythemia can pose life-threatening challenges to O_2 consumption that are only partially explained by their impact on cardiac output.[3] Studies performed in animal models demonstrate

that hematocrit (Hct), a primary determinant of viscosity, bears a nonlinear relationship to D_{O_2} that varies somewhat with circulating blood volume.[4] At low values of Hct a rising hemoglobin concentration predictably adds to O_2 content. Above an Hct of 30% to 34%, however, it is difficult to demonstrate in critically ill patients additional O_2 consumption or outcome benefit from increases of O_2 content that arise from further increments of hemoglobin.[5] At an Hct of 55% to 57%, D_{O_2} reaches its maximum in normal subjects, falling sharply with each further rise (Fig. 61-1). Above an Hct of approximately 65% phlebotomy may be required to avert a hemodynamic crisis, because vital tissues may be deprived of delivered O_2. Viscosity, and therefore tolerance for higher Hct, is partially determined by the circulating blood volume; the polycythemia associated with intravascular volume contraction is much less well tolerated than that of polycythemia vera.[3] As might be expected, patients with vascular disease are less tolerant to the adverse rheologic effects of high Hct.

At the mitochondrial level, O_2 acts as the terminal acceptor in a chain of organic electron donors known as the cytochromes. The P_{O_2} within the mitochondrion needed to sustain this process is very low—estimated to be much less than 1 mm Hg.[6] To provide that needed level of P_{O_2}, an appropriate O_2 diffusion gradient must be established from the arterial blood, across tissue and cellular boundaries, and into the cellular organelles. At sea level, normal levels of mitochondrial O_2 are achieved at a PaO_2 of about 95 mm Hg. The actual P_{O_2} within the mitochondrion, however, is affected by many factors other than arterial P_{O_2}, such as tissue metabolic rate, microvascular control, tissue properties, and blood flow. Over time, varying degrees of accommodation occur to subnormal PaO_2 by adjustments of the cardiovascular system, hemoglobin concentration, capillary system, and mitochondrial density.[7] Although this adaptive phenomenon is commonly observed in patients with chronic lung diseases, the extent to which accommodation to hypoxemia can occur and should be encouraged in patients who are critically ill is a provocative and largely unexplored question.

OXYGEN TRANSFER ACROSS THE LUNG

Oxygen is driven from the airspace to the pulmonary capillary by a diffusion gradient determined by the P_{O_2} difference between them and the resistance to diffusion presented by the intervening tissues and fluids. To keep the alveolar O_2 tension adequate, the O_2 supplied to the alveolus must be replaced at a rate equal to or greater than that at which the O_2 is removed by the passing capillary blood. Classically, six mechanisms can account for hypoxemia:

1. Low F_{IO_2}
2. Hypoventilation
3. Impaired pulmonary diffusion capacity
4. Ventilation-perfusion ($\dot{V}/\dot{Q}$) imbalance
5. Shunt
6. Desaturation of pulmonary arterial (mixed venous) blood

Low F_{IO_2} is an important mechanism of hypoxemia occurring at altitude and in fires that occur in confined spaces. Although the relationship is not a linear function, as a rough estimate, inspired O_2 declines approximately 15 mm Hg for each 1000 meters of altitude above sea level.[8] For practical purposes, however, a lack of inspired O_2 does not account for hypoxemia occurring in the setting of critical illness. Hypoventilation alters the alveolar oxygen tension (P_AO_2) in proportion to the rise of $PaCO_2$ (and P_ACO_2) and becomes an important factor when it occurs during breathing of room air (as in narcotic overdose) or of relatively low inspired concentrations of supplemental O_2 (e.g., via nasal cannulae). The importance of impaired diffusion as a hypoxemic mechanism is sometimes debated, because the transfer of O_2 from alveolus to hemoglobin usually requires only a brief time for completion—somewhat less than the normal transit time of the erythrocyte through the capillary.[9] Yet, under many conditions that are commonly encountered, the rate at which blood flows through the lung is accelerated, diffusion distances are lengthened, and the O_2 driving gradient is reduced by disease. For this reason, impaired diffusion is likely to contribute to hypoxemia occurring in the stressed patient with critical illness who receives near-normal F_{IO_2}.

$\dot{V}/\dot{Q}$ imbalance is the most common contributor to clinical hypoxemia, and perhaps the mechanism least well understood among practitioners. Here, it is the relative *distribution* of ventilation and perfusion that is critical to effective oxygenation. Ventilation must take place where perfusion does, or else the same levels of each that normally allow oxygenation and alveolar ventilation may produce both hypoxemia and wasted ventilation (ventilatory deadspace). With respect to impaired oxygenation, this concept is perhaps best understood by considering the P_AO_2 to fall as a result of regional alveolar hypoventilation. Owing to the sigmoidal shape of the oxyhemoglobin dissociation curve, excess ventilation of normal alveoli cannot fully compensate for regional desaturation elsewhere, so that the net PaO_2 declines after blood from these two types of unit admix in the pulmonary venous blood. Like hypoxemia due to low F_{IO_2}, hypoventilation, and diffusion impairment, hypoxemia resulting from $\dot{V}/\dot{Q}$ imbalance responds to supplementation of inspired O_2. Poor ventilation of a given lung unit can be compensated for by raising the O_2 concentration of the inspired gas it receives.

Whereas the relationship of F_{IO_2} to PaO_2 is more or less linear for the first three O_2-responsive mechanisms already covered, the response to O_2 supplementation for $\dot{V}/\dot{Q}$ imbalance depends on the distribution of abnormal $\dot{V}/\dot{Q}$ units contributing to the problem.[10] Hypoxemia due to a relatively small number of lung units with very low $\dot{V}/\dot{Q}$ characteristics may not respond noticeably to O_2 therapy unless a very high F_{IO_2} is employed. Conversely, a lung characterized by a large

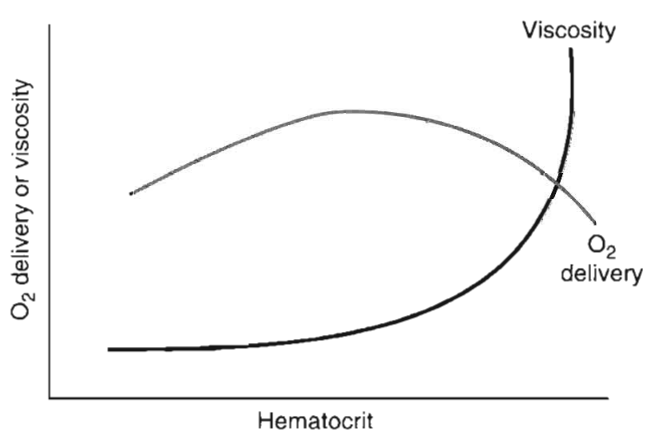

FIGURE 61–1. Effect of hematocrit on viscosity and oxygen delivery. Raising hematocrit simultaneously increases oxygen content and viscosity, which adversely affects blood rheology. Consequently, oxygen delivery reaches a maximum at hematocrit values in the upper mid range.

number of lung units with mild $\dot{V}/\dot{Q}$ impairment tends to respond in more linear fashion (Fig. 61-2). It is also possible to convert very poorly ventilated lung units into airless, unventilated units with inspired gas having a very high F_IO_2, owing to replacement of unabsorbable nitrogen with absorbable O_2, leading to the unit's contraction and eventual collapse as this process continues below the closing volume of the compromised region (absorption atelectasis).[11] Unless compensation by hypoxic vasoconstriction is complete, raising F_IO_2 can paradoxically increase shunt even as it improves O_2 transfer in units that remain patent.

Given the importance of matching blood flow to ventilation, it is not surprising that several mechanisms have developed to effect pulmonary microvascular regulation. Autonomic control, although less prominent and less precise than in the peripheral vasculature, is important nonetheless. Severe head injury, for example, can cause dysregulation and hypoxemia via this mechanism.[12] Local acidosis, such as that existing in poorly ventilated areas, tends to vasoconstrict the pulmonary arterial microvessels. The strength of this reflex, however, pales before that of hypoxic pulmonary vasoconstriction, which for most individuals is a well-developed protection against perfusing underventilated areas.[13] These mechanisms may be overpowered by pathologic processes or by pharmacologic interventions. For example, local release of inflammatory mediators or use of certain vasoactive drugs (e.g., nitroprusside) may counter these protective reflexes[14] and an abrupt rise of pulmonary artery pressure may overwhelm them.

Shunting occurs when venous blood is not brought into proximity with the inspired gas. Shunt can originate in the heart (e.g., through a patent communication at the atrial or ventricular level). Rarely, direct venous to arterial transfer occurs through microvascular or macrovascular defects known as pulmonary arteriovenous fistulas. Such communications are encountered in relatively common diseases, such as hepatic cirrhosis, as well as in other settings, exemplified by the heritable Osler-Weber-Rendu abnormality. Diseases that affect the lung parenchyma are much more common causes of shunt than these cardiovascular disorders. Filling of the airspaces with fluid (e.g., edema) or cellular infiltrate (e.g., pneumonia) prevents gas-blood contact. Inflammatory conditions may inhibit hypoxic vasoconstriction, worsening arterial hypoxemia, as does hypocapnic alkalosis.[15] Collapse of lung units may occur at any anatomic scale, resulting in shunt through the affected regions. Causes for collapse vary from compression (e.g., by a pleural effusion), to disease-induced surfactant depletion or inactivation, to airway plugging by retained secretions. Sustained reversal of atelectasis requires attention to the inciting cause as well as recruitment of the problem area by deep lung expansion. Pure O_2 breathing will not improve hypoxemia due to shunting. Conversely, reduction of F_IO_2 in that setting will not cause shunt-related hypoxemia to worsen and may spare ventilated areas exposure to potentially toxic concentrations of inspired O_2 (Fig. 61-3).

Under normal circumstances, variations in mixed venous O_2 content do not influence PaO_2 perceptibly, because recharging of desaturated hemoglobin with O_2 takes place at the alveolar-capillary junction, even during exercise. In the presence of shunt or very low $\dot{V}/\dot{Q}$ units, however, the influence of mixed venous O_2 content may be profound, owing to its admixture with well-oxygenated pulmonary venous blood. Because mixed venous O_2 content is influenced primarily by the ratio of O_2 consumption to D_{O_2}, hypoxemia may be at least partially alleviated by reducing O_2 demand or improving D_{O_2}. The equation relating these variables, which is easily derived by rearrangement of the Fick equation for O_2, is:

$$S\bar{v}O_2 \approx SaO_2 - V_{O_2}/([Hgb][SaO_2] \bullet Q).$$

Online measurements of $S\bar{v}O_2$ with a fiberoptic Swan-Ganz catheter enable venous desaturation to be detected and monitored without effort.

RELATIONSHIP OF P_{O_2} TO BLOOD O_2 CONTENT

Even though the oxyhemoglobin dissociation relationship is implicitly used for clinical decision making, many practitioners do not fully understand important nuances (Fig. 61-4). Over the clinically relevant range, the oxyhemoglobin dissociation

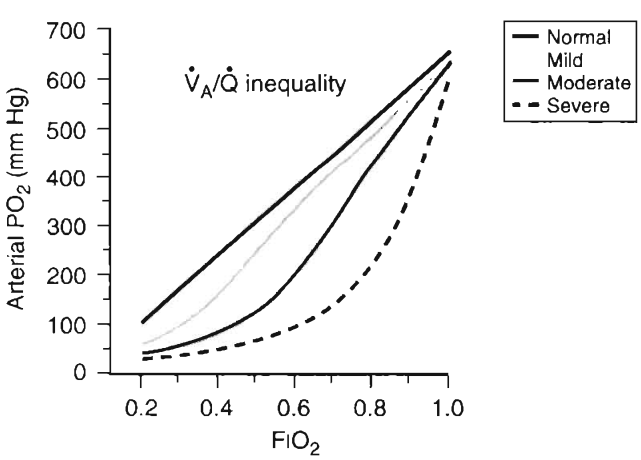

FIGURE 61–2. Influence of severity of $\dot{V}/\dot{Q}$ on the F_IO_2 to arterial PO_2 relationship. Arterial PO_2 rises linearly in normal and mildly affected lungs, whereas very high inspired oxygen fractions may be necessary to raise arterial PO_2 when the $\dot{V}/\dot{Q}$ abnormality is severe.

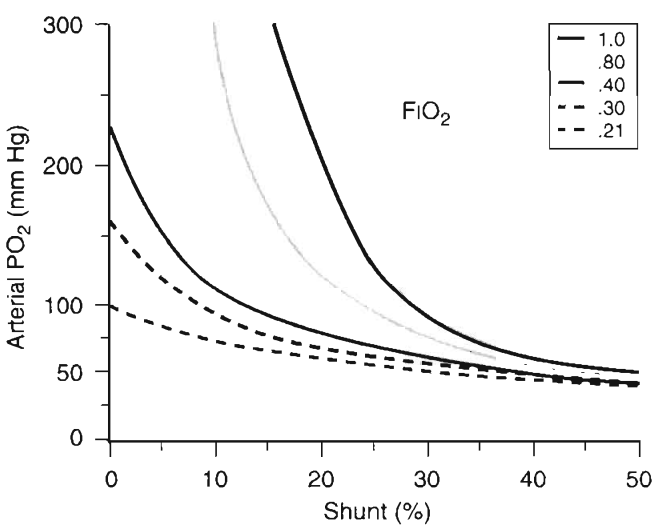

FIGURE 61–3. Effect of shunt percentage on arterial PO_2 for a range of F_IO_2. When shunt percentage exceeds 35% to 40%, variations of F_IO_2 only modestly affect arterial PO_2. Moreover, because the risk of oxygen toxicity rises hyperbolically with inspired oxygen concentration, reductions of F_IO_2 from 1.0 to 0.8 may yield benefit with only marginal impact on arterial oxygenation.

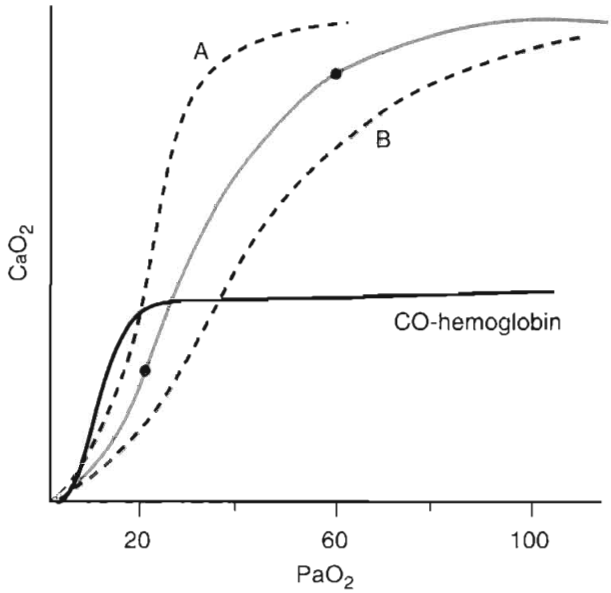

FIGURE 61–4. Relationship of PaO_2 to blood oxygen content (CaO_2). The oxyhemoglobin dissociation curve normally plateaus at a PO_2 of approximately 100 mm Hg *(upper solid line)*. Alkalosis and hyperthermia (A) shift the relationship up and to the left, whereas acidosis and hyperthermia (B) shift it downward to the right. Carbon monoxide causes tighter binding of oxygen to hemoglobin but reduces the capacity of hemoglobin to bind oxygen.

curve is highly nonlinear, so that a drop of a few percentage points in SaO_2 over the 95% to 100% interval reflects a much larger change in PaO_2 than does a similar decrement that occurs over the 80% to 85% interval. Pulse oximeters record the relative absorption of light by oxyhemoglobin and deoxyhemoglobin. Therefore, for a fixed value of viable hemoglobin, the saturation parallels its relative O_2 content, but a high saturation guarantees neither its total O_2 content nor the adequacy of tissue D_{O_2}. For example, a patient may have a "full" SaO_2 after inhaling a high concentration of carbon monoxide and, yet, directly measuring arterial O_2 *content* per deciliter of blood (e.g, using a co-oximeter) may demonstrate profound arterial O_2 depletion (see Fig. 61-4). Moreover, a patient in circulatory shock may maintain a perfectly normal SaO_2 despite serious O_2 privation. Because cyanide blocks the uptake of O_2 by the tissues, O_2 consumption is low, even as arterial and mixed venous saturations remain normal or increased. It is occasionally forgotten that SaO_2 bears no direct relationship to the adequacy of ventilation; a patient breathing a high inspired concentration of O_2 will maintain a nearly normal SaO_2 for a brief period in the presence of a full respiratory arrest.

DELIVERY DEPENDENCE OF OXYGEN CONSUMPTION

Controversy has surrounded the concept of supply dependency of O_2 consumption for patients having sustained trauma, massive surgery, or sepsis. Prognosis in these conditions is somewhat better for critically ill patients in whom higher D_{O_2} is manifest. By inference, it has been suggested that in these settings supranormal D_{O_2} is needed to satisfy the O_2 demands of certain vital organs.[16] Whereas there is little doubt that prompt and vigorous resuscitation must be carried out[17] or that patients who do not spontaneously generate sufficient D_{O_2} or who cannot extract O_2 effectively have a worse prognosis than other patients undergoing the same stress who do, it is highly questionable whether attempts to sustain D_{O_2} at supranormal values are well advised. Some data even suggest potential harm. Specific subgroups of surgical patients could, in fact, benefit, but there are no tightly controlled clinical trial data available to settle this question in either direction. Patients having sustained massive trauma or extensive surgery may represent a fundamentally different physiologic problem and respond more favorably than patients with medical crises. On the strength of a well-designed multicenter Italian trial,[18] it now seems clear that maintaining supranormal values for D_{O_2} confers no routine benefit for patients in the latter category. For nonmoribund patients with sepsis and/or acute respiratory distress syndrome (ARDS), supply dependency may not, in fact, exist. Without better evidence, therefore, maximizing V_{O_2} cannot be accepted as the primary target variable for circulatory support in patients admitted to the ICU. The data for patients with septic shock in the emergency department may be somewhat different, because there is evidence that they may benefit from therapies aimed at improving central $S\bar{v}O_2$ if applied in the period immediately after admission to the emergency department.[17]

ASSESSING THE EFFICIENCY OF OXYGEN EXCHANGE

Mean P_AO_2 must first be computed to judge the efficiency of gas exchange across the lung. The ideal P_AO_2 is obtained from the modified alveolar gas equation:

$$P_AO_2 = P_IO_2 - (PaCO_2/R) + \{(PaCO_2 \times F_IO_2 \times (1 - R)/R)\}$$

where R is the respiratory exchange ratio and P_IO_2 is the inspired O_2 tension, adjusted for F_IO_2 and water vapor pressure at body temperature (47 mm Hg at 37°C).

Therefore,

$$P_IO_2 = (\text{barometric pressure} - 47) \times F_IO_2 .$$

Under steady-state conditions, R normally varies from 0.7 to 1.0, depending on the mix of metabolic fuels (see later). When the same patient is monitored over time, R generally is assumed to be 0.8 or neglected entirely. Under most clinical conditions, the alveolar gas equation can be simplified to:

$$P_AO_2 = P_IO_2 - (1.25 \times PaCO_2)$$

For example, at sea level with a normally ventilated patient breathing room air:

$$\begin{aligned} P_AO_2 &= 0.21 \times (760 - 47) - 1.25 \times (PaCO_2) \\ &= 150 - (1.25 \times 40) \\ &\cong 100 \text{ to } 110 \text{ mm Hg} \end{aligned}$$

Alveolar-Arterial Oxygen Tension Difference $P(A\text{-}a)O_2$

The difference between alveolar and arterial O_2 tensions, $P(A\text{-}a)O_2$, takes account of alveolar CO_2 tension, thereby eliminating hypoventilation and hypercapnia from consideration as the sole cause of hypoxemia. However, a single value of $P(A\text{-}a)O_2$ does not characterize the efficiency of gas exchange across all F_IO_2 measurements, even in normal subjects. The $P(A\text{-}a)O_2$ normally ranges from ~10 mm Hg (on room air)

to ~100 mm Hg (on an F_IO_2 of 1.0). Moreover, PAO_2 changes nonlinearly with respect to F_IO_2 as the extent of $\dot{V}/\dot{Q}$ mismatch increases. Thus, when the $\dot{V}/\dot{Q}$ abnormality is severe and nonhomogeneously distributed among gas exchanging units, the P_AO_2 may vary little with F_IO_2 until high fractions of inspired O_2 are given (see Fig. 61-2). Finally, the $P(A\text{-}a)O_2$ may be influenced by fluctuations in venous O_2 content.

Simplified Measures of Oxygen Exchange

Several pragmatic approaches have been taken to simplify bedside assessment of O_2 exchange efficiency. The first is to quantitate $P(A\text{-}a)O_2$ during the administration of pure O_2. After a suitable wash-in time (5 to 15 minutes depending on the severity of the disease), pure shunt accounts for the entire $P(A\text{-}a)O_2$. Furthermore, if hemoglobin is fully saturated with O_2, dividing the $P(A\text{-}a)O_2$ by 20 approximates shunt percentage (at $F_IO_2 = 1$). As pure O_2 replaces alveolar nitrogen, some patent but poorly ventilated units may collapse—the process of absorption atelectasis.[11] Moreover, because shunt percentage is affected by changes in cardiac output and mixed $S\bar{v}O_2$, these simplified measures may give a misleading impression of changes within the lung itself.

The P_aO_2/F_IO_2 (or P/F) ratio is a convenient and widely used bedside index of O_2 exchange that attempts to adjust for fluctuating F_IO_2. However, although simple to calculate, this ratio is affected by changes in $S\bar{v}O_2$ and does not remain equally sensitive across the entire range of F_IO_2, especially when shunt is the major cause for admixture. Another easily calculated index of O_2 exchange properties, the P_aO_2/P_AO_2 (or "a/A") ratio, offers similar advantages and disadvantages as F_IO_2 is varied. Like the P/F ratio, it is a useful bedside index that does not require blood sampling from the central circulation but loses reliability in proportion to the degree of shunting. Furthermore, in common with all measures that calculate an "ideal" P_AO_2, even the a/A ratio can be misleading when fluctuations occur in the primary determinants of $S\bar{v}O_2$ (hemoglobin and the balance between O_2 consumption and delivery).

None of the indices discussed thus far accounts for changes in the functional status of the lung that result from alterations in positive end-expiratory pressure (PEEP), auto-PEEP, or other techniques for adjusting average lung volume (e.g., inverse ratio ventilation, lateral or prone positioning). If the objective is to categorize the severity of disease or to track the true O_2 exchanging status of the lung in the presence of such interventions, the P/F ratio falls short. The *oxygenation index* (OI) is shown as:

$$OI = P_aO_2/(F_IO_2 \times \text{mean Paw}).$$

This calculation takes the effects of PEEP and inspiratory time fraction into account, has gained widespread popularity in neonatal and pediatric practice, but has yet to catch hold in adult critical care. Although preferable, this index, too, is imperfect; mean airway pressure (Paw) and F_IO_2 bear complex and alinear relationships to P_aO_2 when considered across their entire ranges.

CO_2 EXCHANGE

PHYSIOLOGIC EFFECTS OF CO_2

For the major waste product of oxidative metabolism, CO_2 is a relatively innocuous gas. Apart from its key role in regulation of ventilation, the clinically important effects of CO_2 relate to changes in cerebral blood flow, pH, and adrenergic tone. Hypercapnia dilates the cerebral vessels and hypocapnia constricts them, a point of importance for patients with raised intracranial pressure. Acute increases in CO_2 depress consciousness probably as the result of intraneuronal acidosis. Slowly developing increases in CO_2 are well tolerated, presumably because buffering has time to occur. Nonetheless, a higher P_aCO_2 signifies alveolar hypoventilation that tends to cause a decrease in alveolar and arterial PO_2. With hypoxemia and acidosis averted by supplemental O_2 and compensatory acidosis, some outpatients with P_aCO_2 levels that chronically exceed 90 mm Hg continue to lead active lives. Conversely, patients with renal insufficiency lack the ability to buffer carbonic acid and tolerate hypercapnia poorly.

The adrenergic stimulation that accompanies acute hypercapnia causes cardiac output to rise and peripheral vascular resistance to increase. During acute respiratory acidosis these effects may have partially offset those of hydrogen ion on cardiovascular function, allowing better tolerance of pH than with metabolic acidosis of similar degree. Constriction of glomerular arterioles also occurs by adrenergic stimulation producing oliguria in some patients. Muscular twitching, asterixis, and seizures may be observed at extreme levels of hypercapnia in patients made susceptible by electrolyte or neural disorders. Prompted by a favorable experience with "permissive hypercapnia" (discussed elsewhere in this text) on important clinical outcomes of life-threatening asthma[19] and acute respiratory distress syndrome,[20] considerable attention has been directed toward the beneficial actions of CO_2 as an antioxidant and anti-inflammatory agent.[21,22] It is conceivable that in selected circumstances hypercapnia may not only be acceptable but also desirable.

The major cardiovascular effects of acute hypocapnia relate to alkalosis. Alkalosis adversely affects myocardial conduction, cellular energy kinetics, and neuronal function.[23] Abrupt lowering of P_aCO_2 reduces cerebral blood flow and raises neuronal pH, altering cortical and peripheral nerve function. Lightheadedness, circumoral and fingertip paresthesia, and muscular tetany can result. Sudden major reductions of P_aCO_2 (e.g., shortly after initiating mechanical ventilation) can produce life-threatening arrhythmias and seizures, albeit rarely. Because of the importance of adrenergic compensation for the vasodilatory effects of hypercapnic acidosis, hemodynamic manifestations of acute hypercapnia are more profound in the presence of beta- and/or alpha-adrenergic blockade.

CO_2 PRODUCTION AND STORAGE

The quantity of CO_2 produced for excretion is a function of O_2 consumption and any CO_2 that is liberated in the buffering of hydrogen ion. The metabolic exchange ratio, R, varies with the mix of metabolic fuels, with carbohydrate, protein, and fat associated with ratios of 1.0, 0.7, and 0.6, respectively. CO_2 is both more diffusible and more soluble than O_2, and most CO_2 carried in the blood is in dissolved form. A smaller but very significant proportion of CO_2 is bound within the erythrocyte as bicarbonate through the action of carbonic anhydrase. In passing through the lung it is evolved by the same enzyme.

Body stores of CO_2 are far greater than those of O_2. When breathing room air, only about 1.5 L of O_2 is stored (much of it in the lungs); and some of this stored O_2 remains unavailable for release until life-threatening hypoxemia is under way. Although breathing pure O_2 can fill the alveolar

compartment with an additional 2 to 3 L of O_2 (a safety factor during apnea or asphyxia), these O_2 reserves are still much less than the approximately 120 L of CO_2 normally stored in body tissues. Because of limited O_2 reserves, PaO_2 and tissue PO_2 change rapidly during apnea, at a rate that is highly dependent on FiO_2.

CO_2 stores are held in several forms (dissolved, bound to protein, fixed as bicarbonate) and distributed in compartments that differ in their volumetric capacity and ability to exchange CO_2 rapidly with the blood.[24] Well-perfused organs constitute a small reservoir for CO_2 capable of quick turnover, skeletal muscle is a larger compartment with sluggish exchange, and bone and fat are high-capacity chambers with very slow filling and release. From a practical point of view, the existence of large CO_2 reservoirs with different capacities and time constants of filling and emptying means that equilibration to a new steady-state $PaCO_2$ after a step change in ventilation (assuming a constant rate of CO_2 production, V_{CO_2}) takes longer than generally appreciated-especially for step *reductions* in alveolar ventilation (Fig. 61-5). With such a large capacity and only a modest rate of metabolic CO_2 production, the CO_2 reservoir fills rather slowly, so that $PaCO_2$ rises only 6 to 9 mm Hg during the first minute of apnea and 3 to 6 mm Hg each minute thereafter. Depletion of this reservoir can occur at a faster rate.

Measurement of CO_2 excretion is valuable for metabolic studies, computations of deadspace ventilation, and evaluation of hyperpnea. Estimates of CO_2 production are representative when the sample is collected carefully in the steady state over adequate time. The rate of CO_2 elimination is a product of minute ventilation ($\dot{V}E$) and the expired fraction of CO_2 in the expelled gas. If gas collection is timed accurately and the sample is adequately mixed and analyzed, an accurate value for excreted CO_2 can be obtained. However, whether this value faithfully represents metabolic CO_2 production depends on the stability of the patient during the period of gas collection, not only with regard to V_{O_2} but also in terms of acid-base fluctuations, perfusion constancy, and ventilation status with respect to metabolic needs. During acute hyperventilation or rapidly developing metabolic acidosis, for example, the rate of CO_2 excretion overestimates metabolic rate until surplus body stores of CO_2 are washed out or bicarbonate stores reach equilibrium. The opposite obtains during abrupt hypoventilation or transient reduction in cardiac output.

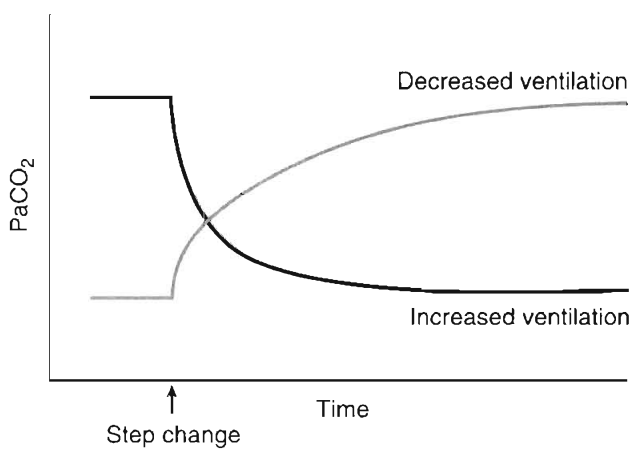

FIGURE 61–5. Effect of step changes of ventilation on $PaCO_2$. A stepped-increase in ventilation will cause $PaCO_2$ to fall in approximately exponential fashion. A stepped decrease in ventilation will cause $PaCO_2$ to approach equilibrium exponentially at a slower rate that is influenced by the magnitude of CO_2 storage capacity and CO_2 production.

EFFICIENCY OF CO_2 EXCHANGE

The volume of CO_2 produced by the body tissues varies with metabolic rate (e.g., fever, pain, agitation, sepsis). In the mechanically ventilated patient, many vagaries of CO_2 flux can be eliminated by controlling ventilation and quieting muscle activity with deep sedation with or without paralysis. $PaCO_2$ must be interpreted in conjunction with the V_E. For example, the gas-exchanging ability of the lung may be unimpaired even though $PaCO_2$ rises when reduced alveolar ventilation is the result of diminished respiratory drive or marked neuromuscular weakness. As already noted, alveolar and arterial CO_2 concentrations respond quasi-exponentially after step changes in ventilation, with a half-time of about 3 minutes during hyperventilation but a slower half-time (16 minutes) during hypoventilation.[25] These differing time courses should be taken into account when sampling blood gases after making ventilator adjustments.

Deadspace

The physiologic deadspace (V_D) refers to the "wasted" portion of the tidal breath that fails to participate in CO_2 exchange. A breath can fail to accomplish CO_2 elimination either because fresh (CO_2-free) gas is not brought to the alveoli or because fresh gas fails to contact systemic venous blood. Thus, tidal ventilation is wasted whenever CO_2-laden gas is recycled to the alveoli with the next tidal breath. Alternatively, a portion of the tidal volume is wasted if fresh gas distributes to inadequately perfused alveoli, so that CO_2-poor gas is exhausted during exhalation (Fig. 61-6). If this concept is understood, then it becomes clear why V_D should not be considered as a composite of physical volumes. Nonetheless, wasted ventilation traditionally is characterized as the sum of the "anatomic" (or "series") dead space and the "alveolar" dead space. Because the airways fill with CO_2-containing alveolar gas at the end of the tidal breath, the physical volume of the airways corresponds rather closely to their contribution to wasted ventilation (the series or "anatomic" dead space), provided that mixed alveolar gas is similar in composition to the gas within a well-perfused alveolus. This is almost true for a quietly breathing normal subject, in whom the alveolar deadspace (poorly perfused alveolar volume) is negligible. When the parenchyma is well aerated and well perfused, the anatomic deadspace is relatively fixed at approximately 1 mL per pound (0.4 kg) of body weight.[26] (Patients with endotracheal tubes and tracheostomies have less series deadspace, whereas those with attached breathing apparatus may have more). Anatomic deadspace becomes an important concern at very low tidal volumes. For patients with lung disease that affects the lung parenchyma, and those ventilated at pressures that overinflate some lung units, alveolar deadspace predominates. Here, the lung is composed of well and poorly perfused units, so that the *mixed* alveolar gas within the airways at end exhalation has a CO_2 concentration lower than that of pulmonary arterial blood.

For normal subjects, deadspace increases with advancing age and body size and is reduced modestly by recumbency, extended breath holding, and decelerating inspiratory flow patterns. External apparatus attached to the airway that

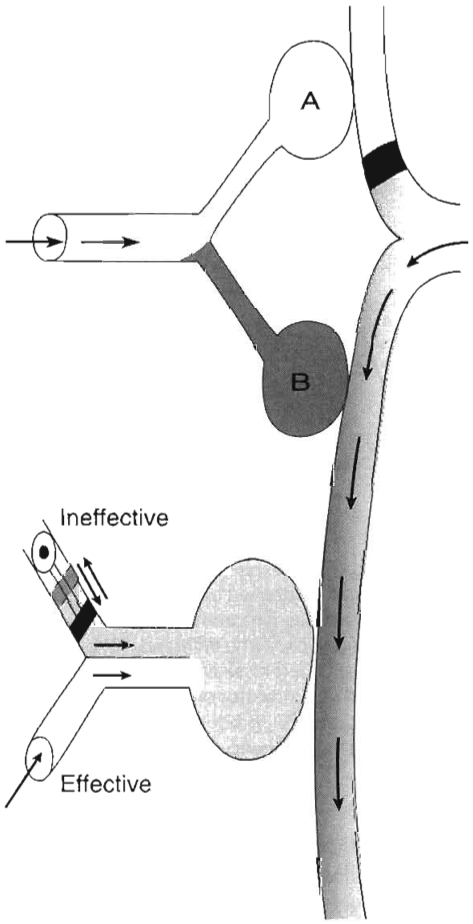

FIGURE 61–6. Concept of ventilatory deadspace. Wasted ventilation (deadspace) develops as the result of inadequate perfusion (alveolar compartment, A) or from the failure of ventilation to eliminate carbon dioxide from the conducting airways. In both instances efforts expended in ventilation do not result in effective CO_2 elimination from the affected lung units.

remains unflushed by fresh gas may add to the series deadspace, whereas tracheostomy reduces it. The supine position reduces deadspace by decreasing the average size of the lung and by increasing the number of well-perfused lung units.

Numerous diseases increase V_D. Destruction of alveolar septa, low output circulatory failure, pulmonary embolism, pulmonary vasoconstriction or vascular compression, and mechanical ventilation with high tidal volumes or PEEP are common mechanisms that often act in combination.

Deadspace Fraction

In the setting of parenchymal lung disease, deadspace varies in proportion to tidal volume over a remarkably wide range. Series deadspace tends to remain fixed but generally constitutes a small percentage of the total V_D, overwhelmed by the alveolar deadspace component. Therefore, except at very small tidal volumes, the *fraction* of wasted ventilation (V_D/V_T) tends to remain relatively constant as the depth of the breath varies. The deadspace fraction can be estimated from analyzed specimens of arterial blood and mixed expired (P_ECO_2) gas:

$$(V_D/V_T) = (PaCO_2 - P_ECO_2)/PaCO_2$$

where P_ECO_2 is the CO_2 concentration in mixed expired gas. (This expression is known as the Enghoff-modified Bohr equation.) As already noted, P_ECO_2 can be determined on a breath-by-breath basis if exhaled volume is measured simultaneously. Alternatively, exhaled gas can be collected over a defined period. The P_{CO_2} of gas exiting a mixing chamber attached to the expiratory line provides a continuous "rolling average" value. In collecting the expired gas sample during pressurized ventilator cycles, an adjustment should be made for the volume of any sampled gas stored in the compressible portions of the ventilator circuit.

In healthy persons, the normal V_D/V_T during spontaneous breathing varies from 0.35 to 0.15, depending on the factors noted earlier (e.g., position, exercise, age, tidal volume, pulmonary capillary distention, breath holding). In the setting of critical illness, however, it is not uncommon for V_D/V_T to rise to values that exceed 0.7. Indeed, increased deadspace ventilation usually accounts for most of the increase in the V_E requirement and the CO_2 retention that occurs in the terminal phase of acute hypoxemic respiratory failure. High and increasing deadspace values may portend an adverse outcome in ARDS.[27] Conversely, improving deadspace has been reported as a propitious sign in prone positioning.[28] In addition to pathologic processes that increase deadspace, changes in V_D/V_T occur during periods of hypovolemia or overdistention by high airway pressures. This phenomenon often is apparent when progressive levels of PEEP are applied to support oxygenation. Conversely, recruitment of functioning lung tissue tends to reduce the deadspace fraction. Examination of the airway pressure tracing under conditions of controlled, constant inspiratory flow ventilation may demonstrate concavity or a clear point of upward inflection, indicating overdistention, accelerated deadspace formation, and escalating risk of barotrauma. Small reductions in PEEP or tidal volume may then dramatically reduce peak cycling pressure and V_D/V_T.

$PaCO_2$ is influenced by CO_2 production, minute ventilation, and the ventilatory deadspace according to the following equation:

$$PaCO_2 = (V_{CO_2}/V_A) \bullet 0.863.$$

In a different form:

$$PaCO_2 = P_B \times V_{CO_2}/[V_E(1 - VD/VT)].$$

where $PaCO_2$, V_A, and P_B refer to alveolar PCO_2, alveolar ventilation, and barometric pressure, respectively. In view of the hyperbolic relationship of $PaCO_2$ to alveolar ventilation (Fig. 61-7), it can be understood that relatively small changes of effective ventilation can profoundly influence $PaCO_2$ and pH when alveolar ventilation is low and $PaCO_2$ is high. Once $PaCO_2$ has climbed to approximately double its normal value, fluctuations of pH and $PaCO_2$, with their attendant adverse effects on hemodynamics and pulmonary artery pressure, place the critically ill patient at risk. Moreover, ventilatory drive is blunted when $PaCO_2$ values are increased. Conversely, small changes in ventilation may cause $PaCO_2$ to plummet. In this context it is interesting to consider tracheal gas insufflation, a novel technique in which fresh gas is injected near the carina during expiration so as to wash the proximal airway free of CO_2 and thereby improve ventilation efficiency.[29] In this setting of extreme hypercapnia, the improvement in alveolar ventilation proves valuable in reducing $PaCO_2$ and its attendant consequences.

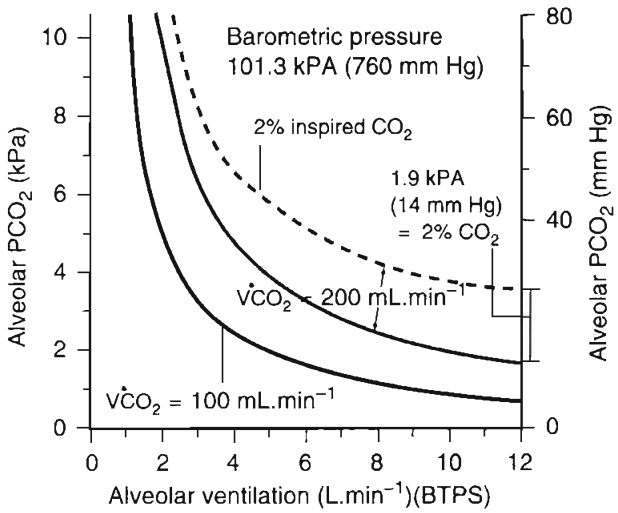

FIGURE 61–7. Relationship of alveolar ventilation and alveolar CO_2. Despite the varying conditions depicted, the hyperbolic function that relates them implies that small changes of effective ventilation translate into marked changes of alveolar PCO_2, and consequently of $PaCO_2$ and pH.

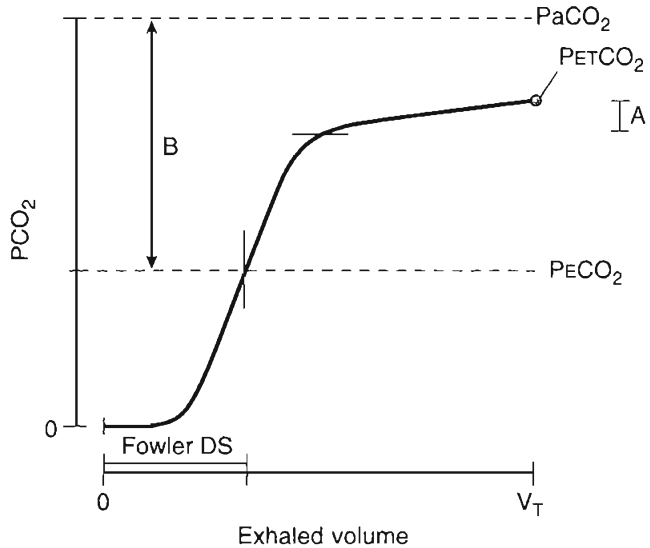

FIGURE 61–8. Capnogram with expired PCO_2 plotted against exhaled volume. Important data can be derived from the expired capnogram obtained under steady-state passive conditions: anatomic or "Fowler" deadspace; physiologic deadspace (the difference [B] between $PaCO_2$ and mixed expired CO_2 $PECO_2$, expressed as a fraction of $PaCO_2$); slope of the "alveolar plateau" (A), an indicator of the heterogeneity of ventilation; and an estimate of CO_2 production (obtained from the product of mixed expired CO_2 referenced to total barometric pressure and exhaled volume).

MONITORING OF EXHALED GAS

Capnography analyzes the CO_2 concentration of the expiratory air stream, plotting CO_2 concentration against time or, more usefully, against exhaled volume. After anatomic deadspace has been cleared, the CO_2 tension rises progressively to its maximal value at end exhalation, a number that reflects the CO_2 tension of mixed alveolar gas. For normal subjects, the transition between phases of the capnogram is sharp and, once achieved, the alveolar plateau rises only gently. Furthermore, when ventilation and perfusion are evenly distributed, as they are in healthy subjects, end-tidal P_{CO_2} ($PETCO_2$) closely approximates $PaCO_2$. ($PETCO_2$ normally underestimates $PaCO_2$ by 1 to 3 mm Hg.) This difference widens when ventilation and perfusion are matched suboptimally, so that alveolar deadspace gas admixes with CO_2-rich gas from well-perfused alveoli.

When plotted against a *volume* axis, as opposed to the more commonly encountered time axis, the capnogram offers data of considerable clinical value. Inspection of such tracings can yield estimates for the "anatomic" (Fowler) deadspace, as well as for the end-tidal and mixed expired CO_2 concentrations (Fig. 61-8). By knowing the barometric pressure, the mixed expired value can be expressed as a percentage of the exhaled volume, which is also immediately available from the tracing. If the V_T remains constant, the product of the $PECO_2$:P_B ratio and V_E is the VCO_2, and the mixed expired CO_2 concentration can be used in the Enghoff-modified Bohr equation to estimate the physiologic deadspace fraction.

As with other monitoring techniques, exhaled CO_2 values must be interpreted cautiously. The normal capnogram is composed of an ascending portion, a plateau, a descending portion, and a baseline. In disease, the sharp distinctions between phases of the capnogram, as well as the slopes of the composite segments, are blurred. Moreover, failure of the airway gas to equilibrate with gas from well-perfused alveoli invalidates $PETCO_2$ as a reflection of $PaCO_2$, especially as respiratory frequency fluctuates. (The $PECO_2$ per cycle, however, remains valid.) End-tidal PCO_2 gives a low range estimate of $PaCO_2$ in virtually all clinical circumstances, so that a high $PETCO_2$ strongly suggests hypoventilation. Abrupt changes in $PETCO_2$ may reflect such acute processes as aspiration or pulmonary embolism, if the $\dot{V}E$ and breathing pattern (f, V_T, and I:E ratio) remain unchanged. Although breath-to-breath fluctuations in $PETCO_2$ can be extreme, the trend of $PETCO_2$ over time helps identify underlying changes in CO_2 exchange.

CONCLUSION

Because effective exchange of respiratory gases is fundamental to cellular function, elaborate mechanisms have evolved to ensure its regulation. When the clinician confronts life-threatening disorder of the heart or lung, mastery of the underlying physiologic principles of gas exchange facilitates appropriate and timely intervention. Careful monitoring of the variables in play is fundamental to successful therapy.

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An instructive overview of the complex interrelationships between the blood and gas flows to the lung.

Chapter 62

ARTERIAL BLOOD GAS INTERPRETATION

Robin L. Gross • R. Phillip Dellinger

KEY POINTS

1. **Arterial blood gases (ABGs) are the gold standard for the assessment of oxygenation** and are particularly valuable in the setting of low flow states or abnormal hemoglobin when SpO_2 does not correlate with PaO_2.
2. Because **many factors lead to variability in ABG results,** standards have been established for the collection and processing of ABG samples.
3. Before assessing the acid-base status of a patient, **one should ensure that ABG and chemistry data are internally consistent by using a modified Henderson-Hasselbalch equation.**
4. **Compensatory changes occur in response to primary metabolic and respiratory disturbances;** alterations from anticipated responses indicate the presence of superimposed metabolic or respiratory aberrations that warrant investigation.
5. In some settings, such as diabetic ketoacidosis, **venous blood gases may be used as an alternative to ABGs.**
6. **In shock states,** PCO_2 differences between ABGs and venous blood, as well as measurement of gastric tonometric pH and PCO_2, may provide information regarding the adequacy of oxygen delivery.

INTERPRETATION OF ARTERIAL BLOOD GASES

INDICATION FOR ABG ANALYSIS

Arterial blood gas analysis became available approximately 50 years ago when techniques developed by Clark,[1] Stow and coworkers,[2] and Severinghaus and Bradley[3] permitted the measurement of the partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$). ABGs have been demonstrated to be the most frequently ordered test in the ICU[4] and have become so essential to the management of critically ill patients that recent critical care guidelines[5] recommend 24-hour ABG availability.

In the appropriate clinical scenario, hypoxemia is suggested by tachypnea, tachycardia, or cyanosis, although these signs are not consistently reliable.[6] With the widespread availability of noninvasive techniques to measure oxygenation, the primary role of ABG has evolved into the assessment of ventilatory and metabolic disturbances. However, when pulse oximetry (PO) cannot be obtained (profound hypotension or cardiac arrest) or would be predicted not to correlate with PaO_2 (known or suspected abnormal hemoglobin values), ABGs may indicate the presence of significant hypoxemia.[7] Clinical changes such as respiratory distress, deterioration in mental status, and shock are clear indications for ABG analysis.[8] Patients with refractory exacerbations of chronic obstructive pulmonary disease (COPD) require ABG analysis to detect hypercapnia and acidosis. However, ABGs are not routinely needed in acute exacerbations of asthma because CO_2 retention does not usually occur until FEV_1,[9] or peak flow[10] falls to less than 25% predicted. Thus, oxygenation is assessed with SaO_2 and only those patients who decompensate require ABG to determine whether they are progressing to respiratory failure. In this setting, repeat ABG samples should be drawn to assess the adequacy of either invasive or noninvasive ventilatory support.

In the setting of severe metabolic derangement, ABGs identify the presence of inadequate respiratory compensation or a mixed acid-base disturbance. However, in certain settings, such as diabetic ketoacidosis, ABGs may not influence treatment.[11] Finally, when immediate hemoglobin and chemistry data are required for the management of surgical and unstable patients, the capability of some analyzers to measure these values along with ABGs provides faster results than most stat laboratories.

COMPLICATIONS

When drawing blood for ABG, efforts to properly position the patient facilitate the procedure and limit complications, which are rare.[12] Fleming and Bowen[13] reported a 0.58% incidence of hematoma after ABG analysis with a 5-minute compression time, which is shortened by using a smaller (25-gauge) needle.[14] Other complications include vasospasm,[15] arterial aneurysm, and fibrosis.[16] Infection is extremely rare.[13] Pain is usually not severe and may be minimized by local anesthesia without raising the level of difficulty or length of time required to complete the procedure.[17]

Arterial line placement is associated with more frequent ABGs,[4] and the catheter size and material may contribute to arterial thrombosis (less occlusion with Teflon than polyethylene), particularly in the setting of decreased perfusion.[18] Iatrogenic anemia[19] may be minimized by using the minimal necessary discard volume (twice the catheter deadspace or 1 mL of blood)[20] and collecting the smallest sample size necessary. Although newer instruments are capable of analyzing

microliter sample sizes, the recommended minimum sample amount is 1 mL of blood.[21]

TECHNIQUE/EQUIPMENT

ABG analysis is typically performed on whole blood. PaO_2, $PaCO_2$, and pH are directly measured with standard electrodes and digital analyzers; oxygen saturation is calculated from standard O_2 dissociation curves and may be directly measured with a co-oximeter. Bicarbonate (HCO_3^-) concentration is calculated using the Henderson-Hasselbalch equation:

$$pH = pK_A + \log\{[HCO_3^-]/[CO_2]\}$$

where pK_A is the negative logarithm of the dissociation constant of carbonic acid.

Base excess (BE, the amount of base necessary to return pH to 7.4) is also calculated.

FACTORS THAT MAY ALTER RESULTS

Inconsistent results with ABGs occur owing to a number of factors. Intrasubject variability may affect PaO_2, $PaCO_2$,[22-24] and pH.[24] Severe hypotension[25] may require forceful aspiration of the sample, and results, particularly for PaO_2, may be falsely low.[26] Hyperventilation resulting from anxiety and/or pain may acutely alter results from baseline values.[15,27] Leukocytosis and thrombocytosis accelerate the decline of PaO_2 and pH and elevation of $PaCO_2$[28] within a stored sample. This PaO_2 decrease is more pronounced at higher PaO_2 levels, is attributable to cellular oxygen consumption, and may be attenuated when samples are stored at colder temperatures.[28-30] Red blood cell glycolysis may generate lactic acid[31] and change pH.

Significant increases in $PaCO_2$ and decreases in pH occur when samples are stored at room temperature for more than 20 minutes.[32] At lower temperatures, the pK′ for carbonic acid[33] and pH rise and $PaCO_2$[34] and PaO_2 fall.[35] Here, the solubility of O_2 increases and hemoglobin has greater affinity for O_2.[28] However, although measured PaO_2 is elevated, O_2 saturation remains constant.[36] Whereas temperature correction formulas and nomograms were previously applied to pH, $PaCO_2$, and PaO_2,[36-38] newer analyzers can automatically correct these values to patient temperature. However, temperature correction is not always performed for PaO_2[39] and is not required for pH and $PaCO_2$.[40]

Collection equipment and technique influence results. Increased deadspace in the syringe lowers $PaCO_2$ content,[41] and both $PaCO_2$[28] and PaO_2 (particularly at high O_2 tensions)[42] may diffuse out of plastic syringes.[43] Needle size rarely causes variability,[25] and the smaller (25 g) needle is recommended, because it causes less patient discomfort.[14] Heparin is usually added to prevent coagulation, and dilution with older liquid solutions caused spuriously low $PaCO_2$.[41,44,45] Today, dry (sodium or lithium) heparin in ABG kits may interfere with electrolyte measurement and, when concentrated, may lower pH.[46] Sample preparation is important[26] because air bubbles falsely elevate PaO_2.[32] Also, the timing of ABG collection relative to ventilator changes should permit equilibration of alveolar and arterial P_{O_2}.[47] It has been suggested that PaO_2 values may equilibrate within 10 minutes after FiO_2 adjustment in stable patients,[48] although this may not be the case with either PaO_2 or P_{CO_2} if changes in minute ventilation or positive end-expiratory pressure occur.[49] Also, patients with COPD require a longer equilibration period[50] before ABG draw.

Variation among ABG analyzers is assessed by using bias (the consistent variation of measurement from a standard) and precision (the standard deviation of this variation).[51,52] The accuracy (a combination of precision and bias) of blood gas analyzers for PaO_2 measurement may differ by 10% or more when tested against standard tonometer values.[53] Aside from interlaboratory variation, errors in calibration and electrode contamination with protein[8] or other fluids[54] may alter results.[55]

STANDARDS

Standards are recommended for sample collection[15,56] and analysis of ABG specimens. Blood gases should be drawn 20 to 30 minutes after ventilator setting changes.[15] The International Federation of Clinical Chemistry[31] recommends that ABG drawn in plastic syringes should be measured immediately to ensure accurate PaO_2 measurement; glass syringes (although rarely used) may allow more accurate measurement when PaO_2 is greater than 200 mm Hg. Either sodium or lithium heparinate should comprise less than 5% of the sample. The specimen should be collected anaerobically with immediate removal of air bubbles.[31] Universal precautions should be maintained at all times.[15] If the sample is stored, it should be on ice and remixed before analysis.[15]

The U.S. Department of Health and Human Services has published accepted parameters for limits of ABG error as ± 0.04 units for pH, ± 5.0 mm Hg (or 8%; whichever is greater) for $PaCO_2$, and ± 3.0 interlaboratory standard deviation of the ABG analyzer for PaO_2.[57] Laboratories should routinely practice quality control measures[58] and perform proficiency testing with fluorocarbon-based control solutions[59] or tonometry.[60] Newer electrodes have less drift and usually perform calibrations before measurement of each sample.[61]

ABG VALIDITY

Despite the adherence to collection and measurement standards, it is important to ascertain that the data are consistent before proceeding to interpretation of results. Kassirir and Bleich[62] demonstrated that this could be done using a modified Henderson-Hasselbalch equation by determining the proton concentration $[H^+]$:

$$[H^+] = 24 \bullet \{[PaCO_2]/[HCO_3^-]\}$$

where 24 is a constant that reflects a combination of the solubility coefficient of CO_2 and the pK′. $[H^+]$ is used to estimate the pH; a divergence of 1 nmol/L from the baseline of 40 will cause the pH to change reciprocally by approximately 0.01 unit[62] within the range of pH 7.1 to 7.5. Data may not correlate owing to breach of collection procedure, specimen mislabeling, laboratory error, or inappropriate timing of chemistry and ABG sample collection after therapeutic interventions. If this is the case (i.e., the calculated pH differs from the measured pH) the specimens should be redrawn before proceeding with further calculations.

TABLE 62–1. NORMAL ARTERIAL BLOOD GAS VALUES ON ROOM AIR

	Normal Values
pH	7.35 to 7.45
$PaCO_2$	35 to 45 mm Hg
PaO_2	86 to 100 mm Hg
HCO_3^-	22 to 26 mmol/L
Base excess	0 mmol/L
O_2 saturation	94% to 100%

NORMAL VALUES

Normal blood gas values are shown in Table 62-1. Although physiologic deadspace (the amount of ventilated air that does not participate in gas exchange)[63] increases with age, $PaCO_2$ usually does not decline.[64,65] Alveolar oxygen tension (P_AO_2) remains constant, but PaO_2 decreases with age,[66] probably because of ventilation/perfusion ($\dot{V}/\dot{Q}$) inequalities.[67-69] Thus, several equations have been suggested to correct measurements,[67-69] and PaO_2 may be roughly estimated using 100 mm Hg − 0.3 × age (years). Recently, Crapo assessed values with newer ABG analyzers and demonstrated that PaO_2 generally declines by 0.245 mm Hg/yr after age 25 and should be corrected for atmospheric pressure.[40] Although weight may affect PaO_2 by altering $\dot{V}/\dot{Q}$ relationships in some age groups,[68] correction formulas are not necessary.

OXYGENATION

NORMAL RELATIONSHIPS AND DELIVERY

As mentioned, ABG permits the assessment of oxygenation, which is dependent on O_2 content, delivery, and utilization. O_2 content is calculated using the following equation:

$$O_2 \text{ content} = \text{Hgb (g/dL)} \times O_2 \text{ saturation (\%)} \times 1.39 + (PaO_2 \times 0.0031)$$

where Hgb is hemoglobin and 1.39 represents the amount of O_2 (mL) carried by hemoglobin (g). Oxygen delivery is:

$$VDO_2 \text{ (mL/min/M}^2\text{)} = O_2 \text{ content} \times CO \text{ (L/min)}$$

where CO is cardiac output. Thus, O_2 saturation, and not PaO_2, is the parameter of oxygenation that contributes most to O_2 delivery.

The relationship between PaO_2 and SaO_2 is demonstrated by the oxygen-hemoglobin dissociation curve (Fig. 62-1),[70] which is "S" shaped owing to allosteric alterations in the O_2-hemoglobin complex.[71] Although SaO_2 reflects PaO_2 on the steep portion of the curve, small variations or errors in SaO_2 produce large variations in PaO_2 on the higher segment.[72] Factors that shift the curve to the right facilitate the release of O_2 into tissues by decreasing the affinity of hemoglobin for O_2 and include higher temperature, 2,3-diphosphoglycerate (DPG), $[H^+]$, and CO_2. Carbon monoxide alters both the position (left shift) and contour of the curve in that it competitively binds hemoglobin to displace O_2 from binding sites,[73] resulting in less available oxygen for tissue delivery.

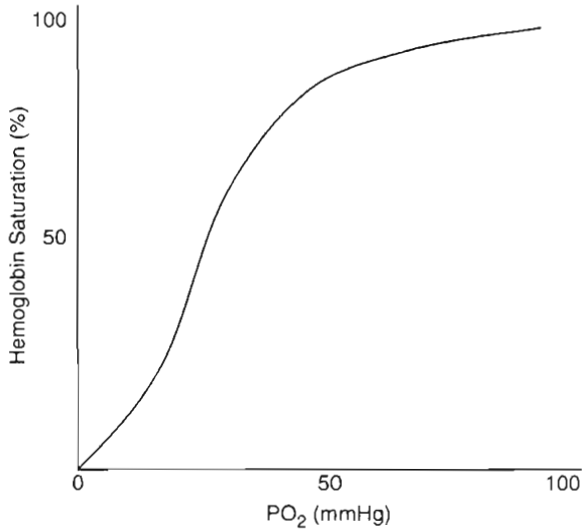

FIGURE 62–1. The oxygen-hemoglobin dissociation curve. Oxygen delivery to tissues is increased when the curve is shifted to the right by acidosis, increased temperature, and increased 2,3-diphosphoglycerate. On the higher portion of the curve, small variations in SaO_2 produce large variations in PaO_2.

HYPOXEMIA

Hypoxemia differs from hypoxia in that hypoxemia defines decreased PaO_2 whereas hypoxia defines inadequate cellular oxygen uptake or utilization. Hypoxemia results from decreased PIO_2 (secondary to high altitude or decreased FIO_2), shunt (intracardiac or intrapulmonary), low $\dot{V}/\dot{Q}$ ratio (typically called $\dot{V}/\dot{Q}$ mismatch), and diffusion abnormalities. Cellular hypoxia results from decreased cardiac output or decreased O_2 content, that is hypoxemia, decreased hemoglobin, or abnormal hemoglobin.[7] Hypoventilation also causes hypoxemia to a lesser degree. Some disease states have more than one cause of hypoxemia, such as acute respiratory distress syndrome (ARDS), in which aberrant $\dot{V}/\dot{Q}$ relationships[74] occur in addition to shunt. Abnormalities in $\dot{V}/\dot{Q}$ relationships account for most episodes of hypoxemia.[75] Arterial blood gases are particularly useful in assessing a shunt when results collected at room air are compared with those at 100% FIO_2. Several shunt equations have been proposed. The classic equation requires a pulmonary arterial (PA) catheter:

$$Qs/Qt = (CcO_2' - CaO_2)/(CcO_2' - CvO_2)$$

where Qs is blood flow through the shunt, Qt is total blood flow, CcO_2' is the oxygen content of pulmonary capillary blood, CaO_2 is the oxygen content of arterial blood, and CvO_2 is the oxygen content of mixed venous blood. The estimated shunt equation does not require a PA catheter and assumes a $C(a\text{-}v)O_2$ of 3.5 vol%[76]:

$$Qs/Qt = (CcO_2' - CaO_2)/3.5 + (CcO_2' - CaO_2)$$

and the modified equation makes the above assumption as well as a PaO_2 greater than or equal to 100 mm Hg:

$$Qs/Qt = [(P_AO_2 - PaO_2) \times 0.003]/[3.5 + (P_AO_2 - PaO_2) \times 0.003]$$

Despite little clinically significant difference between the results of these equations, the limits of agreement are wide,

so a PA catheter with the classic shunt equation is preferred when assessing hemodynamically unstable patients.[77] It should be recognized that the presence of carbon monoxide may alter results, because the calculated shunt value may be erroneously high if a co-oximeter is not used to estimate O_2 content.[72]

PaO_2/FiO_2 RELATIONSHIP

Hypoxemia may be assessed using the PaO_2/FiO_2 ratio, which varies based on its point on the O_2-hemoglobin dissociation curve, lung $\dot{V}/\dot{Q}$ relationships,[78] and the degree of shunt.[75] For example, in the setting of a normal or high $\dot{V}/\dot{Q}$ ratio, as FiO_2 is raised, PaO_2/FiO_2 increases and then stabilizes. However, the same rise in FiO_2 in an alveolus with a low $\dot{V}/\dot{Q}$ ratio might initially decrease PaO_2/FiO_2, particularly on the steep portion of the curve.[78] In this alveolus, additional increases in FiO_2 cause absorption atelectasis[79] and subsequent alterations in $\dot{V}/\dot{Q}$ relationships due to vascular adaptation.[80] The result is a variable PaO_2/FiO_2 ratio that becomes a less reliable index of oxygenation if measured at only one point in time.[81]

ALVEOLAR-ARTERIAL OXYGEN TENSION DIFFERENCE

The alveolar-arterial difference ($AaDO_2$) considers the impact of the amount of CO_2 present in the blood and alveoli on O_2 exchange. The alveolar air equation is used to calculate the ideal alveolar oxygen tension (PAO_2):

$$PAO_2 = PiO_2 - PaCO_2 \times (FiO_2 + [1 - FiO_2]/RQ)$$

where RQ is the respiratory exchange ratio (the ratio of CO_2 production to O_2 consumption) and is assumed to be 0.8. Here,

$$PiO_2 = FiO_2\,(PB - PH_2O)$$

where PB is barometric pressure and PH_2O is water vapor pressure. At sea level, ambient pressure is 760 mm Hg and PH_2O = 47 mm Hg.

A more simplified version is used in common practice:

$$PAO_2 = PiO_2 - PaCO_2/R$$

$AaDO_2$ is then calculated using the PaO_2 from the ABG:

$$AaDO_2 = PAO_2 - PaO_2$$

In the setting of increased $PaCO_2$ and normal oxygen exchange, the $AaDO_2$ should be normal. Thus, an elevated $AaDO_2$ warrants a search for a cause of hypoxemia other than hypoventilation.[82] The normal value is 3 to 16 mm Hg and increases with age because of $\dot{V}/\dot{Q}$ inequalities[40,64,66] and increased closing volumes.[65] Factors that influence $AaDO_2$ calculation include temperature (hypothermia may increase $AaDO_2$)[83] and changes in the respiratory exchange ratio (R). R may exhibit both intrasubject[84] and intersubject[85] variability and be significantly altered in the setting of hyperventilation.[27] Moreover, in COPD patients with significant hypercapnia, the $AaDO_2$ may be misleading because normal values may mask underlying sources of hypoxemia, such as shunt.[86] Although $AaDO_2$ increases with higher FiO_2 levels, normal $AaDO_2$ values are not known for intermediate ranges of FiO_2[47] leading some investigators to suggest other methods for assessing hypoxemia.

OTHER INDICES OF OXYGENATION

The $a/APaO_2$ ratio may be used in the assessment of oxygenation:

$$a/APO_2 = 1 - AaDO_2/PAO_2$$

While some suggest that it is a better index of oxygenation than $AaDO_2$,[47] this value has limitations. a/APO_2 appears to be more stable than $AaDO_2$ in the setting of respiratory failure with a large shunt but is less accurate in the setting of low $\dot{V}/\dot{Q}$ ratio or when PaO_2 is greater than 100 mm Hg.[87] In some cases the a/APO_2 may be used to predict PaO_2[88] during FiO_2 adjustment (and thus obviate the need for additional ABG), but at times the ratio may overestimate PaO_2.[89]

Another value, the respiratory index, is occasionally used:

$$\text{Respiratory index} = P[A\text{-}a]O_2/PaO_2$$

Like $AaDO_2$ and a/APO_2, it incorporates the effect of $PaCO_2$ by including PAO_2. Although usually minimal, the effect of $PaCO_2$ may become important in the setting of permissive hypercapnia if FiO_2 is not adequate.[75,90] Because the relationship between PaO_2 and oxygen content is not linear, it has been suggested that a preferred index of oxygenation would be independent of FiO_2.[81]

ASSESSMENT OF ACID-BASE DISTURBANCES

NORMAL ACID-BASE RELATIONSHIPS

Interpretation of ABGs includes the assessment of acid-base status. Whereas acidosis and alkalosis reflect accumulation of acid or base, acidemia is defined as a pH less than 7.35 and alkalemia as a pH greater than 7.45. Detailed reviews of acid-base balance and metabolic disturbances are presented in Chapters 12 and 127, respectively. ABG reports often include the base excess (BE), which is not dependent on the respiratory physiology (i.e., $PaCO_2$)[91] and therefore provides information regarding the metabolic acid-base status of the patient. Siggaard-Anderson[92] first proposed evaluating BE in whole blood, defined as the quantity (mM) of strong acid needed to restore pH to 7.4 in a blood sample equilibrated at $PaCO_2$ = 40 mm Hg using the Van Slyke equation[91,93]:

$$BE = \{[HCO_3^-] - 24.4 + (2.3 \times [Hgb] + 7.7) \times (pH - 7.4)\} \times (1 - 0.023 \times [Hgb])$$

A negative BE is called a base deficit. The BE may be further adjusted to eliminate the effects of ventilation and $PaCO_2$ alterations on the value; thus the standard base excess (SBE) is usually reported by most ABG analyzers using Hgb = 3.1 mM (5 g/dL).[94] However, recently the original BE has been shown to be reliable, despite changes in $PaCO_2$ or Hgb.[91] The relationship between $PaCO_2$ and ΔSBE has been described[95]:

$$\text{Acute } PaCO_2\ \Delta\text{: } \Delta SBE = 0 \times \Delta PaCO_2$$

Chronic $PaCO_2$ Δ: $\Delta SBE = 0.4 \times \Delta PaCO_2$

Metabolic acidosis: $\Delta PaCO_2 = 1.0 \times \Delta SBE$

Metabolic alkalosis: $\Delta PaCO_2 = 0.6 \times \Delta SBE$

Acid-base relationships are affected by protein values, particularly albumin. Hypoproteinemia is associated with elevation of chloride[96] and low calculated anion gap[97] (see Chapter 127) as well as mild hyperventilation.[98] Thus, the protein state should be considered when using ABG and chemistry results to assess the acid-base status of a patient.

DISTURBANCES OF VENTILATION

Assessment of Normal Ventilation

Ventilation is controlled by the brainstem's response to chemoreceptor feedback. The central chemoreceptor is located near the medulla and responds to extracellular and cerebrospinal fluid pH[99]; variations in $PaCO_2$ therefore affect the central receptor through pH alterations, which then effect ventilatory changes through the medulla. The peripheral chemoreceptors include the carotid bodies, which respond to decreases in PaO_2 and pH and increases in $PaCO_2$, and the aortic bodies, which play a less active role in humans.[100] The ventilatory response to both hypoxia and hypercapnia varies among individuals and may be influenced by genetic factors.[101,102] Significance bands describing responses to respiratory acidosis[103] and alkalosis[104] are available for acid-base analysis, although they may not adequately detect mixed respiratory and metabolic disorders.[104]

Because the estimation of alveolar ventilation (V_A) by patient observation is extremely difficult, hypoventilation may go unnoticed.[105] Thus, the ABG analysis is essential because $PaCO_2$ is used for the calculation:

$$V_A = K \cdot V_{CO_2}/P_ACO_2$$

where K = 0.863, V_{CO_2} is CO_2 production, and V_A is alveolar ventilation. P_ACO_2 is assumed to be equal to $PaCO_2$ because CO_2 readily diffuses across the alveolar-capillary membrane.[84] However, in the presence of significant $\dot{V}/\dot{Q}$ abnormalities or shunt, $PaCO_2$ may be lower than P_ACO_2.[63] V_A is influenced by several factors, as demonstrated by the following equation:

$$V_A = f\,(V_T - V_D)$$

where f is frequency, V_T is tidal volume, and V_D is deadspace volume. Thus, factors that decrease f or V_T will decrease V_A and increase P_ACO_2. Physiologic deadspace consists of anatomic and alveolar deadspace and can be estimated with the Bohr equation:

$$V_D/V_T = [P_ACO_2 - P_ECO_2]/P_ACO_2$$

where P_ECO_2 is expired CO_2.

Ventilation usually increases with hypoxemia. Whereas the relationship between oxygen content (CaO_2) and ventilation is linear, that of ventilation and P_AO_2 is hyperbolic (similar to the O_2-Hgb dissociation curve).[106] The ventilatory response to hypoxemia is increased in the setting of acute hypercapnia and decreased in the setting of acute hypocapnia,[106] when the inverse linear correlation between SaO_2 and ventilation becomes nonlinear.[107] The ventilatory response to hypoxemia is also decreased during chronic exposure to high altitude.[108] O_2 influences CO_2 through the Haldane effect[109] because hemoglobin collects H^+ ions easily after carbonic acid dissociation. Thus, in the setting of lower hemoglobin O_2 saturation, a particular $PaCO_2$ level will be associated with a higher CO_2 content.

TABLE 62-2. DISORDERS ASSOCIATED WITH RESPIRATORY ACIDOSIS

Central respiratory depression (drug overdose, obesity hypoventilation syndrome)
Neuromuscular disorders (Guillain-Barré, neuropathy, myopathy, malnutrition)
Parenchymal disorders progressing to respiratory failure (pneumonia, ARDS, pulmonary edema)
Metabolic disorders (hypophosphatemia)
Abnormalities of chest wall motion (kyphoscoliosis)
Disturbances in ventilation/perfusion
Airflow obstruction (asthma or COPD exacerbation)
Upper airway obstruction (foreign body, laryngospasm)
Iatrogenic (permissive hypercapnia or inadequate ventilator settings)
Increased CO_2 production (carbohydrate load, malignant hyperthermia)
Compensation for metabolic alkalosis

Respiratory Acidosis

Causes of hypoventilation and subsequent respiratory acidosis are listed in Table 62-2. Patients with CO_2 retention may present with lethargy, confusion, and, in some cases, agitation. Elevated $PaCO_2$ is also associated with central nervous system (CNS) toxicity (seizures), cardiac arrhythmias, and pulmonary vasoconstriction.

In patients without COPD, acute respiratory failure may be defined as a state in which PaO_2 falls below the predicted normal range for the patient's age or $PaCO_2$ is above 50 mm Hg (in the absence of compensation for metabolic alkalemia).[110] When respiratory failure occurs secondary to $\dot{V}/\dot{Q}$ inequalities, eventual muscle fatigue often leads to respiratory muscle failure.[111] In patients with COPD during acute exacerbations, hypercapnia due to O_2 administration occurs because of several factors and not simply respiratory drive suppression. Although minute ventilation initially decreases, $\dot{V}/\dot{Q}$ inequality is a major factor.[112,113] Loss of pulmonary vasoconstriction occurs,[79] and alveolar deadspace increases.[114] Impaired respiratory muscle function secondary to hyperinflation also contributes to respiratory failure.[115]

Although deleterious effects may occur with acute hypercapnia, permissive hypercapnia[90] is used quite frequently in the treatment of mechanically ventilated patients with ARDS. Although shunt is increased,[116] there are usually few or no untoward effects. In fact, it is possible that hypercapnia, through the resulting acidosis, improves oxygen exchange in areas of $\dot{V}/\dot{Q}$ inequality by increasing vasoconstriction.[25] Also, acidosis may be protective in certain settings by decreasing inflammation.[117] Thus, treatment of respiratory acidosis should be individualized and, when appropriate, targeted to facilitate CO_2 elimination (e.g., intubation) or decrease CO_2 production.

Respiratory Alkalosis

Causes for respiratory alkalosis are listed in Table 62-3. During hyperventilation, equilibration of PaO_2 and $PaCO_2$ requires several minutes because of body stores, which are

TABLE 62–3. DISORDERS ASSOCIATED WITH RESPIRATORY ALKALOSIS

Central neurologic insults with high respiratory drive (intracranial hemorrhage, cerebrovascular accident, trauma)
Hypoxemia
Pain
Anxiety
Salicylate intoxication
Sepsis
Iatrogenic (hyperventilation on ventilator)
End-stage liver disease
Pregnancy
Fever
High altitude
Compensation for metabolic acidosis

larger for $PaCO_2$ due to blood and interstitial fluid bicarbonate.[118] The effect of hyperventilation on PaO_2 is usually small.[119] However, as mentioned, the ventilatory response to hypoxemia is blunted during hypocapnia, possibly owing to the effect of PCO_2 (and thus pH) on the central chemoreceptor.[119] The converse is also true.

Whether respiratory or metabolic, alkalosis is associated with increased mortality, particularly when the pH exceeds 7.65.[120] Very high pH levels are often due to mixed metabolic and respiratory disorders or high minute ventilation due to inappropriate ventilator settings. Severe alkalosis is associated with decreased hypoxic pulmonary vasoconstriction, abnormalities in cardiac contractility, and seizures. However, in the proper setting, alkalosis may simply represent a normal physiologic response and treatment is not always necessary. In fact, the cerebral vasoconstriction produced by lesser degrees of hypocapnia may be therapeutic in patients with neurologic injury and high intracranial pressures.

EXPECTED COMPENSATORY CHANGES IN RESPONSE TO METABOLIC AND RESPIRATORY ABNORMALITIES

Compensatory mechanisms are much stronger for acidosis than alkalosis.[121] The body's buffering systems include bicarbonate/carbonic acid, erythrocytes, tissues, and plasma proteins.[121,122]

Respiratory Acidosis

In acute hypercapnia, the relationship between $[H^+]$ and PCO_2 is linear.[103] Early metabolic buffering mechanisms are primarily extrarenal[103] with small changes in bicarbonate. This response is influenced by the underlying metabolic state. In the canine model,[123] chronic metabolic acidosis is associated with a larger increase in H^+ and HCO_3^- whereas chronic metabolic alkalosis is associated with a smaller increase. The underlying ventilatory state is also important. Chronic respiratory acidosis results in higher compensatory HCO_3^- levels and smaller alterations of pH at the central chemoreceptor, causing a reduced ventilatory response to acute hypercapnia.[63]

Although chronic hypercapnia is associated with a better compensatory response than acute hypercapnia, the pH does not completely normalize.[103] In the canine model,[124] chronic hypercapnia causes the bicarbonate concentration to rise initially and then reach a steady state within 3 to 5 days. The rise in H^+ concentration correlates linearly with the change in $PaCO_2$. In patients with lung disease, bicarbonate can rise to a level of 65 mmol/L[122] and acidosis will develop after that point. Until HCO_3^- reaches this level, the pH may actually be alkalotic (possibly secondary to treatment). Thus, ABG interpretation of the primary process may be difficult (i.e., whether there is a primary metabolic alkalosis or primary respiratory acidosis with metabolic compensation).[122]

The expected compensatory changes of HCO_3^- and H^+ in response to acute respiratory acidosis are[125]:

$$10\ \Delta[HCO_3^-] = \Delta PaCO_2 \text{ and } \Delta[H^+] = 0.8\ \Delta PaCO_2[103]$$

For chronic respiratory acidosis, the expected HCO_3^- and H^+ are:

$$10\ \Delta[HCO_3^-] = 3.5\ PaCO_2 \text{ and } \Delta[H^+] = 0.3\ \Delta PaCO_2[124]$$

Measured values that do not correlate with calculated values suggest the presence of an underlying metabolic acidosis or alkalosis.

Respiratory Alkalosis

In acute hypocapnia, HCO_3^- initially decreases, owing to buffering by hemoglobin and tissue,[104] followed by kidney buffering. Chronic hypocapnia reduces bicarbonate levels and decreases renal acid excretion, although patients initially remain alkalemic because the metabolic response is weaker than the respiratory response.[126] In recovery, as $PaCO_2$ normalizes there is an initial metabolic acidosis, followed by acid excretion that is associated with cation retention.[127] The underlying metabolic state may influence the compensatory response to chronic hypocapnia. For example, a preexisting metabolic acidosis inhibits the compensatory decrease in renal acid excretion[126] and a chronic metabolic alkalosis may result in a larger decline in HCO_3^- in response to hypocapia.[128] However, in the absence of an underlying metabolic disorder, the expected HCO_3^- and H^+ changes for acute respiratory alkalosis may be estimated[125]:

$$10\ \Delta[HCO_3^-] = 2\ \Delta PaCO_2 \text{ and } \Delta[H^+] = 0.8\ \Delta PaCO_2[104]$$

For chronic respiratory alkalosis, the compensatory changes are:

$$10\ \Delta[HCO_3^-] = 5\ \Delta PaCO_2 \text{ and } \Delta[H^+] = 0.17\ \Delta PaCO_2[127]$$

Results that differ from calculated values indicate the presence of an underlying metabolic disturbance, and a cause should be sought.

Metabolic Acidosis

Because respiratory compensation and the fall in $PaCO_2$ are rapid, determining whether a metabolic acidosis is acute or chronic is difficult.[95] The expected $PaCO_2$ may be estimated using Winter's formula[129]:

$$PaCO_2 = 1.5[HCO_3^-] + 8 \pm 2$$

Thus, a measured PCO_2 above or below the calculated $PaCO_2$ value indicates the presence of an additional respiratory acidosis or alkalosis, respectively.

Metabolic Alkalosis

The compensatory mechanism for metabolic alkalosis is hypoventilation, accomplished primarily by decreasing

tidal volume.[130] This compensatory mechanism is the weakest of all because profound compensation is limited by hypoxemia. A suggested formula for estimation of $PaCO_2$ is:

$$PaCO_2 = 0.9[HCO_3^-] \pm 15$$

As discussed earlier, if measured $PaCO_2$ differs from the calculated value, an additional respiratory disturbance exists.

AN ALGORITHMIC APPROACH TO ABG INTERPRETATION

The Stewart approach[131] to acid-base disorders provides a rational method for the assessment of a patient's acid-base status and is discussed in Chapter 12. Here we present an alternative approach. When interpreting ABG data, one should ask the following questions:

1. Are the data internally consistent? Kassirer's[62] modified Henderson-Hasselbalch equation is used to predict pH by calculating the expected $[H^+]$ and pH.
2. What is the underlying acid-base abnormality? The pH will almost always reflect the primary abnormality, unless a respiratory alkalosis coexists with an underlying metabolic acidosis.[126]
3. Is the primary problem an acidosis? If yes, is it metabolic or respiratory?
4. If a metabolic acidosis is present, is there an anion gap (AG) (i.e., is the acidosis caused by unmeasured anions?)[132]

$$AG = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$$

   Usually, the AG is calculated without K^+ and a normal value is 8 to 12 mEq/L. Causes of an AG acidosis are discussed in Chapter 127.
5. In the setting of an AG, is an additional metabolic disturbance present? Calculate the delta (Δ) gap, that is, the difference between this AG and a normal AG: Δ gap = AG − 12. The Δ gap, when added to the measured $[HCO_3^-]$ should equal 24. If the result is less than 24, a non-AG acidosis is present; and if it is greater than 24, a metabolic alkalosis exists.
6. Is the respiratory process purely compensatory, or is there an underlying respiratory acidosis or alkalosis? Use Winter's formula to calculate the expected $PaCO_2$ in the setting of pure compensation.
7. Is the primary problem an alkalosis? If so, is it respiratory and/or metabolic? The BE is helpful in this setting. Is it chronic or acute?
8. Determine the underlying causes for the metabolic and respiratory derangements.

OTHER ISSUES

VENOUS BLOOD ANALYSIS AS AN ALTERNATIVE TO ABG ANALYSIS

Mixed venous blood ($S\bar{v}O_2$) represents an admixture of blood from many tissues. Normal $S\bar{v}O_2$ is 65%, and lower values may represent decreased oxygen delivery or aberrant tissue oxygen uptake.[7] Mixed venous blood gases have been demonstrated to be superior to arterial blood gases for the diagnosis of early hemorrhagic shock[133] because the early low pH that is seen in mixed venous blood may not be apparent in arterial blood. During cardiac arrest,[134] an elevated $PaCO_2$ may be detected in mixed venous blood before being mixed in arterial blood. This is thought to be due to decreased pulmonary CO_2 clearance and possibly increased CO_2 production.[134] Continuous $S\bar{v}O_2$ may be used as a monitor of oxygen delivery. However, $S\bar{v}O_2$ monitors measure values on the steeper part of the HbO_2 dissociation curve, so a larger error in oxygen content will be introduced with small errors in $S\bar{v}O_2$ measurements.[72] Thus, if $S\bar{v}O_2$ results are questionable, a sample of blood should be drawn to directly measure mixed venous oxygen content.

Central venous blood (CVB) can be used for screening because normal CVB values usually reflect normal ABG values.[135] Generally, CVB pH is lower and P_{CO_2} is higher than arterial blood. Trends in venous pH measurements are also useful in the management of diabetic ketoacidosis when ABGs are not routinely ordered.

ARTERIAL-TONOMETRIC PCO_2 GAP

In shock states (particularly sepsis) gastric tonometry may signal early inadequate O_2 delivery before other hemodynamic parameters because splanchnic O_2 consumption rises. The gastric mucosa subsequently experiences regional hypoperfusion as blood flow is directed toward vital organs.[136] A nasogastric balloon with a saline- or air-filled tonometer measures the PCO_2 of the fluid in the gut lumen, which is believed to reflect the PCO_2 of the mucosa. The mucosal pH (pH_i) is then calculated using the blood bicarbonate value (assumed to be equal to mucosal bicarbonate) and a known time-dependent equilibration factor in the Henderson-Hasselbalch equation.[137]

A normal pHi is 7.35 or greater; decreased levels are associated with higher mortality.[136] It has been suggested that pHi-guided treatment may improve survival,[138] although this has not been consistently demonstrated. The pHi has limitations because it is altered by fluctuations in $PaCO_2$[139] and SBE[140]; although HCO_3^- is used to calculate the pHi, it is not localized to the gastric mucosa.[137] For these reasons, it has been suggested that the $PtCO_2$-$PaCO_2$ difference (the PCO_2 gap) may be a better indicator of gastric ischemia.[139-141] A high PCO_2 gap early in admission may predict multisystem organ failure and mortality,[142,143] although this has not been consistently demonstrated. The effect of vasoactive medication on tonometry parameters is also unpredictable and may vary based on disease severity.[144,145] Although gastric tonometry may facilitate the management of critically ill patients, it is expensive and has not gained widespread acceptance for clinical use.

VENOUS-ARTERIAL PCO_2 GRADIENT

As mentioned previously, during tissue hypoperfusion, the difference in pH and PCO_2 between venous and arterial blood may be significant.[134] The PCO_2 gradient ($VAPCO_2$) increases as cardiac index decreases secondary to decreased elimination of CO_2 at the tissue level,[146,147] resulting in venous hypercapnia and arterial hypocapnia.[148] In animal models, both $VAPCO_2$ and VApH increase as oxygen delivery (DO_2) declines, and this response is augmented as critical

DO_2 is reached.[147,149] In septic shock an elevated $VAPCO_2$ is seen in those patients with low cardiac output as well as those with pulmonary disease who cannot eliminate CO_2.[150] In patients with cardiogenic shock, $VAPCO_2$ decreases as hemodynamic variables improve with dobutamine.[151] This has led to the suggestion that this ratio be used to determine whether cardiac output is sufficient for the degree of oxygen demand[146,151] in the setting of hypoperfusion.

OTHER SURROGATE MONITORS

END-TIDAL CO_2 AS AN ESTIMATE OF $PaCO_2$

Whereas capnometry measures the CO_2 concentration in a gas, capnography is a graphic representation of CO_2 at the end of the alveolar plateau, or end-tidal CO_2 ($PetCO_2$).[152] Generally, this value correlates with $PaCO_2$.[152] However, changes in $PetCO_2$ do not always reflect those of $PaCO_2$ owing to the effects of $\dot{V}/\dot{Q}$ inequalities, breathing patterns,[153] and particularly deadspace; in low flow states,[154] when poorly perfused units are ventilated, the $PetCO_2$ may not adequately reflect the $PaCO_2$.

PULSE OXIMETRY AS AN ESTIMATE OF PaO_2

Pulse oximetry uses a photodetector and light source to measure SpO_2 by calculating the differential absorption of light by oxygenated and reduced capillary hemoglobin. Its use is associated with fewer ABGs[155,156] and may reduce cost when the assessment oxygenation is important and knowledge of ventilation and acid-base status is not necessary. Manufacturers usually recommend 95% of PO readings be within 5% of the co-oximeter reading. Inconsistency with ABG readings is usually due to motion artifact, hypothermia, or hypotension[157] with poor perfusion. With high PaO_2, just as with SaO_2, minimal SpO_2 error may be associated with large error in PaO_2, owing to the shape of the oxygen dissociation curve. Also, readings may be altered by the presence of carboxyhemoglobin and methemoglobin. In any of these settings where SpO_2 is thought not to correlate with ABG values, samples should be drawn for ABG analysis.

TRANSCUTANEOUS MONITORS

$PtcO_2$ and $PtcCO_2$ depend on arterial values, hemoglobin concentration, the oxygen-hemoglobin dissociation curve, skin thickness, and adequate blood flow.[158] Although TcO_2 correlates with PaO_2, wide variations have been reported,[159] leading some to suggest analysis of the $PtcO_2$ index [$P(a\text{-}tc)O_2/PO_2$], because it may reflect decreased perfusion and cardiac output.[160] Tc-CO_2 has been shown to correlate with $PaCO_2$, but results vary at higher CO_2 levels.[161] It is thought that transcutaneous monitors generally reflect O_2 and CO_2 transport to and from skin electrodes and may not reflect arterial values.[158] Thus, transcutaneous monitoring is not routinely used in the ICU setting as a replacement for ABG analysis.

CONTINUOUS ABG MONITORS

Continuous ABG monitors intermittently or continuously display ABG results on a bedside screen and permit the observation of trends over time.[159] The newer ABG analyzers have sensors called optodes that detect variations of light and fluorescence.[61] The O_2 sensor uses a fluorescent die, and the H^+ and CO_2 sensors use fluorescent acids; fluorescent intensity is inversely proportional to the amount of substance being measured.[24] Some monitors have cartridges that permit measurements every 2 to 3 minutes; these closed systems minimize health care worker exposure to blood and do not require interruption of the arterial line for sample collection. Also, measured blood is returned to the patient and is thus conserved.[162]

Several limitations are associated with these monitors. Lower precision is more frequent with PaO_2 measurements,[162,163] and less accurate readings occur at higher PaO_2 and $PaCO_2$ levels.[164] Motion artifact affects values[163,165] and clot may form on the catheter tip. Finally, "wall effect" may alter PaO_2 readings; here, a sensor adjacent to the vessel wall may combine blood and tissue PaO_2 readings.[24,162,163] Although continuous ABG monitors are not used routinely, they may show promise in the future.

ANNOTATED REFERENCES

AARC clinical practice guideline. Sampling for arterial blood gas analysis. Respir Care 1992;32:913-917.

This review includes standards for the collection and processing of ABG samples.

Aubier M, Murciano D, Milic-Emili J, et al: Effects of the administration of O_2 on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. Am Rev Respir Dis 1980;122:747-754.

This prospective study demonstrated that CO_2 retention due to O_2 administration during COPD exacerbation was not simply the result of a decreased "hypoxic drive to breathe" but most likely due to ventilation-perfusion inequalities.

Bakker J, Vincent JL, Gris P, et al: Veno-arterial carbon dioxide gradient in human septic shock. Chest 1992;101:509-515.

This observational study in patients with septic shock documented venoarterial CO_2 gradient elevations in patients with lower cardiac index, as well as those with pulmonary injury. Although not predictive of survival, nonsurvivors had a higher gradient than survivors.

Krapf R, Beeler I, Hertner D, Hulter HN: Chronic respiratory alkalosis: The effect of sustained hyperventilation on renal regulation of acid-base equilibrium. N Engl J Med 1991;324:1394-1401.

The effects of hypoxia-induced respiratory alkalosis were evaluated in normal subjects with and without an underlying induced metabolic acidosis. Regardless of the underlying metabolic state, both groups experienced an increase in pH, suggesting that the compensatory metabolic response was not as strong as the $PaCO_2$ decline.

Schmidt C, Müller-Plathe O: Stability of P_{O_2}, P_{CO_2} and pH in heparinized whole blood samples: Influence of storage temperature with regard to leukocyte count and syringe material. Eur J Clin Chem Clin Biochem 1992;30:767-773.

The effects of both temperature and leukocytosis on ABG results were found to be significant. Because the permeability of plastic (vs. glass) syringes affected values, it was suggested that samples in plastic syringes be measured within 15 minutes of collection.

Chapter 63

RESPIRATORY SYSTEM MECHANICS AND RESPIRATORY MUSCLE FUNCTION

Sean M. Caples • Rolf D. Hubmayr

KEY POINTS

1. A simple model of the respiratory system is useful in assessing mechanics in the ICU. Mechanical ventilator models using linear one-compartment analogs are helpful in detecting the presence of lung disease or respiratory muscle activity and may assist in guiding disease-specific ventilatory strategies.
2. Pressures applied to the respiratory system are either stored as a function of elasticity or dissipated as resistive energy. A basic understanding of the mechanics and derivation of these pressures from mechanical ventilator output is useful during the bedside assessment of ICU patients.
3. Evidence supporting the use of the pressure-volume curve to determine specific ventilator settings is circumstantial. However, information about respiratory system mechanics derived from the pressure-volume curve can be helpful in identifying patients at risk for ventilator-associated lung injury.
4. Respiratory muscle fatigue is an important factor in respiratory failure. Current methods of quantifying muscle fatigue, based on surrogate measurements of muscle strength in the time domain, are limited by their low specificity and interaction with systemic disease, such as sepsis.
5. Critical illness polyneuropathy and myopathy are important causes of respiratory muscle dysfunction in the ICU and are associated with certain modifiable risk factors, including the use of neuromuscular blocking agents.

In its simplest form, the respiratory system can be modeled as a balloon connected to a tube. The balloon represents the elastic element (lungs and chest wall), and the tube represents the resistive element (conducting airways). To serve the purpose of ventilation, the respiratory pump (or a mechanical ventilator) must generate sufficient pressure to overcome both the elastic and flow-resistive properties of the respiratory system.

Classic respiratory mechanics are based on Newtonian physics, as expressed in the equation of motion. The respiratory system model is derived from an elementary monodimensional system, as depicted by a block with an attached spring, acted on by a unidirectional force (Fig. 63-1*A*).[1]

Upon application of the force, the response of the system can be characterized in terms of displacement, velocity, and acceleration of a block with a mass of M. The balance of forces acting on the block can be expressed as follows:

$$F_{appl(t)} = F_{el(t)} + F_{res(t)} + F_{in(t)} \qquad \text{(Equation 1)}$$

where the total force applied to the system (F_{appl}) at a given time (t) is equal to the sum of the elastic (F_{el}), resistive (F_{res}), and inertial (F_{in}) forces. The equation may be rewritten as

$$F = Kx + R(dx/dt) + M(d^2x/dt^2) \qquad \text{(Equation 2)}$$

where the elastic force originates in the spring and is the product of the spring constant (K) and the distance (x) that the block is displaced. The resistive force is constituted by friction between two surfaces and equals the cross-product of the resistance constant (R) and velocity (dx/dt), whereas inertance (I) is determined by mass (M) and acceleration (d^2x/dt^2). Accordingly, the equation of motion for a three-dimensional pneumatic system may be written as

$$P_{(t)} = E(V_{(t)}) + R\dot{V}_{(t)} + I\ddot{V}_{(t)} \qquad \text{(Equation 3)}$$

where $P_{(t)}$ is the pressure exerted on the system at a given time; E is the elastance (the reciprocal of compliance, i.e., 1/C), which relates pressure to volume (V); and R is the resistance constant, relating pressure to flow. The third term of the equation describes the pressure required to accelerate tissue and gas in the airway, which is an important factor under certain circumstances, such as coughing or high-frequency oscillatory ventilation. The inertance constant (I) relates pressure to linear acceleration ($\ddot{V}$). However, the third term is usually omitted in this model of the respiratory system, because inertive forces are negligible during quiet breathing and most forms of mechanical ventilation.[2] Thus, in most applications, the respiratory system derivative of the equation of motion considers only the elastic and flow-resistive elements that oppose an applied pressure at time (t).

$$P_{(t)} = E(V)_{(t)} + R\dot{V}_{(t)} \qquad \text{(Equation 4)}$$

which may also be expressed as

$$P_{(t)} = 1/C(V)_{(t)} + R\dot{V}_{(t)} \qquad \text{(Equation 5)}$$

Thus, in this model, any force applied to the respiratory system is either stored as elastic energy or dissipated as resistive

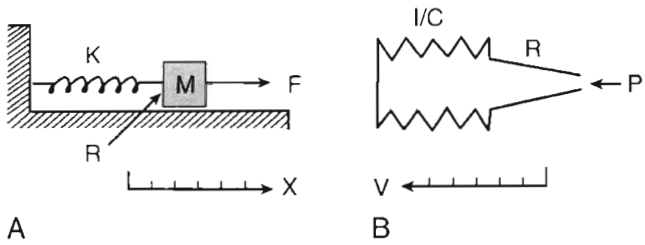

FIGURE 63–1. Mechanical analogs of the equation of motion. *A*, System with unidirectional motion. *B*, Three-dimensional system. (From Rodarte JR, Rehder K: Dynamics of respiration. In Macklem PT, Mead J [eds]: Handbook of Physiology, sec 3, The Respiratory System. Baltimore, Williams & Wilkins, 1986, pp 131-144.)

energy. Figure 63-1*B* shows a three-dimensional model of the respiratory system as it relates to the equation of motion.

This simple model of respiratory system mechanics is useful because, in the normal operating range, the relationships among airway pressure, volume, and flow can be approximated by straight lines. Linear one-compartment analogs are particularly well suited for modeling mechanical ventilation, because the pressure applied to lungs and chest wall can be readily measured and displayed. In turn, departures from linearity provide useful clues about concurrent respiratory muscle activity, alert the health care provider to the presence of lung disease, or serve as a warning that the lungs are being ventilated at inappropriately high or low volumes.

STATIC BEHAVIOR OF THE RESPIRATORY SYSTEM

In accordance with the model described in the preceding section, in the absence of gas flow, a pressure applied to the respiratory system is opposed by elastic forces (P_{el}). During flow, this pressure can be approximated by alveolar pressure (P_{alv}), which, upon interruption of airflow, equilibrates with airway opening pressure (P_{ao}).

The elastic element of the respiratory system (rs) consists of two component structures, the chest wall (w)—functionally, the thoracic cage and abdomen—and the lungs (l). The forces that act on these two structures can be summed, because the lungs and chest wall behave like springs in series.

$$P_{el,rs} = P_{el,w} + P_{el,l} \qquad \text{(Equation 6)}$$

The net distending pressure applied to the lung by contraction of the inspiratory muscles or by positive-pressure ventilation is represented by transmural forces, termed the transpulmonary pressure (P_L). Transpulmonary pressure is determined by the difference between alveolar pressure and pleural pressure (P_{pl}):

$$P_L = P_{alv} - P_{pl} \qquad \text{(Equation 7)}$$

The pressure across the chest wall (transthoracic pressure, P_w) is determined by the difference between pleural pressure and atmospheric pressure (P_{bs}).

$$P_w = P_{pl} - P_{bs} \qquad \text{(Equation 8)}$$

Because it is used as a reference to all other measured pressures, atmospheric pressure is considered to be zero, thus,

$$P_w = P_{pl} \qquad \text{(Equation 9)}$$

An esophageal balloon catheter can be used to approximate pleural pressure, keeping in mind that pleural pressure is nonuniform and that topographic gradients in pleural pressure vary with posture.[3] Particularly in the recumbent posture, there is no site in the esophagus at which local pressure approximates average lung surface pressure (i.e., average pleural pressure). However, at least in normal lungs, the average change in surface or pleural pressure can be inferred using esophageal manometry.

The static pressure across the entire respiratory system can be summarized as follows:

$$P_{rs} = P_l + P_w = (P_{ao} - P_{pl}) + (P_{pl} - P_{bs}) = P_{ao} \qquad \text{(Equation 10)}$$

The static respiratory system pressure-volume (P-V) curve is often measured in intubated, mechanically ventilated patients to make inferences about the mechanical properties of the lungs. Although the utility of P-V measurements in clinical decision-making remains to be established, the determinants of the P-V relationship should nevertheless be understood. The P-V curve is generated by inflating and deflating the relaxed respiratory system in a stepwise fashion between residual volume and total lung capacity. The airway occlusion pressure at each volume defines the corresponding elastic recoil pressures of the lungs and chest wall. Because the inflation and deflation relationships differ from each other, the resulting curve is often referred to as a P-V loop. The respiratory system P-V loop is the summation of individual lung and chest wall P-V loops, termed a Rahn diagram (Fig. 63-2).

As seen in Figure 63-2, during normal tidal volume breathing (30% to 70% vital capacity), the relationship between elastic pressure and volume is essentially linear, and the system's elastic properties can be defined by a constant, namely, elastance. The term *compliance* is more frequently

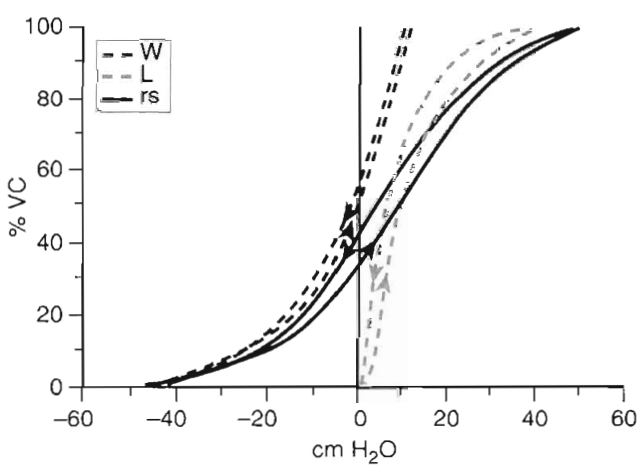

FIGURE 63–2. Pressure-volume (P-V) loop (Rahn diagram) of the respiratory system (rs), and summation of individual chest wall (W) and lung (L) loops. VC, vital capacity. (From Agostoni E, Hyatt RE: Static behavior of the respiratory system. In Fishman AP [ed]: Handbook of Physiology. Baltimore, Williams & Wilkins, 1986, pp 113-130.)

used and is simply the inverse of elastance, defined as the change in volume per unit change in applied pressure. Static respiratory system compliance can be determined by the slope of the P-V curve. In the quiet breathing range, the normal respiratory system elastance averages 8 to10 cm H_2O/L, corresponding to a static respiratory system compliance of 0.08 to 0.1 L/cm H_2O.

Figure 63-2 also shows the P-V curves of the respiratory system's component structures, the lung and chest wall. At high lung volumes, the total respiratory system compliance is reduced (the P-V curve is concave to the pressure axis), primarily because the lung reaches total capacity, its structural limit. In contrast, the P-V curve of the chest wall remains linear at high volumes (i.e., the chest wall offers much less resistance to further lung expansion). At low lung volumes, a decrease in chest wall compliance is the major contributor to the low respiratory system compliance. At relaxation volume (functional residual capacity), the inward recoil of the lung is equal to the outward recoil of the chest wall, so that alveolar pressure is atmospheric. At a volume of 60% of vital capacity, the chest wall reaches a "resting" position, that is, it exerts no force on the lungs, and the pleural pressure is atmospheric. In the normal tidal breathing range, the slopes of the lung and chest wall P-V curves are similar (i.e., lung and chest wall contribute about equally to overall respiratory system compliance). Figure 63-3 shows the volume dependence of the inwardly and outwardly directed forces of the respiratory system during inflation.[3]

Lung recoil is the collapse force of the lung that is in equilibrium with the transpulmonary distending pressure originating from the chest wall and inspiratory muscles. It is generated by:

1. Tension carried by lung parenchyma, including the collagen network that extends from the alveolar septae to the visceral pleura.
2. Surface forces originating from air-liquid interfaces in distal lung units.[4]

Surface forces (i.e., surface tension) are generated because liquid molecules, in contact with air, attempt to conserve energy by decreasing the area available for interaction. In the lung, the resulting force acts parallel to the alveolar septa and balances a helical fiber network that supports alveolar ducts and forms alveolar entrance rings.[5]

As demonstrated in Figure 63-4, the elimination of surface tension has two important consequences on lung mechanics:

1. There is an approximately 50% reduction in recoil pressure at all lung volumes.
2. The difference in isovolume recoil pressure between inflation and deflation (hysteresis) is largely abolished.

Findings indicate not only that surface tension is an important source of lung elastic recoil but also that recoil pressure varies with volume, volume history, and time. In the normal lung, hysteresis is caused by volume- and time-dependent changes in the molecular composition and hence the biophysical properties of surfactant. Surfactant is a protein-enriched lipid film that coats air-liquid interfaces in distal lung units and lowers surface tension. Hysteresis implies that energy added to the system during inflation is not fully recovered during deflation. The hysteretic loss of energy does not scale with frequency and flow the way a Newtonian viscous resistance does, underscoring one of the many limitations of linear resistance-compliance circuits in modeling lung mechanics.[6] Whereas interfacial phenomena are the

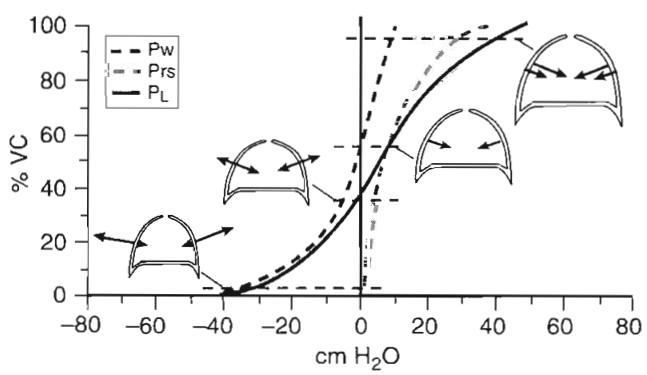

FIGURE 63–3. Static pressure-volume curves of the chest wall (P_w), lungs (P_L), and respiratory system (P_{rs}). Drawings of the thorax (from left to right) at residual volume, functional residual capacity, resting position (no force exerted by the chest wall), and total lung capacity. Arrows indicate the direction of elastic recoil. VC, vital capacity. (From Agostoni E, Hyatt RE: Static behavior of the respiratory system. In Fishman AP [ed]: Handbook of Physiology. Baltimore, Williams & Wilkins, 1986, pp 113-130.)

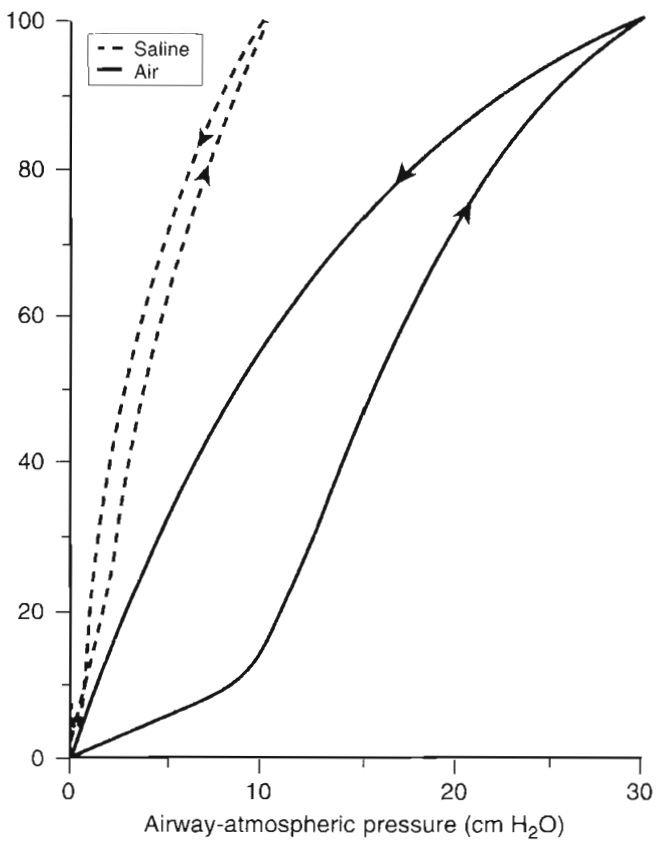

FIGURE 63–4. Plot of airway–atmospheric pressure gradient for an isolated lung inflated with air *(solid line)* and saline *(dashed line)*. The reduction in surface tension in the saline-filled lung results in increased compliance. (From Taylor A, Rehder K, Hyatt R, et al: Mechanics of breathing: Static. In Taylor AE [ed]: Clinical Respiratory Physiology. Philadelphia, WB Saunders, 1989, pp 89-105.)

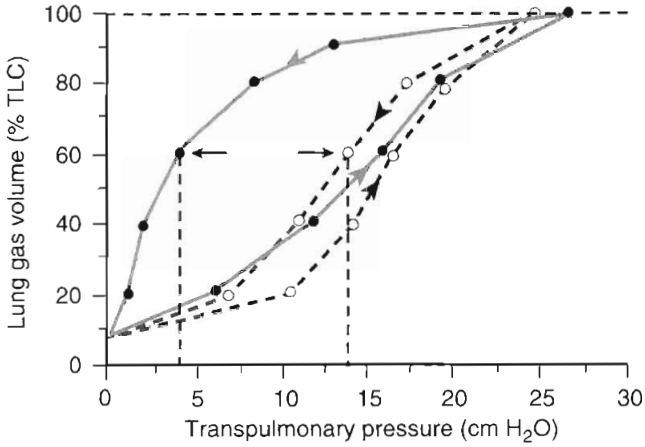

FIGURE 63–5. Pressure-volume loop of a normal lung *(solid line)* and a surfactant-depleted lung *(dashed line)*. TLC, total lung capacity. (From Taylor A, Rehder K, Hyatt R, et al: Mechanics of breathing: Static. In Taylor AE [ed]: Clinical Respiratory Physiology. Philadelphia, WB Saunders, 1989, pp 89-105.)

primary source of hysteresis in the normal lung, alveolar recruitment and derecruitment are important sources of hysteresis in disease.

According to the law of Laplace, the pressure (P) required to inflate a bubble is directly related to the surface tension (T) and is inversely proportional to the radius of curvature (r) ($P = 4T/r$). Applied to the lung, this means that changes in alveolar dimensions at low lung volumes would promote alveolar collapse were it not for surfactant's surface tension–lowering properties. A surfactant-depleted lung exhibits alveolar instability and collapse in the tidal breathing range.[7] Therefore, larger than normal transpulmonary pressures are required to keep the surfactant-depleted lung inflated, as illustrated in Figure 63-5.

DYNAMIC BEHAVIOR OF THE RESPIRATORY SYSTEM

The transpulmonary pressure generated by the respiratory pump must also overcome the resistive forces related to gas flow. The respiratory system resistance constant scales resistive pressure and flow in the equation of motion discussed previously. The reciprocal of resistance is conductance, which is proportional to lung volume as the airways, tethered to the entire connective tissue network, are pulled open with larger inflation volumes.

According to Ohm's law, resistance (R) can be calculated by dividing the driving pressure by flow:

$$R = (P_{alv} - P_{ao})/\dot{V} \qquad \text{(Equation 11)}$$

Total pulmonary resistance reflects the gas flow–dependent pressure dissipation in conducting airways (airway resistance) and the frequency-dependent loss of energy associated with parenchymal deformation (tissue resistance). Originally ignored as only a minor component of total pulmonary resistance, it is now appreciated that the so-called tissue resistance dominates the measurement, at least at low frequencies.[8] As elegantly outlined by Fredberg and Stamenovic,[6] tissue resistance and tissue hysteretic properties are model-specific descriptors of energy loss, the structural and molecular basis of which remains uncertain.[9]

The physical laws governing fluid flow in tubes can be applied to gas flow in the airways. According to fluid mechanics, tube length and geometry and gas velocity and physical properties (i.e., density and viscosity) determine whether flow is laminar or turbulent. These determinants can be captured by the Reynold's number, a quantity that represents the ratio of inertial forces to viscous forces.[10] A low Reynold's number (<50) corresponds to laminar flow, and a Reynold's number greater than 2300 is associated with turbulent flow. Accordingly, the low gas velocity in peripheral airways favors laminar flow, and the acceleration associated with the decrease in total cross-sectional area in central airways promotes turbulence. In the presence of laminar flow, frictional pressure losses are linearly related to flow and viscosity and inversely proportional to tube radius to the fourth power (Poiseuille's equation). In contrast, turbulent flow is associated with nonlinear pressure-flow relationships that are gas-density dependent. The density dependence of turbulent flow is occasionally exploited in the medical use of heliox, a low-density helium-oxygen mixture given to patients with central airway lesions or asthma.[11]

The flow-dependent shift from laminar to turbulent flow is captured in the Rohrer equation:

$$P = K_1\dot{V} + K_2\dot{V} \qquad \text{(Equation 12)}$$

where K_1 and K_2 are constants that scale frictional pressure dissipation associated with laminar and turbulent flow, respectively.

A second mechanism of pressure loss during gas flow is related to the Bernoulli principle, which describes convective pressure dissipation. That is, as a gas flows from a large cross-sectional area to a smaller area, velocity must increase to maintain flow. This results in energy dissipation and a drop in pressure and correlates to expiratory flow of gas from the bronchioles to the central airways.

As mentioned previously, ohmic resistance can be computed by dividing resistive pressure by inspiratory flow (equation 11). In a mechanically ventilated patient, where endotracheal and ventilator tube resistance dominate measured total respiratory system resistance, the derived value of respiratory resistance must be interpreted with caution. Artificial tubing is not a truly ohmic resistor, and estimates of resistance are highly dependent on inspiratory flow rates. Even after correction for tube size, high inspiratory resistance may be confounded by inspissated secretions or "tube biting." When using inspiratory flow settings of less than 1 L/sec with an endotracheal tube greater than 7 mm internal diameter, resistive pressure is usually less than 10 cm H_2O. A resistive pressure exceeding this value, in the absence of obvious intrinsic airway disease, should prompt an investigation for a possible ventilator hardware problem. It should be kept in mind that a normal inspiratory resistance does not preclude the presence of severe airflow obstruction, as seen in chronic obstructive pulmonary disease (COPD).

The respiratory time constant (τ) is the time required for the lungs to fill or passively discharge approximately 63% of its contents. It can be determined from the slope of the passive expiratory flow-volume curve (Fig. 63-6) or calculated directly by the equation

$$\tau = R_{rs}/E_{rs} = R_{rs} \cdot C_{rs} \qquad \text{(Equation 13)}$$

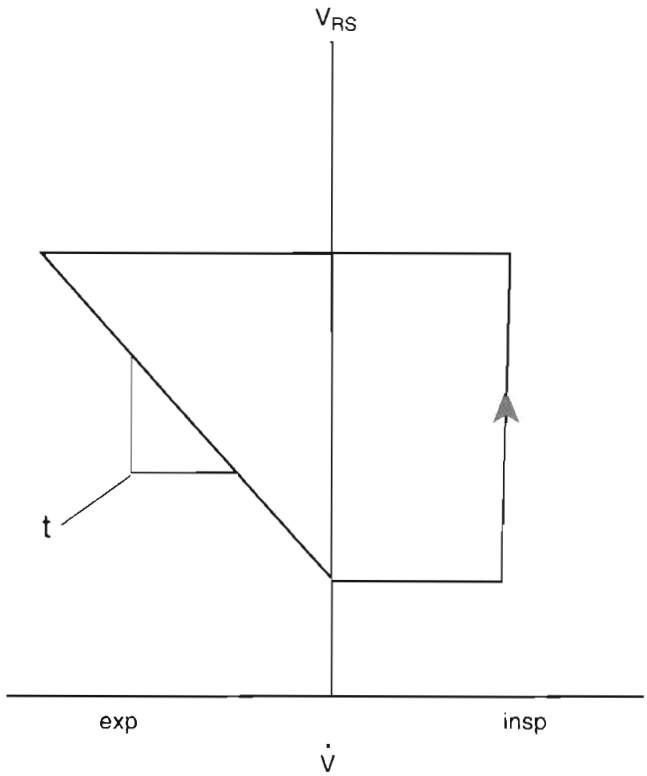

FIGURE 63–6. Flow-volume curve. The expiratory time constant (τ) is equal to the slope of the expiratory limb. $\dot{V}$, flow; V_{RS}, volume of respiratory system. (From Loring SH: Mechanics of the lung and chest wall. In Marini JJ, Slutsky AS [eds]: Physiological Basis of Ventilatory Support. New York, Marcel Dekker, 1998, pp 177-205.)

Because respiratory system resistance (R_{rs}) is expressed in units of pressure • time • volume^{-1} and respiratory system compliance (C_{rs}) is expressed in units of volume • pressure^{-1}, the product τ has the unit of time (E_{rs}, respiratory system elastance). The value of τ for a normal respiratory system is approximately 0.3 second.[2] As can be inferred from the equation, patients with high respiratory system resistance or compliance, such as those with COPD, have correspondingly large τ values. The added resistance of the artificial tubing in a mechanically ventilated patient increases τ to 1 second or more. Depending on the set expiratory time, patients with even minimally elevated τ values may not fully empty the lungs during mechanical ventilation. Consequently, the demand for expiratory flow is not met as the lungs near relaxation volume, resulting in dynamic hyperinflation.

Some basic concepts regarding flow limitation are helpful as a prelude to a discussion of bedside assessment in the ICU. The left side of Figure 63-7 shows an expiratory flow-volume plot for a normal subject, similar to that generated by a forced vital capacity maneuver in the pulmonary function lab. The right side of the figure shows three driving pressure–flow curves at progressively smaller lung volumes from A to C. The curves are nonlinear, and each has a driving pressure–dependent and –independent limb, separated by the critical driving pressure. In a classic set of experiments performed on normal subjects, Fry and Hyatt demonstrated that maximal expiratory flow is determined by lung volume.[12] That is, higher lung volumes (curve A) yield higher expiratory flow rates compared with the flow seen at lower lung volumes (curve C). They concluded that, on the basis of volume-related dynamic airway collapse, this expiratory flow plateau cannot be exceeded, irrespective of the magnitude of subject effort or applied transpulmonary pressure. Herein lies the value of the forced vital capacity maneuver as a reproducible measure of maximal expiratory flow. Although this seems most applicable to ambulatory outpatients, these general principles can help guide bedside decision-making in the ICU, as discussed later.

ASSESSMENT OF RESPIRATORY SYSTEM MECHANICS IN THE INTENSIVE CARE UNIT

The preceding sections defined the basics of respiratory system mechanics as they relate to volume, pressure, and flow. With this foundation, we can proceed to the correlation of mechanics with clinical conditions encountered in the ICU. To examine basic concepts, we use the example of expected waveforms generated by a volume-preset mechanical ventilator in a relaxed patient with otherwise normal respiratory system mechanics.

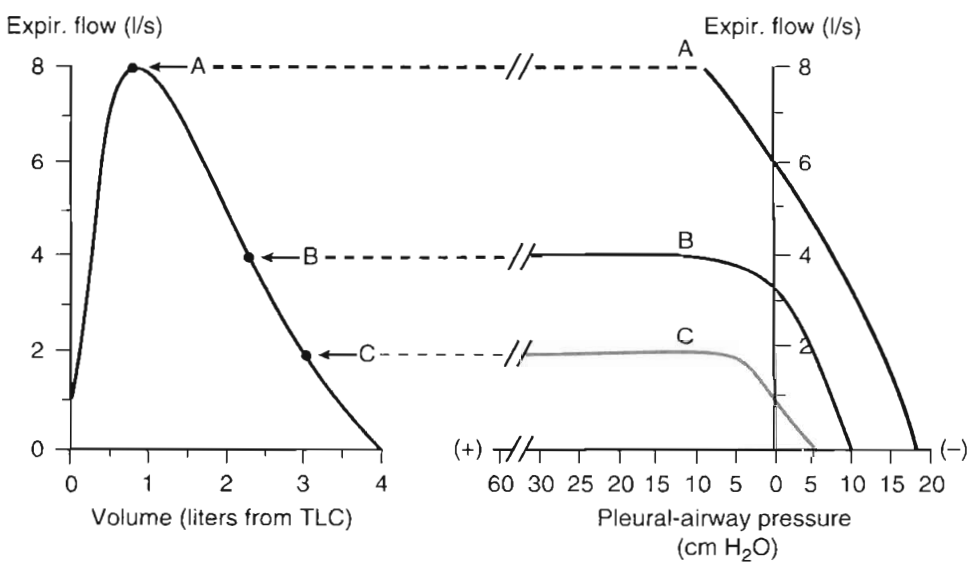

FIGURE 63–7. *Left*, maximal expiratory flow-volume curve. *Right*, three isovolume pressure-flow curves at different lung volumes (A, B, C). Note flow limitation associated with submaximal lung volumes B and C. TLC, total lung capacity. (From Hyatt RE: Forced expiration. In Macklem PT, Mead J [eds]: Handbook of Physiology, sec 3, The Respiratory System. Baltimore, Williams & Wilkins, 1986, pp 295-314.)

The typical waveform output is demonstrated by Figure 63-8, with a model of the system represented on the right. Pressures are measured at the ventilator inlet. Assuming inflation onset with a constant (square wave) flow, an initial step change in driving pressure is recorded, which precedes alveolar filling, and corresponds to resistive pressure related to gas flow in the airways. In the otherwise normal lung, an identical step-off in resistive pressure may be noted during an applied airway occlusion at end-inspiration, when gas flow falls to zero (see the arrow in Fig. 63-8). The resultant remaining value is referred to as the plateau pressure and represents the static summation of elastic recoil forces corresponding to the applied tidal volume. The purported significance of plateau pressure is discussed later.

Assuming constant flow in a relaxed or paralyzed patient without respiratory muscle contribution, pressure at the ventilator inlet increases linearly with time and volume to a peak airway pressure. (Inspiratory muscle activity would be represented by transient perturbations in the linearity of the airway opening pressure curve with a constant inspiratory flow rate). Peak airway pressures that deviate from the inspiratory occlusion pressure by more than 10 cm H_2O should prompt an investigation of an endotracheal tube resistance problem, such as tube kinking or inspissated secretions.

As previously mentioned, the elastic properties of the respiratory system can be determined from the slope of the P-V curve. Provided there is no contribution from respiratory muscles (as evidenced by a perfectly linear inspiratory P-V curve), the elastance (E_{rs}), or reciprocal of compliance, can be derived from time-based curves with the following equation:

$$E_{rs} = \Delta P_{el}/\Delta vol = dP/dt \times dt/dV = dP/dt \times 1/\dot{V} \qquad \text{(Equation 14)}$$

where dP = change in pressure; dt = change in time; and dV = change in volume.

Positive end-expiratory pressure (PEEP) can be applied to the system manually (extrinsic PEEP) or may be inadvertent, known as intrinsic or auto PEEP, related to dynamic hyperinflation. Intrinsic PEEP can occur in any mechanically ventilated patient, once a certain threshold of ventilation is reached. In patients with deranged respiratory system

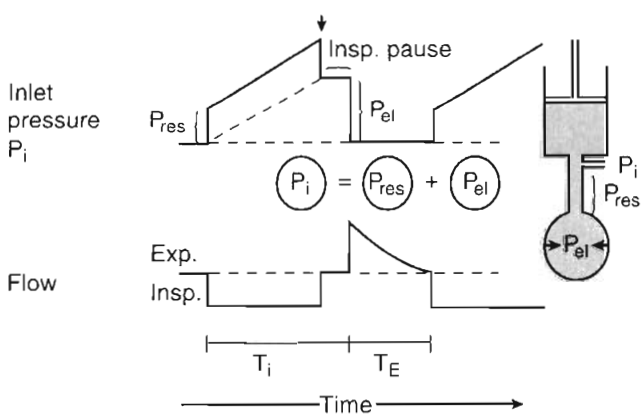

FIGURE 63–8. Airway pressure and flow wave patterns during volume-preset mechanical ventilation. Schematic of a linear one-compartment model is shown at the right. P_{el}, elastic pressure; P_i, pressure at ventilator inlet; P_{res}, resistive pressure; T_E, expiratory time; T_i, inspiratory time. (From Gay PC, Rodarte JR, Tayyab M, et al: The evaluation of bronchodilator responsiveness in mechanically ventilated patients. Am Rev Respir Dis 1987;136:880-885.)

mechanics, particularly obstructive lung disease (with abnormally large τ values), the propensity to develop intrinsic PEEP is increased. PEEP (extrinsic or intrinsic) is represented on the pressure waveform by end-expiratory pressures exceeding zero.

Passive expiration of the respiratory system is driven by elastic recoil, as manifested by alveolar pressure at a corresponding lung volume. Expiratory flow is a function of the elastance and resistance and is demonstrated as

$$\dot{V}exp_{(t)} = P_{el(t)}/R_{rs} \qquad \text{(Equation 15)}$$

Because the elastic pressure is determined by elastance and the corresponding lung volume, the equation may be rewritten as

$$Vexp_{(t)} = [E \times V_{(t)}]/R = V_{(t)}/(\tau) \qquad \text{(Equation 16)}$$

As noted previously, τ is the product of resistance and compliance. It is possible to overwhelm the expiratory function of either a normal or a diseased lung during mechanical ventilation with a combination of relatively large tidal volume and relatively short expiratory time, leading to intrinsic PEEP. The volume of trapped gas that corresponds to the inadvertent PEEP can be calculated by the formula

$$V_{trapped} = \dot{V}T/(e^{Te/\tau} - 1) \qquad \text{(Equation 17)}$$

where Te is the expiratory time.

SPECIFIC APPLICATIONS

INJURED LUNGS

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are associated with impaired lung barrier function. Pulmonary capillary leak and overwhelming of the lungs' ability to clear water and solute from airspaces results in so-called noncardiogenic pulmonary edema.[13] Flooding of alveolar spaces leads to the functional loss of these units from effective ventilation, a process termed derecruitment, particularly in the dependent portions of the lungs.[14] This results in what has been termed the "baby lung," where gas flow is directed to aerated low-impedance units.[15] Because respiratory system elastance scales with lung size, injured lungs appear stiff.[16] Total respiratory system resistance is also increased, particularly in the dependent regions of the lungs.[17] Whether abnormal lung mechanics reflect the collapse of dependent units or are the consequence of alveolar flooding remains controversial.[18]

There is unimpeachable evidence that the injured lung is susceptible to further injury related to mechanical ventilation, termed ventilator-associated lung injury.[19] An understanding of respiratory mechanics provides some insight into the possible pathogenetic mechanisms of this injury. First, the number of recruitable alveoli, capable of expanding during inspiration, is reduced—the "baby lung" concept noted earlier. Thus, tidal volumes are distributed to fewer lung units and produce a greater local deformation. Second, the heterogeneous distribution of liquid and associated surface tension in distal airspaces results in adjacent units with vastly different mechanical properties (i.e., opening pressure). This invokes the theory of injury related to interdependence, whereby, during the opening of a flooded unit juxtaposed

with an open unit, a shear stress across the tissue attachment results that is substantially higher than the average transpulmonary pressure.[20]

Although there continues to be debate about the dominant pathogenetic mechanisms of ventilator-associated lung injury, it is clear that low tidal volume ventilation (~6 mL/kg ideal body weight) of ARDS patients translates to reduced mortality when compared with the traditional (≥10 mL/kg) tidal volume assignment.[19] Still, ARDS remains a devastating disease, with high mortality and morbidity. Although further efforts have been made to modify ventilatory strategies based on mechanical principles, as will be discussed later, no other interventions have been shown to affect clinical outcome.

Much attention has been focused on the pressure-volume relationship in injured lungs, as a means to both improve gas exchange and prevent ventilator-associated lung injury in predisposed lungs. Use of the P-V curve in clinical decision-making, however, has been the subject of much controversy.[18,21] First, there are technical limitations related to the numerous methods used to generate a P-V curve. The supersyringe method for static P-V curve recordings has been associated with spurious changes in lung volume, on account of gas absorption during measurement.[22] There are also issues related to user interpretation, such as difficulties in defining morphologic characteristics of the curve, and interobserver variability is often high.[23,24] Some have advocated inductive machine learning in an attempt to standardize interpretation.[25]

Compared with the static P-V curve shown in Figure 63-2, the P-V curve in ARDS and ALI (Fig. 63-9) has a number of distinguishing features. These include:

1. Sigmoidal shape with two "knees"—the upper and lower inflection points.
2. Increased recoil pressure at all lung volumes.
3. Reduced compliance defined by the slope of the inflation curve between the lower and upper inflection points.

Traditionally, the lower inflection point has been interpreted as the pressure at which previously underventilated or collapsed airways or alveoli are recruited, corresponding to the pressure at which "best PEEP" should be set. Similarly, the upper inflection point, where the inflation curve loses its linearity, is thought to be the pressure at which no further increases in lung recruitment occur, thereby representing the highest airway pressure safely administered before overdistention occurs. If these assumptions are correct, ventilator settings should be adjusted until lung expansion is restricted to the linear midrange of the inflation P-V curve. This hypothesis finds application in stress index monitoring,[26] which allows for breath-by-breath assessment of adherence to this treatment target.

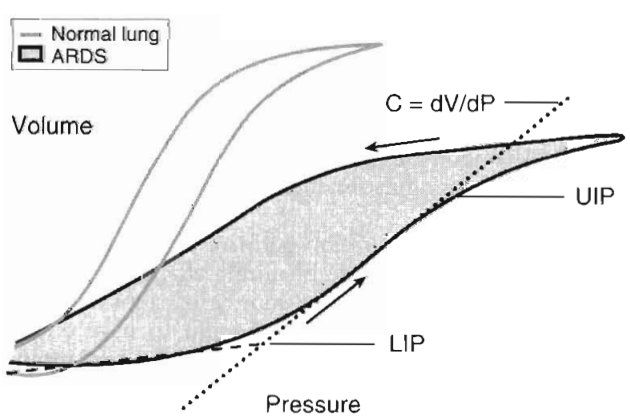

FIGURE 63–9. Pressure-volume curve in acute respiratory distress syndrome (ARDS) compared with the normal respiratory system. C, compliance; dV/dP, change in volume/change in pressure; LIP, lower inflection point; UIP, upper inflection point. (From de Chazal I, Hubmayr RD: Novel aspects of pulmonary mechanics in intensive care. Br J Anaesth 2003;91:81-91.)

Critical appraisal of the P-V curve has revealed low specificity for some derived parameters. For example, a prominent lower inflection point has been associated with conditions of high surface tension rather than actual closure or collapse of airways, such as with mineral oil rinses or air insufflation into saline-filled lungs.[27,28] Attention has been refocused on edema, airway liquid, and interfacial phenomena as causes of higher opening pressures and increased lung impedance.[18]

The lower inflection point may originate in the chest wall rather than the lung in some patients, particularly in those with low end-expired thoracic volumes (recall that the P-V curve of the chest wall is nonlinear at low lung volumes; see Fig. 64-2).[29] Because of concerns about chest wall–related P-V artifacts, esophageal manometry has been used to guide the ventilatory management of patients with injured lungs. Data from esophageal catheters may be misleading, however, because derecruited dependent lung units that appose the esophageal probe may fail to generate local pressure swings, thereby biasing the measurement.[30]

It is clear that adjustments in PEEP are helpful in optimizing gas exchange, with improvements noted in the ratio of arterial oxygen pressure to inspired oxygen fraction (PaO_2/FiO_2). However, PEEP adjustments via P-V loop guidance do not necessarily translate into improvements in outcome or survival. Indeed, in the ARDSnet trial, early improvements in arterial oxygenation were noted in patients who were ventilated with higher tidal volumes but turned out to have increased mortality.[19] A subsequent study by the same group showed no difference in mortality between ARDS patients randomized to higher "optimal" PEEP and "conventional" PEEP.[31]

Many clinicians have advocated using the upper inflection point as an analog of plateau pressure (end-inspiratory occlusion pressure), and recommendations not to exceed 30 to 35 cm H_2O are pervasive. Although some regions of the lungs may approach their maximal volume at pressures near the upper inflection point, the evidence is circumstantial that ventilating patients near these airway pressures (with relatively low tidal volume) causes injury.

It appears that respiratory mechanics in patients with injured lungs are helpful in identifying those at greatest risk for ventilator-associated lung injury, and reassessment of the ventilation strategy (applied PEEP, tidal volume) should be triggered when static airway pressures exceed 30 to 35 cm H_2O. Most experts agree that a routine PEEP setting of 5 cm H_2O is too low, although the use of specific P-V curve–generated indices has not proved beneficial.

OBSTRUCTIVE LUNG DISEASE

COPD and its bedside monitoring are reviewed extensively elsewhere in this text. Some points about the disease as it relates to the respiratory system's mechanical properties are warranted, however, particularly in mechanically ventilated patients.

A hallmark finding of all patients with obstructive lung disease is the inability to generate normal expiratory flows, which, in a mechanically ventilated patient, leads to dynamic hyperinflation. One of the most readily available means to detect hyperinflation is the measurement of intrinsic PEEP by the end-expiratory airway occlusion method. Intrinsic PEEP is defined as total PEEP minus applied or extrinsic PEEP, and it reflects the elastic recoil of the respiratory system at end-expiration.[32] It should be noted, however, that intrinsic PEEP is not a specific marker of airway obstruction. Patients with "normal" lungs can hyperinflate above a critical minute ventilation, as explained by equation 16. Moreover, the presence of intrinsic PEEP and dynamic hyperinflation does not necessarily indicate an absolute increase in end-expiratory volume. For example, on the basis of mass loading of the chest wall in the recumbent position, many patients with ascites or obesity breathe at lung volumes near residual volume.[33] It should also be noted that the reliability of the end-expiratory occlusion method is dependent on complete respiratory muscle inactivity and therefore may not be reliable in a patient who assists the ventilator.

In assessing for the presence of airflow limitation, the expiratory time constant, τ, can be determined by the slope of the flow-volume curve (see Fig. 63-6) or by the product of resistance and compliance (see equation 16). However, a more readily available tool for detecting airway obstruction is simple pattern recognition of ventilator-generated waveforms. Recall from Figure 63-8 that the initial step change in airway pressure during lung inflation should be equal to the recovery of pressure at the end of the tidal volume, that is, the difference between peak and plateau or airway occlusion pressure. The early step change is determined by any load that must be overcome to commence lung inflation. This includes resistive pressure as well as intrinsic PEEP, which drives expiratory flow. Thus, dynamic hyperinflation should be considered when the initial pressure step change significantly exceeds the terminal pressure recovery. This concept is also demonstrated in Figure 63-10, which shows an example of typical volume, airway pressure, and flow curves in an obstructed, dynamically hyperinflated patient.[34] The arrow pointing to the airway opening pressure curve denotes the intrinsic PEEP that must be counterbalanced before lung inflation begins. This method of assessing for hyperinflation has the added advantage of being less susceptible to patient effort, becauase thoracic neuromechanical feedback mechanisms tend to blunt effort at end-inspiration. The initial flow spike, or transient, in Figure 64-10 represents the rapid expulsion of gas that occurs during dynamic airway collapse early in expiration. Following the initial spike, there is deterioration in expiratory flow, as opposed to the monoexponential reduction expected in normal lungs. Indeed, the persistence of flow during the shift from expiration to inspiration suggests that the lung has not completely emptied. The terminal portions of the curves in Figure 63-10 were recorded during stepwise lung deflation. At end-expiration, intrinsic PEEP is measured by airway occlusion pressure as 16 cm H_2O.

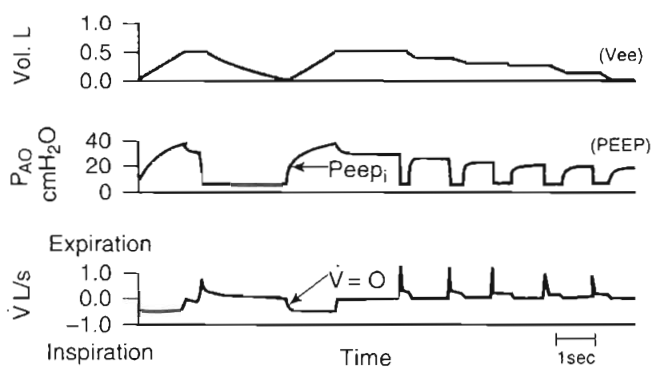

FIGURE 63-10. Volume, pressure (P_{AO}), and flow ($\dot{V}$) tracings during mechanical ventilation of an obstructed, dynamically hyperinflated patient. PEEP, positive end-expiratory pressure; $PEEP_i$, intrinsic PEEP; V_{ee}, end-expiratory volume. (From Gay PC, Rodarte JR, Tayyab M, et al: The evaluation of bronchodilator responsiveness in mechanically ventilated patients. Am Rev Respir Dis 1987;136:880-885.)

In the normal lung, expiratory driving pressure is determined by the difference between alveolar pressure and airway opening pressure. In the relaxed or paralyzed state, this driving pressure is the respiratory system recoil pressure at that particular end-inspiratory lung volume. In normal lungs, the net driving pressure may be reduced by the application of extrinsic PEEP, which serves as a load that must be overcome before volume can be expired. Consequently, in a volume-preset ventilatory mode, this would result in reduced expiratory flow, hyperinflation, and elevated peak airway pressures over subsequent breaths. As explained in Figure 64-7, if extrinsic PEEP does not affect expiratory flow, flow limitation is present. In other words, in patients with severe airway obstruction who are breathing in the tidal volume range, end-inspiratory recoil pressure far exceeds that required for maximal expiratory flow. These patients would not exhibit reductions in expiratory flow in response to the application of small levels of extrinsic PEEP.[35] Accordingly, as shown in Figure 63-11, the application of up to 5 cm H_2O of extrinsic PEEP in an obstructed patient fails to raise volume or peak pressure.

RESPIRATORY MUSCLE FUNCTION

The primary task of the respiratory muscles is to drive the respiratory pump. To do so, they must generate forces necessary to overcome the elastic and resistive elements of the respiratory system described in the preceding sections. The respiratory muscles are striated in nature and thus subscribe to Starling's law regarding length-tension relationships. As such, inspiratory muscles that act to expand the chest wall exert their greatest forces at low lung volumes (Fig. 63-12). Conversely, expiratory muscles, working to actively deflate the lungs, are most efficient at high lung volumes.[3]

Dynamic hyperinflation, as described earlier, is frequently encountered in mechanically ventilated patients and can lead to disruption of the optimal length-tension relationships of respiratory muscles, thereby contributing to respiratory failure.[36]

The muscles of respiration perform in a complex, integrated fashion to maximize breathing efficiency. Although the diaphragm is the primary muscle of respiration, it is known that muscles previously thought to have only an accessory role in breathing are actively taking part in quiet respiration to aid in movement of the chest wall.[37] These include the intercostal and scalene muscles. Relaxation allows passive recoil of the respiratory system to its resting functional residual capacity position. During exercise, phasic contraction of expiratory muscles drives the respiratory system below its resting position. Subsequent relaxation at end-expiration increases lung volume, thereby reducing

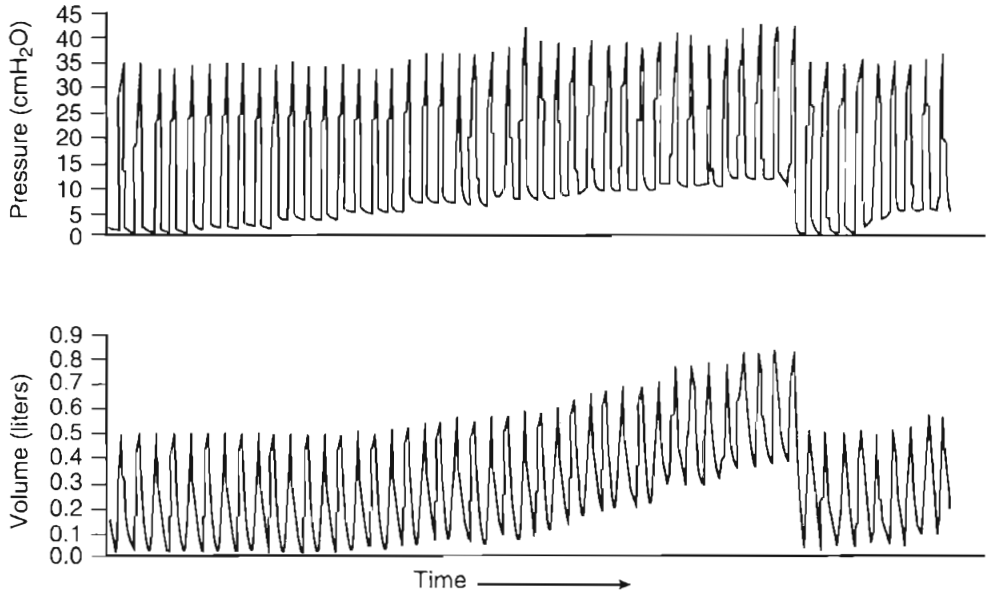

FIGURE 63–11. Response of airway pressure and volume to extrinsic positive end-expiratory pressure in a dynamically hyperinflated, mechanically ventilated patient with chronic obstructive pulmonary disease. (From Gay PC, Rodarte JR, Hubmayr RD: The effects of positive expiratory pressure on isovolume flow and dynamic hyperinflation in patients receiving mechanical ventilation. Am Rev Respir Dis 1989;139:621-626.)

the load on the inspiratory muscles for the next respiratory cycle.[2]

CHEST WALL

The chest wall collectively includes the thoracic cage and the abdominal compartment, which compose a parallel circuit. The rib cage is the most extensive portion of the chest wall and therefore contributes most to thoracic displacement during breathing. The ribs, during rest, are situated ventrally, with a downward slope. Because of their articulations with the sternum and spinal transverse processes, they are confined and move in a stereotypical manner during breathing. During inspiration, the ribs are displaced cranially to become more horizontal, so that both the anteroposterior and transverse diameters of the rib cage increase.

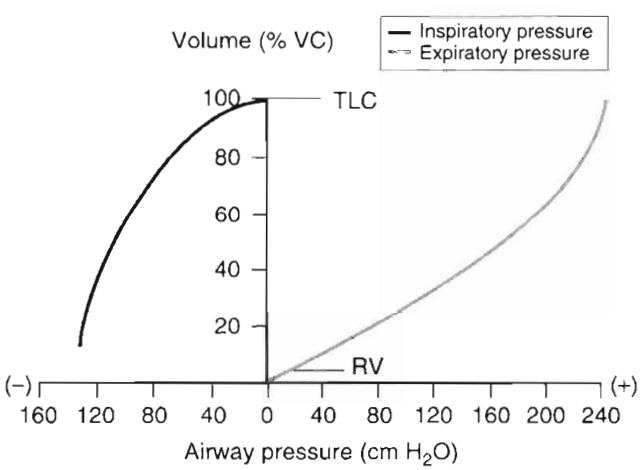

FIGURE 63–12. Plot of inspiratory and expiratory pressures as a function of lung volume. Note the higher pressures generated by expiratory muscles. TLC, total lung capacity; VC, vital capacity. (From Taylor A, Rehder K, Hyatt R, et al: Mechanics of breathing: Static. In Taylor AE [ed]: Clinical Respiratory Physiology. Philadelphia, WB Saunders, 1989, pp 89-105.)

The intercostal muscles, innervated by the intercostal nerves, act directly on the ribs to effect movement. Three different intercostal muscle groups have varying effects on respiration, depending on their origin and insertion points, which dictate orientation. The external (and parasternal) intercostals serve as inspiratory muscles by raising the ribs during contraction. In contrast, the internal intercostal muscles, which run at right angles to the externals, serve an expiratory function by contracting during expiration to induce caudal motion of the lower ribs.

The scalene muscles, considered primary muscles of respiration, originate at the cervical spine transverse processes and insert on the first two ribs anteriorly. Their contraction aids inspiration by expanding the rib cage. A number of muscles serve an accessory role, facilitating the primary muscles' role during periods of increased effort (exercise, fatigue). These muscles include the sternocleidomastoids, pectoralis minor, and erector spinae, all of which elevate the ribs during contraction.[2]

DIAPHRAGM

The most important inspiratory muscle is the dome-shaped diaphragm. It is composed of muscle fibers that radiate from the central tendon to attach to the lower rib cage. The crural portion inserts on the anterior portions of lumbar vertebrae 1 through 3, and the costal portion inserts on the xiphoid process and the upper, inner margins of the lower six ribs. The majority of the muscular portion of the diaphragm lies directly beside the lower rib cage, referred to as the zone of apposition (Fig. 63-13). Also referred to as the costophrenic sulcus, the zone of apposition is 6 to 9 cm in height and occupies 25% to 30% of the total interior surface of the rib cage.[37]

The diaphragm exerts two types of forces upon contraction. First, there is an insertional force during contraction, related to the shortening of muscle fibers, to displace the dome caudally. This increases intra-abdominal pressure, which causes ventral displacement of the anterior abdominal wall. The net effect is the lowering of pleural pressure to effect lung expansion. In other words, diaphragmatic contraction increases transdiaphragmatic pressure (P_{di}), which is

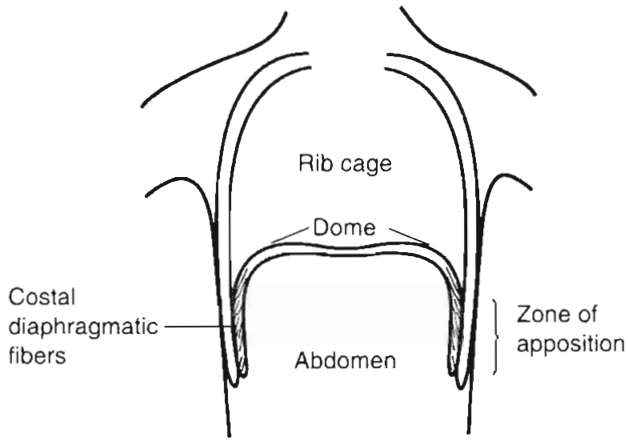

FIGURE 63–13. Chest wall, frontal section, at end-expiration. The costal diaphragmatic fibers are cranially oriented, resulting in apposition to the lower rib cage. (From De Troyer A: Respiratory muscle function. In Pinsky MR [ed]: Textbook of Critical Care. Philadelphia, WB Saunders, 2000, pp 1172-1184.)

partially dependent on abdominal pressure (P_{ab}), as shown in the equation

$$P_{di} = P_{pl} - P_{ab} = P_{ga} - P_{es} \qquad \text{(Equation 18)}$$

where P_{ga} is gastric pressure and P_{es} is esophageal pressure. Second, the contracting diaphragm exerts what is termed an appositional force. This is related to the configuration of the muscle fibers in the zone of apposition, which, in contrast to fibers in the dome, have a much larger radius of curvature (i.e., less of a curve). In accordance with the law of Laplace, less pressure is generated to move the diaphragm. Instead, the pleural space in the zone of apposition is exposed to approximate abdominal pressure, thereby acting directly to push the lower rib cage in an outward direction.[38] Thus, the rise in abdominal pressure caused by descent of the diaphragmatic dome is transmitted through the appositional portion of the diaphragm to expand the lower rib cage.[39] Accordingly, pressure in the pleural recess between the apposed diaphragm and the rib cage actually *increases* during inspiration.

It should be noted that diaphragmatic contraction can have inspiratory *or* expiratory effects on the thoracic cage, depending on several factors.[2] For example, mechanical properties of the abdominal compartment have a marked influence on diaphragmatic function. Low compliance (tense ascites) results in reduced dome excursion and decreased insertional force, whereas decrements in abdominal resistance (evisceration) cause loss of the zone of apposition, with resultant expiratory actions on the lower rib cage.[37] There are also important effects related to lung volume. The area of apposition increases as the lungs approach residual volume, causing a greater inspiratory effect on the lower rib cage. Conversely, near total lung capacity, the zone of apposition is nearly absent, resulting in an expiratory force. Studies of diaphragmatic contraction in subjects with cervical spinal cord transection have demonstrated expiratory effects on the upper rib cage and inspiratory effects on the lower rib cage.[40,41]

ABDOMINAL MUSCLES

The abdomen, with the exception of the diaphragm superiorly and the anterior abdominal wall (and small amounts of gas in the gastrointestinal tract), is an essentially incompressible compartment with fixed boundaries. As such, the movement of the diaphragm and thoracic cage is coupled with movement of the anterior abdominal wall. This is a clinically important relationship that should be assessed during a physical examination, because asynchronous and paradoxical motion of the rib cage and abdomen has been associated with an increased respiratory drive[42] and possible risk of ventilatory failure.[43]

The respiratory muscles of the abdominal wall, including the obliques, rectus abdominis, and transversus abdominis, are primarily expiratory in function, by virtue of the increase in abdominal pressure upon contraction. This becomes important when flow demands are not met by passive elastic recoil. As mentioned previously, they aid in unloading the inspiratory muscles during times of stress by their effects on lung volume. In addition, the tonic contraction of the abdominal muscles to help maintain posture in the upright position elongates the diaphragm, thus improving its length-tension relationship.

ASSESSMENT OF CHEST WALL FUNCTION

Pressure measurements across the chest wall can be readily obtained to assess the ability of the respiratory muscles to perform the work of breathing. As mentioned earlier with regard to the respiratory system, the chest wall can be studied during static as well as dynamic maneuvers to obtain important information about function. It should be noted that although these functional tests are of interest to physiologists and researchers, their clinical application is limited.

The Rahn diagram is a graphic representation of the relaxed respiratory system's P-V characteristics (see Fig. 63-2). It provides information on the passive elastic properties of the components of the respiratory system. For accurate chest wall measurements, complete respiratory muscle relaxation is required.

The function of the active chest wall can be assessed with the Campbell diagram (Fig. 63-14), which plots changes in lung volume against pleural pressure. Two curves are generated, one representing a passive inflation of the lungs similar to the Rahn tracing, and the other representing an active inspiration, correlating progressively negative pleural pressures with increasing volume. The work performed by the inspiratory muscles,

$$\int (\text{Pmus } \Delta V,) \qquad \text{(Equation 19)}$$

is represented by the hatched areas of the Campbell diagram. The sum of both areas gives the total work of breathing per inspired breath. The average total work of breathing has been found to be 2.2 ± 0.92 g * cm/mL at a frequency of 15 breaths per minute.[44] Muscle force reserve can be determined from a Campbell diagram that includes plots of maximal respiratory pressures. Here, the difference between the maximal static inspiratory pressures and actual peak pressure can provide an estimation of the likelihood of fatigue.

These methods are difficult to use in mechanically ventilated patients. In this setting, simple ventilator waveform analysis can be helpful. For example, deviation of the inspiratory flow waveform from the relaxed tracing indicates active patient effort as a result of flow deprivation—that is, the patient's demands are not being met by the set inspiratory flow.[45] Maximal inspiratory pressure is a commonly used measurement in the ICU, particularly in weaning protocols.

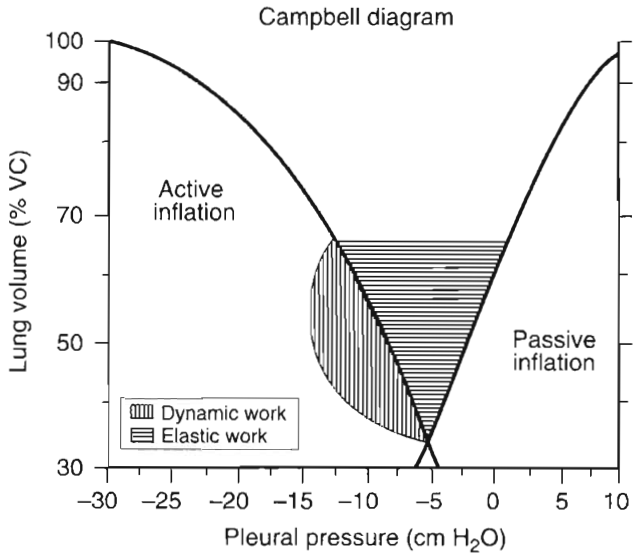

FIGURE 63–14. Campbell diagram, representing work performed by inspiratory muscles during a breathing cycle. *Vertical hatching,* Work done to overcome resistive pressures. *Horizontal hatching,* Work done to overcome respiratory system elastance. VC, vital capacity. (From American Thoracic Society/European Respiratory Society: ATS/ERS statement on respiratory muscle testing. Am J Respir Crit Care Med 2002;166:518-624.)

High generated pressures probably correlate with adequate muscle strength, but low values may be related to volitional factors. Moreover, standardized testing has shown poor reproducibility.[46]

RESPIRATORY MUSCLE FUNCTION IN DISEASE

Impairment or failure of the respiratory pump can occur at any of several levels. Dysfunctional central respiratory control, such as during coma or intoxication, alters neural output to the respiratory muscles. Neuromuscular diseases, such as myasthenia gravis or muscular dystrophy, result in primary muscle weakness, whereas metabolic abnormalities (malnutrition, thyroid disease) affect the muscle tension-generating machinery. Lung hyperinflation, such as occurs in COPD or asthma, puts the chest wall at a mechanical disadvantage because of alterations in the length-tension relationship.

Much attention has been given to the concept of respiratory muscle fatigue,[47] both in acute respiratory failure and in relation to chronic lung disease. Muscle fatigue is defined as a condition associated with loss of the capacity for developing force, velocity, or both resulting from muscle activity, which is reversible by rest.[48] This contrasts with the definition of muscle weakness, in which the rested muscle remains impaired. Fatigue can be induced in striated muscle when working against an increased load. This has been reproduced in normal human respiratory muscles forced to work against high inspiratory airflow resistance.[49] Fatigue can be classified as central fatigue, peripheral high-frequency fatigue, or peripheral low-frequency fatigue.[50] It is likely that all three play a role in respiratory muscle fatigue at any given time.

There is no single measurement of force that can adequately measure respiratory muscle fatigue. Rather, fatigue is implied by the deterioration of force during serial measurements over time. The factors important in respiratory muscle fatigue—magnitude and duration of contraction—are incorporated into the calculation of the pressure-time index of the diaphragm (PT_{di}):

$$PT_{di} = (P_{di}/_{P_{di,max}})(T_i/T_{tot}) \qquad \text{(Equation 20)}$$

where P_{di} denotes transdiaphragmatic pressure (a measure of magnitude), T_i is inspiratory time, and T_{tot} is total breath time. When breathing is accomplished primarily by diaphragmatic function, a critical pressure-time index is reached at values of 0.15 to 0.18, above which functional failure readily occurs.[51] Similar ranges have been obtained for rib cage muscles as well.[52] Unfortunately, because these values were experimentally obtained in normal subjects breathing against imposed loads, the true values that apply to patients with impending respiratory failure, in whom other factors (hypoxemia, hemodynamic instability) are in play, is not known.

RESPIRATORY MUSCLE FUNCTION IN ACUTE RESPIRATORY FAILURE

The inability of the respiratory pump to meet metabolic demands, resulting in acute respiratory failure, is a result of either increase in the ventilatory load above a critical level or inability of the respiratory muscles to generate sufficient force. Assessment of the breathing pattern may be helpful in patients with impending respiratory failure. For example, tachypnea and paradoxical motion of the thorax and abdomen are frequently encountered in this setting, but they are not specific or diagnostic of muscle fatigue.

Work of breathing is a global measure of respiratory pump activity and reflects the imposed respiratory load, which is often a result of abnormalities in respiratory mechanics. Most of the work of breathing, in both health and disease states, occurs during inspiration (W_i) and is related to the static elastance (E_{st}) of the respiratory system[53]:

$$W_{i,st} = 0.5\ E_{st} \cdot \Delta V \qquad \text{(Equation 21)}$$

A linear relationship is assumed between elastance and the volumes measured. The contribution of dynamic factors to work of breathing, such as increases in airway resistance in COPD or asthma resulting in dynamic hyperinflation, must also be accounted for. In such cases, the equation becomes:

$$W_{i,st} = 0.5\ E_{st} \cdot \Delta V + PEEP_i \cdot \Delta V \qquad \text{(Equation 22)}$$

Patients with acute respiratory failure related to COPD have been found to have increased inspiratory resistance, increased dynamic elastance, and up to twice the level of intrinsic PEEP ($PEEP_i$) compared with COPD patients not in acute respiratory failure.[54] Dynamic hyperinflation has secondary deleterious effects on respiratory muscle function, related primarily to Starling's law (suboptimal coupling of the tension-generating components of the muscle fibers). The increased work of breathing resulting from dynamic hyperinflation can be demonstrated graphically by the Campbell diagram (Fig. 63-15).[55]

Thus, relatively small insults leading to increased work of breathing and subsequent respiratory muscle fatigue could precipitate acute respiratory failure in patients with "compensated" COPD. Although impairment of inspiratory muscle function related to dynamic hyperinflation is classically

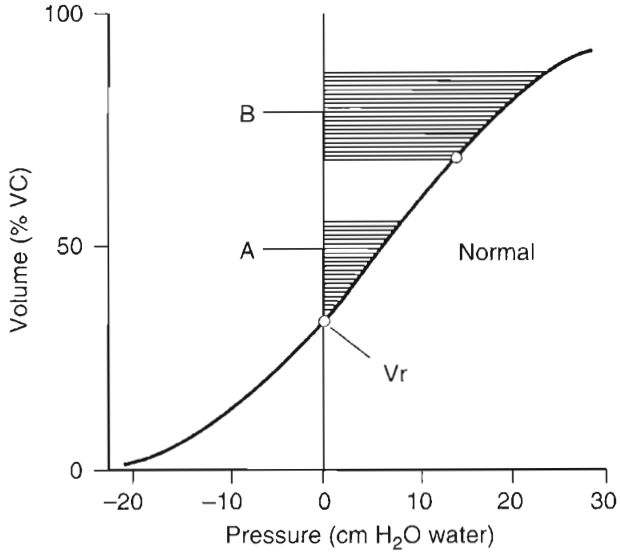

FIGURE 63–15. Volume-pressure (Campbell) diagram of the relaxed respiratory system of a dynamically hyperinflated subject. *Hatched area A,* Elastic work for a breath starting from relaxation volume (Vr). *Hatched area B,* Elastic work for a breath starting from a volume of 29% vital capacity (VC) above Vr. (From Eissa NT, Milic-Emili J: Modern concepts in monitoring and management of respiratory failure. Anesthesiol Clin 1991;9:199-218.)

associated with obstructive lung diseases, it is also seen in cases of pneumonia and chest trauma.[42]

A number of other disorders seen in critical illness have been associated with reduced respiratory muscle force generation. Sepsis, even in the absence of direct lung involvement, can cause respiratory failure related to increased metabolic demands as well as respiratory muscle dysfunction.[56] Direct effects on muscle function have been related to failure of neuromuscular contraction, derangements in excitation-contraction coupling, and direct cytotoxic effects.[56]

Critical illness polyneuropathy, associated with varying degrees of weakness and axonal degeneration on electromyography and denervation atrophy on muscle biopsy, has a reported incidence as high as 25%.[57] The causative role of critical illness polyneuropathy in respiratory failure is controversial, because it is often associated with other conditions that affect global muscle function, such as sepsis and multiorgan system failure.[58] It has, however, been documented in cases of respiratory failure independent of these risk factors.[59] Critical illness myopathy, which can coexist with polyneuropathy, is most commonly reported in cases of severe asthma and may be related to glucocorticoid and neuromuscular blocking agent administration.[60] Finally, there is mounting animal model data showing that mechanical ventilation has direct harmful effects on diaphragmatic structure and function.[61,62] Putative mechanisms include atrophy related to disuse (particularly with prolonged mechanical ventilation), tonic effects of PEEP, and confounding effects of anesthesia and neuromuscular blocking agents.

WEANING FROM MECHANICAL VENTILATION

Clinical assessment alone is insufficient to predict successful weaning from mechanical ventilation,[63] and respiratory muscle function is only one determinant of weaning ability. Unfortunately, the incorporation of many objective methods into weaning paradigms has not proved particularly useful. The shortcomings of breathing pattern assessment were mentioned earlier, and measurements of maximal inspiratory pressures are not easily reproduced. Measurement of pressure-time indices has not been readily adopted in ICU practice, and work-of-breathing determinations are cumbersome and seemingly restricted to the research setting. The most widely adopted and useful predictor of weaning success is the ratio of breathing frequency to tidal volume, as first reported by Yang and Tobin.[64] This involves the simple use of a spirometer attached to the endotracheal tube during a spontaneous breathing trial. A ratio of 105 breaths/min per liter provides the best separation between subjects who will succeed and fail at weaning.

ACKNOWLEDGMENTS

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A wide-ranging discussion of various diseases of respiratory muscles, including an explanation of the molecular mechanisms of clinically applicable disorders encountered in the ICU.

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A comprehensive review of the physiologic basis of classic respiratory system mechanics. Discusses lung and chest wall mechanical properties, as well as assessment of respiratory muscle function.

Chapter 64

HEART-LUNG INTERACTIONS

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KEY POINTS

1. **Spontaneous ventilation is exercise.**
2. In patients with cardiovascular insufficiency and increased work of breathing, initiation of mechanical ventilatory support improves oxygen (O_2) delivery to the remainder of the body by decreasing respiratory muscle O_2 demand. To the extent that mixed venous O_2 also increases (owing to reduced O_2 consumption), arterial O_2 partial pressure also increases, without any improvement in gas exchange.
3. The transition from mechanical ventilatory support to spontaneous ventilation is a cardiovascular stress test. Patients who fail to wean manifest cardiovascular insufficiency during the attempt. Myocardial ischemia, infarction, gut ischemia, and decreasing mixed venous O_2 are all manifestations of failure to wean. Improving cardiovascular reserve or supplementing support with inotropic therapy may allow a patient to bridge from mechanical to spontaneous ventilation.
4. **Changes in lung volume alter autonomic tone and pulmonary vascular resistance** and, at high lung volumes, compress the heart in the cardiac fossa in a fashion analogous to cardiac tamponade.
5. Small increases in lung volume induce vagal withdrawal and inspiration-associated cardiac acceleration. Loss of such respiratory sinus arrhythmia is a manifestation of dysautonomia in diabetics with peripheral neuropathy. Larger increases in lung volume induce withdrawal of sympathetic tone and may be a cause of cardiac depression in patients with acute lung injury, in whom ventilation hyperinflates the remaining aerated lung units.
6. Changes in lung volume are determined by changes in transpulmonary pressure and lung compliance. As lung volume increases, so does the pressure difference between airway and pleural pressure. When this pressure difference exceeds pulmonary artery pressure, pulmonary vessels collapse as they pass from the pulmonary arteries into the alveolar space, increasing pulmonary vascular resistance. Thus, increasing lung volume and hyperinflation may increase pulmonary vascular resistance, pulmonary artery pressure, and right ventricular afterload, impeding right ventricular ejection.
7. Decreases in lung volume below functional residual capacity, as occurs in patients with acute lung injury, are associated with collapse of terminal airways, resorption of alveolar O_2, and subsequent increased pulmonary vasomotor tone by the process of hypoxic pulmonary vasoconstriction. Recruitment maneuvers, positive end-expiratory pressure, and continuous positive airway pressure may all refresh collapsed alveoli, reversing hypoxic pulmonary vasoconstriction and reducing pulmonary artery pressure.
8. Overinflation of the lungs compresses the heart, decreasing biventricular volumes while increasing cardiac filling pressures. At the extreme, this can cause volume-unresponsive hypovolemic shock.
9. **Spontaneous inspiration and spontaneous inspiratory efforts decrease intrathoracic pressure,** and diaphragmatic descent increases intra-abdominal pressure. These combined effects cause right atrial pressure inside the thorax to decrease, but venous pressure in the abdomen to increase, markedly increasing the pressure gradient for systemic venous return.
10. The augmentation in venous return is constrained by the Starling resistor forces, limiting maximal venous flow as intrathoracic pressure becomes negative relative to atmosphere, and vascular compression in the liver from diaphragmatic descent. Right ventricular filling is limited by pericardial constraints that limit maximal biventricular volume.
11. The greater the decrease in intrathoracic pressure, the greater the increase in left ventricular ejection pressure for a constant arterial pressure. With obstructed inspiratory efforts, as occur with obstructive sleep apnea, upper airway obstruction, and bronchospasm, the increase in left ventricular afterload can precipitate acute left ventricular failure, pulmonary edema, and cardiovascular collapse. Mechanical ventilation, by abolishing the negative swings in intrathoracic pressure, selectively decreases left ventricular afterload, as long as the increases in lung volume and intrathoracic pressure are small.
12. Positive-pressure ventilation increases intrathoracic pressure, and diaphragmatic descent increases

intra-abdominal pressure. Thus, the decrease in the pressure gradient for venous return is less than would otherwise occur if the only change were an increase in right atrial pressure. However, in hypovolemic states, positive-pressure ventilation can induce profound decreases in venous return.

13. Increases in intrathoracic pressure decrease left ventricular afterload and augment left ventricular ejection. In patients with hypervolemic heart failure, this afterload-reducing effect can result in improved left ventricular ejection, increased cardiac output, and reduced myocardial O_2 demand.

Ventilation can profoundly alter cardiovascular function. The boundaries of the cardiovascular unit's responsiveness are defined by both cardiovascular and pulmonary factors. These limitations include the myocardial reserve, circulating blood volume, blood flow distribution, autonomic tone, endocrinologic responses, lung volume, intrathoracic pressure (ITP), and surrounding pressures for the remainder of the circulation.

RELATION AMONG AIRWAY PRESSURE, INTRATHORACIC PRESSURES, AND LUNG VOLUME

Since the introduction of positive-pressure ventilation, the concept of relating hemodynamic consequences to airway pressure has been widely accepted.[1,2] This gross simplification has been the source of much confusion in the clinical literature, largely because changes in airway pressure are often equated with changes in both pleural pressure and lung volume. However, the association between airway pressure and other hemodynamically relevant factors is highly variable as ventilatory patterns, airway resistance, and lung compliance change; does not accurately reflect changes in pericardial pressure, which is a primary determinant of transmural left ventricular (LV) pressure; and may mislead the caregiver into altering therapy based on these wrong assumptions. Numerous studies have demonstrated that the primary determinants of the hemodynamic responses to ventilation are due to changes in intrathoracic pressure and lung volume,[3] not airway pressure. We use the term *intrathoracic pressure (ITP)* to refer to a nonspecific intrathoracic surface pressure. When specific intrapleural surface pressures are meant, they are referred to as lateral chest wall, diaphragm, and juxtacardiac pleural pressures or pericardial pressure, as appropriate.

AIRWAY PRESSURE, LUNG VOLUME, AND REGIONAL PLEURAL PRESSURES

During positive-pressure inspiration, increases in airway pressure parallel increases in lung volume. In a sedated and paralyzed patient, only lung and thoracic compliance determines the relation between airway pressure and lung volume at end-inspiration. However, if a ventilated patient actively resists lung inflation or sustains expiratory muscle activity at end-inspiration, end-inspiratory airway pressure will exceed resting airway pressure for that lung volume. Similarly, if patient activity prevents full exhalation by expiratory braking, for the same end-expiratory airway pressure (often measured as positive end-expiratory pressure [PEEP]), lung volume may be much higher than predicted from end-expiratory airway pressure values alone. Finally, even if inspiration is passive and no increased airway resistance is present, airway pressure may rapidly increase over minutes as chest wall compliance decreases. If intra-abdominal pressure increases, end-expiratory airway pressure must also increase for a constant tidal volume. During inspiration, airway pressure increases as a function of both total thoracic compliance and airway resistance. Thus, in subjects with marked bronchospasm, such as asthmatics, peak airway pressure greatly exceeds end-inspiratory plateau airway pressure.

Changes in airway pressure are related to changes in lung volume through the interaction of airway resistance and both lung and chest compliance, as manifested by the relative increase in ITP during inspiration. Several common clinical examples support this statement. If either lung or chest wall compliance changes, airway pressure may change without an actual change in the tidal breath. The two common clinical scenarios of this phenomenon are mucus plugging and fighting the ventilator. Similarly, if spontaneous breaths cause ITP to decrease during positive-pressure inspiration, both peak and mean airway pressures will decrease, whereas if bronchospasm causes airway resistance to increase, for a constant tidal breath, both peak and mean airway pressures will increase.

As the lung expands, it pushes on the surrounding structures, distorting them and causing their surface pressures to increase. This lung expansion induces an increase in lateral wall, diaphragmatic, and juxtacardiac pleural pressure, as well as pericardial pressure. The degree of increase in each of these surface pressures is a function of the compliance and inertance of their opposing structures. These interactions were described by Novak and colleagues, who demonstrated that the changes in pleural pressure induced by positive-pressure ventilation are not similar in all regions of the thorax and increase differently as inspiratory flow rate and frequency increase.[4] Pleural pressure on the diaphragm increases least during inspiration, and juxtacardiac pleural pressure increases most. Because the diaphragm is very compliant, it seems reasonable that diaphragmatic ITP should increase less than lateral chest wall pleural pressure in response to sudden increases in lung volume. However, if abdominal distention develops, the diaphragm becomes relatively noncompliant because of the increase in abdominal pressure. Under these conditions, ITP tends to increase similarly across the thorax.

A hydrostatic pressure gradient exists in the pleural space. Dependent regions have a higher baseline pressure than nondependent regions in proportion to their height above or below the heart (measured in centimeters), which equates with an equal pressure difference (measured in cm H_2O). In a supine subject, steady-state apneic pleural pressures along the horizontal plane from apex to diaphragm are similar, whereas anterior pleural pressure is less and posterior gutter pleural pressure is greater (Fig. 64-1).

Care must be taken to determine not only what types of ventilation are being compared but also how and where estimates of pleural pressure and pericardial pressure are made. For example, if estimates of transpulmonary pressure are needed to define lung compliance and its change with recruitment maneuvers, lateral chest wall pleural pressure more accurately reflects the pressure-volume characteristics of the intact lung.[4] Similarly, if diaphragmatic work is to be

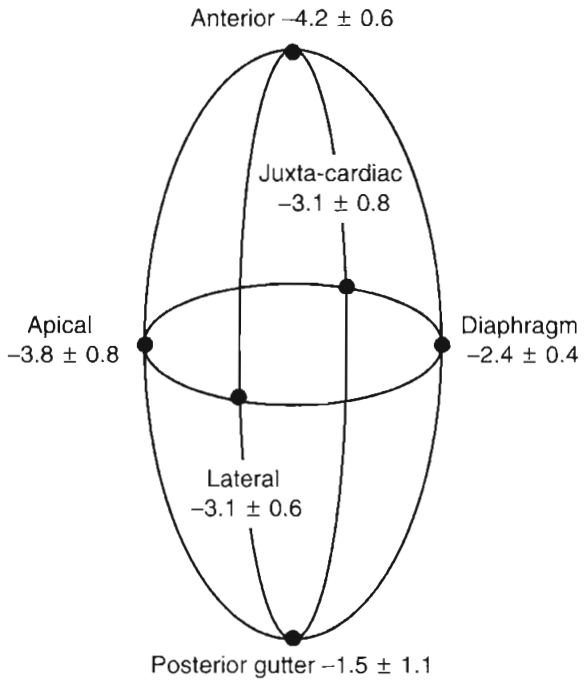

FIGURE 64–1. Apneic pleural pressure (Ppl) (mean ± standard error) in torr for six pleural regions of the right hemothorax of an intact supine canine model: anterior, apical, posterior gutter, diaphragmatic, juxtacardiac, and lateral. Ellipses represenst regional measurements defining three orthogonal planes. (From Novak RA, Matuschak GM, Pinsky MR: Effect of ventilatory frequency on regional pleural pressure. J Appl Physiol 1988;65:1314-1323.)

monitored, either esophageal or diaphragmatic pleural pressure should be used. Finally, if heart-lung interactions are being examined, juxtacardiac pleural pressure is the most accurate measure of pleural pressure; increases during positive-pressure inspiration will be underestimated by esophageal pressure. Because the heart is fixed within a cardiac fossa, juxtacardiac pleural pressure increases more than lateral chest wall or diaphragmatic pleural pressure does. If pericardial volume restraints exist, juxtacardiac pleural pressure will underestimate pericardial pressure. However, with sustained lung compression of the heart overriding tamponade, both juxtacardiac pleural pressure and pericardial pressure will be similar.

PLEURAL PRESSURE AND LUNG VOLUME IN ACUTE LUNG INJURY

The interaction of airway pressure, lung volume, and ITP in the setting of lung disease is complex and can differ in the same pathologic setting, depending on the tidal volume, inspiratory flow rate, ventilatory frequency, and body position. The presence of parenchymal disease, airflow obstruction, and extrapulmonary processes that directly alter chest wall–diaphragmatic contraction also profoundly alters these interactions. Static lung expansion occurs as airway pressure increases because the transpulmonary pressure (airway pressure relative to ITP) increases. If lung injury induces alveolar flooding or increased pulmonary parenchyma stiffness, greater increases in airway pressure will be required to distend the lungs to a constant end-inspiratory volume. Romand and coworkers demonstrated that airway pressure increased more during acute lung injury (ALI) than in control conditions for a constant tidal volume, whereas lateral chest wall pleural pressure and pericardial pressure increased similarly between both conditions if tidal volume was held constant (Fig. 64-2).[5] These data agree with the studies of O'Quinn and associates, which found that the primary determinant of the increase in pleural pressure and pericardial pressure during positive-pressure ventilation is lung volume change, not airway pressure change.[6] Presumably, pericardial pressure does not increase as much as ITP because the increasing lung volume reduces the filling of the ventricles, decreasing their size inside the cardiac fossa. To summarize, for a constant increase in lung volume, ITP increases similarly, despite drastic changes in lung compliance and airway resistance.

AIRWAY, PLEURAL, AND PERICARDIAL PRESSURES

Because the distribution of alveolar collapse and lung compliance in acute respiratory distress syndrome (ARDS) and ALI is nonhomogeneous, lung distention during positive-pressure ventilation must reflect overdistention of some regions of the lung at the expense of noncompliant or poorly compliant regions. Accordingly, airway pressure reflects the distention of lung units that were aerated before inspiration but may

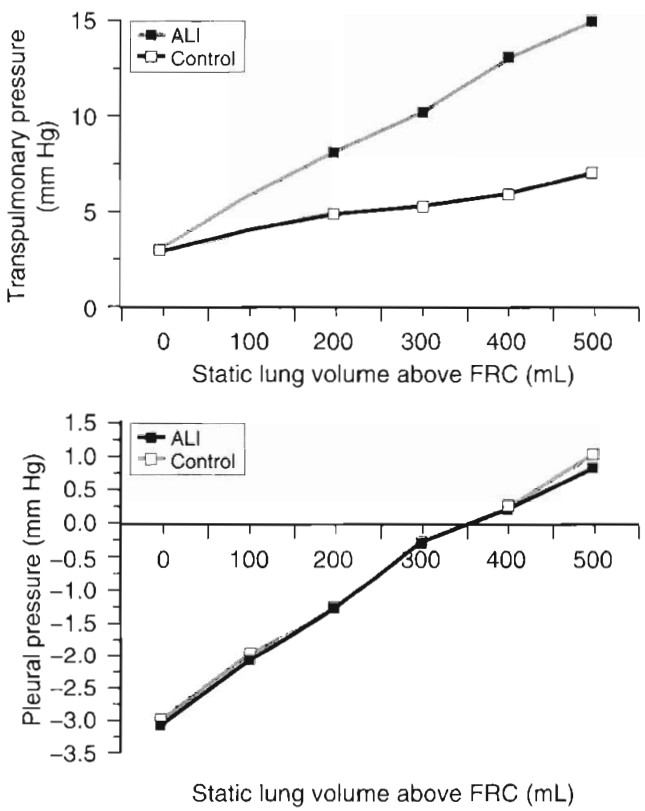

FIGURE 64–2. Relation between airway pressure (Paw) and tidal volume (Vt) and between pleural pressure (Ppl) and tidal volume (Vt) in a control group and in oleic acid–induced acute lung injury (ALI) in a canine model. Note that despite greater increases in airway pressure for the same tidal volume during ALI as compared with control conditions, pleural pressure and pericardial pressure increase similarly in both groups for the same increase in tidal volume. FRC, functional residual capacity. (From Romand JA, Shi W, Pinsky MR: Cardiopulmonary effects of positive pressure ventilation during acute lung injury. Chest 1995;108:1041-1048.)

not reflect the degree of lung inflation of nonaerated lung units. In an animal model of ALI, in which tidal volume was either kept constant at preinjury levels or reduced to match preinjury plateau airway pressure (pressure-limited ventilation), both pleural pressure and pericardial pressure increased less in comparison to both preinjury states and in ALI when tidal volume remained at preinjury levels.[5]

Because ALI is often nonhomogeneous, with aerated areas of the lung displaying normal specific compliance, large increases in airway pressure overdistend aerated lung units.[7] Vascular structures that are distended have a greater increase in their surrounding pressure than do collapsible structures that do not distend.[8] Romand and colleagues[5] and Scharf and Ingram[9] demonstrated that despite this nonhomogeneous alveolar distention, if tidal volume is kept constant, pleural pressure will increase equally, independent of the mechanical properties of the lung. Thus, under constant tidal volume conditions, changes in peak and mean airway pressures reflect changes in the mechanical properties of the lungs and patient coordination but may not reflect changes in ITP. Similarly, these changes in airway pressure may not alter global cardiovascular dynamics. Underscoring airway pressure's limited ability to reflect either ITP or pericardial pressure, Pinsky and coworkers demonstrated in postoperative patients that the percentage of airway pressure increase transmitted to the pericardial surface is not constant from one subject to the next as PEEP is increased (Fig. 64-3).[10] Thus, one cannot predict the amount of increase in pericardial pressure or pleural pressure that will occur in patients as PEEP is increased. Accordingly, assuming some constant fraction of airway pressure transmission to the pleural surface as a means of calculating the effect of increasing airway pressure on pleural pressure is inaccurate and potentially dangerous to patient management.

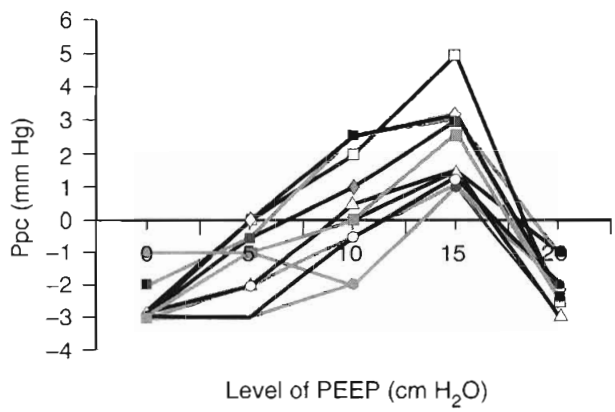

FIGURE 64–3. Relation between pericardial pressure (Ppc) and airway pressure as apneic levels of positive end-expiratory pressure (PEEP) are progressively increased from 0 to 15 cm H_2O and then back to 0 in increments of 5 cm H_2O in patients immediately following open heart surgery. Note that although pericardial pressure increases in all subjects as PEEP is increased from 0 to 15 cm H_2O, the initial pericardial pressure value and the proportional change in pericardial pressure with incremental increases in PEEP are quite different among subjects, such that no specific proportion of airway pressure transmission to the pericardial surface can be assumed to occur in all patients. (From Pinsky MR, Vincent JL, DeSmet JM: Estimating left ventricular filling pressure during positive end-expiratory pressure in humans. Am Rev Respir Dis 1991;143:25-31.)

Although it may be difficult to know the actual pleural pressure, it is possible to determine the ventilation-induced change in pleural pressure. During airway occlusion maneuvers, lung volume does not change, and transpulmonary pressure is also constant; this means that the change in ITP is equal to the change in airway pressure.[11]

Two limitations to the use of intrathoracic vascular pressures to estimate pericardial pressure and ITP exist. First, pericardial pressure and ITP may not be similar and may not increase by similar amounts with the application of positive airway pressure if the pericardium becomes a limiting membrane.[12,13] Operationally, this equates to pericardial pressure exceeding juxtacardiac pleural pressure by the degree to which the pericardium limits biventricular dilatation. Thus, determinations of pericardial pressure using ITP measures may underestimate pericardial pressure and overestimate the increase in pericardial pressure as airway pressure is increased. Second, esophageal pressure is often used clinically to estimate swings in both pleural pressure and pericardial pressure. However, esophageal pressure changes underestimate both the positive swings in pleural pressure and the mean increase in pleural pressure seen with increases in lung volume during positive-pressure ventilation.

HEMODYNAMIC EFFECTS OF VENTILATION

Lung volume increases in a tidal fashion during both spontaneous and positive-pressure ventilation. However, ITP decreases during spontaneous inspiration and increases during positive-pressure inspiration. Thus, changes in ITP and in the metabolic requirements to create these changes represent the primary determinants of the hemodynamic differences between spontaneous and positive-pressure ventilation.[14,15]

Heart-lung interactions can be broadly grouped, based on three concepts that usually coexist in the clinical setting. First, spontaneous ventilatory efforts are exercise; they require oxygen (O_2) and blood flow, thus placing demands on cardiac output and producing carbon dioxide (CO_2), adding ventilatory stress on CO_2 excretion. Second, inspiration increases lung volume above resting end-expiratory volume. Thus, some of the hemodynamic effects of ventilation may be due to changes in lung volume and chest wall expansion. Third, spontaneous inspiration decreases ITP, whereas positive-pressure ventilation increases ITP; thus, the differences between spontaneous ventilation and positive-pressure ventilation reflect primarily the differences in ITP swings and the energy necessary to produce them.

VENTILATION AS EXERCISE

Spontaneous ventilatory efforts are induced by respiratory muscle contraction. Blood flow to these muscles is derived from several arterial circuits whose absolute flow is believed to exceed the highest metabolic demand of maximally exercising skeletal muscle.[16] Thus, under normal cardiovascular conditions, blood flow is not the limiting factor determining maximal ventilatory effort. Although ventilation normally requires less than 5% of total O_2 delivery to meet its demand,[16] in lung disease states in which the work of breathing is increased, such as pulmonary edema or bronchospasm, the work of breathing can increase metabolic demand for O_2 to

25% or 30% of total O_2 delivery.[16-19] Further, if cardiac output is limited, blood flow to other organs and to the respiratory muscles may be compromised, inducing both tissue hypoperfusion and lactic acidosis.[20-23] Starting mechanical ventilation may reduce metabolic demand, increasing venous O_2 saturation for a constant cardiac output and arterial oxygen content (CaO_2). Intubation and mechanical ventilation, when adjusted to the metabolic demands of the patient, may dramatically decrease the work of breathing, resulting in increased O_2 delivery to other vital organs and decreased serum lactic acid levels. These cardiovascular benefits can also be realized with the effective use of noninvasive continuous positive airway pressure (CPAP) by ventilation mask.[24] The obligatory increase in venous O_2 saturation will result in an increase in arterial O_2 partial pressure if fixed right-to-left shunts exist, even if mechanical ventilation does not alter the ratio of shunt blood flow to cardiac output. Finally, if cardiac output is severely limited, respiratory muscle failure will develop despite high central neuronal drive, such that many patients with heart failure die of respiratory failure before cardiovascular standstill.[25]

Ventilator-dependent patients who fail to wean from mechanical ventilation may occasionally have impaired baseline cardiovascular performance,[26] but during weaning attempts, they routinely develop overt signs of heart failure such as pulmonary edema,[26,27] myocardial ischemia,[28-31] tachycardia, and gut ischemia.[32] Jabran and associates demonstrated that although all subjects increase their cardiac output in response to a weaning trial, those who subsequently fail to wean demonstrate a reduction in mixed venous O_2 saturation, consistent with a failing cardiovascular response to increased metabolic demand.[33] Importantly, the increased work of breathing may come from endotracheal tube flow resistance.[34] Thus, weaning from mechanical ventilatory support can be considered a cardiovascular stress test. Investigators have documented weaning-associated signs of ischemia (on electrocardiogram and thallium cardiac blood flow scan) both in subjects with known coronary artery disease[30] and in otherwise normal patients.[29,31] Using this same logic, placing patients with severe heart failure or ischemia on ventilatory support by either intubation and ventilation[35] or noninvasive CPAP[36] can reverse myocardial ischemia.

CHANGES IN LUNG VOLUME

Changing lung volume alters autonomic tone and pulmonary vascular resistance. At high lung volumes, the enlarged lungs compress the heart in the cardiac fossa, limiting absolute cardiac volumes in a fashion analogous to tamponade. But unlike tamponade, wherein pericardial pressure selectively increases, with hyperinflation, both juxtacardiac pleural pressure and pericardial pressure increase together.

Autonomic Tone

The lungs are richly innervated with integrated somatic and autonomic fibers that originate in, traverse, and end in the thorax. Inflation induces immediate changes in autonomic output. The most commonly described inflation-chronotropic responses act through vagal-mediated reflex arcs.[37,38] Lung inflation to normal tidal volumes (<10 mL/kg) increases heart rate via parasympathetic tone withdrawal. Inspiration-associated cardioacceleration is referred to as respiratory sinus arrhythmia[39] and denotes normal autonomic tone.[40] Loss of respiratory sinus arrhythmia denotes dysautonomia. However, some degree of respiratory-associated heart rate change is intrinsic to the heart itself. For example, in denervated human hearts (transplants), a small degree of ventilation-associated heart rate change persists,[41] suggesting that mechanoreceptors in the right atrium can alter sinoatrial tone.

Lung inflation to larger tidal volumes (>15 mL/kg) decreases heart rate. Pulmonary vasoconstriction also may occur through vagal reflex arcs[42] but does not appear to have significant hemodynamic effects. Reflex arterial vasodilatation can also occur with lung hyperinflation.[37,43-47] This inflation-vasodilatation response appears to be mediated by afferent vagal fibers, because it is abolished by selective vagotomy. Interestingly, blocking sympathetic afferent fibers also blocks this reflex,[45,48] presumably by withdrawing central sympathetic tone. Although this inflation-vasodilatation response induces expiration-associated reductions in LV contractility in healthy volunteers[49] and in ventilator-dependent patients with the initiation of high-frequency ventilation[37] or hyperinflation,[45] its clinical significance in other patient groups is unknown. Because patients with ALI often ventilate a small amount of lung, these patients may experience regional hyperinflation and develop reflex cardiovascular depression. Interestingly, several studies comparing larger tidal volume ventilation with pressure-limited ventilation documented better hemodynamic status with pressure-limited ventilation. Importantly, for the same decrease in cardiac output, the heart rate increases less with the application of PEEP than with hemorrhage.[42] The reasons for this difference are not known but may reflect PEEP-induced sympatholytic actions and increased arterial pressure minimizing baroreceptor stimulation.

Ventilation also alters the control of intravascular fluid balance via hormonal release. Both positive-pressure ventilation and sustained hyperinflation stimulate endocrinologic responses that induce fluid retention by means of right atrial stretch receptors. Plasma norepinephrine, plasma rennin activity,[50,51] and atrial natriuretic peptide[52] increase during positive-pressure ventilation with or without PEEP.

Determinants of Pulmonary Vascular Resistance

Changes in lung volume are caused by changes in transpulmonary distending pressure, the pressure difference between alveolar pressure and ITP. Because pulmonary tissue pressure and ITP are nearly identical, increasing lung volume increases the difference between alveolar and tissue pressures, making pulmonary vascular resistance increase independent of any effect of volume change on humeral or autonomic responses.[14,53-58] Lung inflation affects cardiac function and cardiac output primarily by altering right ventricular (RV) preload and afterload.[57]

RV afterload is the maximal RV systolic wall stress during contraction,[59] which, by Laplace's law, equals the product of the RV radius of curvature (a function of end-diastolic volume) and transmural pressure (a function of systolic RV pressure).[60] Changes in ITP that occur without changes in lung volume, as may occur with obstructive inspiratory efforts, do not alter the pressure gradient between the right ventricle and the pulmonary artery, so pulmonary vascular resistance is not changed.

Systolic RV pressure approximates transmural systolic pulmonary artery pressure when no pulmonary stenosis is present. Transmural pulmonary artery pressure can increase

by one of two mechanisms: (1) an increase in pulmonary artery pressure without an increase in pulmonary vasomotor tone, as occurs with increases in blood flow (exercise) or passive increases in outflow pressure (LV failure), or (2) an increase in pulmonary vascular resistance. Usually any increase in transmural pulmonary artery pressure during positive-pressure ventilation is due to an increase in pulmonary vascular resistance, because neither instantaneous cardiac output[61] nor LV filling[11] increases. Increases in transmural pulmonary artery pressure impede RV ejection,[62] decreasing RV stroke volume[63] and causing RV dilatation and passive obstruction to venous return,[64,65] which can rapidly progress to acute cor pulmonale.[66] If RV dilatation and pressure overload persist, RV free wall ischemia and infarction may develop.[67] Importantly, rapid fluid challenges in the setting of acute cor pulmonale can precipitate profound cardiovascular collapse due to excessive RV dilatation, RV ischemia, and compromised LV filling through the process of ventricular interdependence (discussed later). During normal end-inspiration, mild hypoxemia (arterial O_2 partial pressure >65 mm Hg) and low levels of PEEP (<7.5 cm H_2O) should minimally increase transmural pulmonary artery pressure. If slight increases in transmural pulmonary artery pressure are sustained, however, fluid retention occurs, either by intrinsic humeral mechanisms (increased atrial natriuretic peptide secretion) or by therapeutic intravascular volume infusion,[68] resulting in an increase in RV end-diastolic volume and maintenance of cardiac output.[60,69]

The mechanism by which ventilation alters pulmonary vasomotor tone is complex. If regional partial pressure of O_2 in alveolar gas (P_AO_2) decreases below 60 mm Hg, local pulmonary vasomotor tone increases, reducing local blood flow.[70] This process of hypoxic pulmonary vasoconstriction is mediated, in part, by variations in the synthesis and release of nitric oxide by pulmonary vascular endothelial cells. Many pathologic pulmonary processes are associated with regional reductions in P_AO_2, such as atelectasis, airway obstruction, and ventilation-perfusion mismatching. Hypoxic pulmonary vasoconstriction optimizes ventilation-perfusion matching by reducing pulmonary blood flow to those hypoxic regions. However, if alveolar hypoxia occurs throughout the lungs, overall pulmonary vasomotor tone increases, increasing pulmonary vascular resistance and impeding RV ejection.[71] At low lung volumes, alveoli spontaneously collapse as a result of loss of interstitial traction and closure of the terminal airways, causing alveolar hypoxia. Patients with acute hypoxemic respiratory failure have small lung volumes.[72,73] Therefore, pulmonary vascular resistance is often increased in these patients, owing to alveolar collapse and the resultant hypoxic pulmonary vasoconstriction.

Mechanical Ventilation–Induced Changes in Pulmonary Vascular Resistance

Mechanical ventilation can reduce active pulmonary vasomotor tone by one of several related processes. Hypoxic pulmonary vasoconstrictor tone can be decreased by increasing global P_AO_2 by enriching alveolar gas O_2,[74-77] re-expanding collapsed alveolar units by increasing P_AO_2 in those local alveoli,[3,78-80] increasing alveolar ventilation and thus reversing acute respiratory acidosis,[76] or merely decreasing central sympathetic output by allowing patients with ALI to stop fighting for every breath.[81,82] These effects need not require positive-pressure breaths but merely the expansion of collapsed alveoli.[83] This is usually accomplished by the addition of PEEP or CPAP. Thus, if PEEP opens collapsed lung units and replenishes alveolar gas with O_2, hypoxic pulmonary vasoconstriction will be reduced, pulmonary vascular resistance will decrease, and RV ejection will improve.

Changes in lung volume can also profoundly alter pulmonary vasomotor tone by passively compressing the alveolar vessels.[72,79,80] The pulmonary circulation can be separated into two groups of blood vessels, depending on the pressure that surrounds them (Fig. 64-4).[79] The small pulmonary arterioles, venules, and alveolar capillaries sense alveolar pressure as their surrounding pressure and are referred to as alveolar vessels. The large pulmonary arteries and veins, as well as the heart and intrathoracic great vessels of the systemic circulation, sense interstitial pressure or ITP as their surrounding pressure and can be called extra-alveolar vessels. Alveolar pressure minus ITP is the transpulmonary pressure. Increasing lung volume requires transpulmonary pressure to increase. Thus, this extravascular pressure gradient between alveolar and extra-alveolar vessels varies proportionally with changes in lung volume. Importantly, the radial interstitial forces of the lung that keep the airways patent[78,84,85] also act on the extra-alveolar vessels. As lung volume increases, the radial interstitial forces increase, increasing the diameter of both extra-alveolar vessels and airways. This results in a reduction in airway resistance at higher lung volumes and also greater extra-alveolar vessel diameter, increasing their capacitance.[86] This tethering effect is lost with lung deflation, thereby increasing pulmonary vascular resistance.[75,78] The collapse of small airways also induces alveolar hypoxia. Thus, at small lung volumes, pulmonary vascular resistance is increased owing to the combined effect of hypoxic pulmonary vasoconstriction and extra-alveolar vessel collapse.

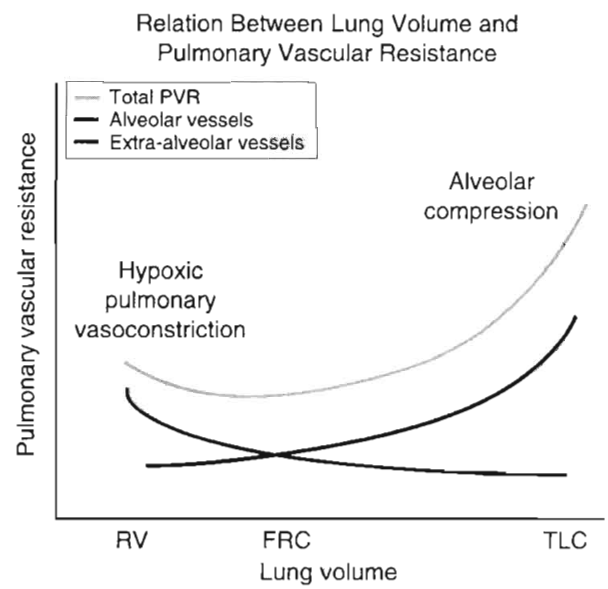

FIGURE 64–4. Schematic diagram of the relation between changes in lung volume and pulmonary vascular resistance (PVR), with the extra-alveolar and alveolar vascular components separated. Note that pulmonary vascular resistance is minimal at resting lung volume or functional residual capacity (FRC). As lung volume increases toward total lung capacity (TLC) or decreases toward residual volume (RV), pulmonary vascular resistance also increases. However, the increase in resistance with hyperinflation is due to increased alveolar vascular resistance, whereas the increase in resistance with lung collapse is due to increased extra-alveolar vessel tone.

Increases in lung volume progressively increase alveolar vessel resistance, becoming noticeable above resting lung volume or functional residual capacity.[75,87] There are two causes of this increased alveolar vessel resistance. First, the heart and extra-alveolar vessels sense ITP as their surrounding pressure, but the alveolar vessels sense alveolar pressure as their surrounding pressure. Thus, an extraluminal transpulmonary pressure gradient exists between these extra-alveolar and alveolar vessels. As lung volume increases, this extraluminal pressure difference increases as well. Because the intraluminal pressure in the pulmonary arteries is generated by RV ejection relative to ITP, but the outside pressure of the alveolar vessels is alveolar pressure, if transpulmonary pressure increases enough to exceed intraluminal vascular pressure, the pulmonary vasculature will collapse where extra-alveolar vessels pass into alveolar loci, reducing the vasculature cross-sectional area and increasing pulmonary vascular resistance. Similarly, increasing lung volume by stretching and distending the alveolar septa may also compress alveolar capillaries, although this mechanism is less well substantiated. Hyperinflation can create significant pulmonary hypertension and may precipitate acute RV failure (acute cor pulmonale)[88] and RV ischemia.[67] Thus, PEEP may increase pulmonary vascular resistance if it induces overdistention of the lung above its normal functional residual capacity. Recently, the effect of inflation on RV input impedance was validated in humans using echocardiographic techniques.[89] Similarly, if lung volumes are reduced, increasing lung volume back to baseline levels by the use of PEEP decreases pulmonary vascular resistance by reversing hypoxic pulmonary vasoconstriction.[90]

Ventricular Interdependence

Changes in RV output must invariably alter LV filling, because the two ventricles are serially linked through the pulmonary vasculature. However, LV preload can also be directly altered by changes in RV end-diastolic volume. If RV volume increases, LV diastolic compliance will decrease by the mechanism of ventricular interdependence.[91] Ventricular interdependence functions through two separate processes. First, increasing RV end-diastolic volume induces a shift of the intraventricular septum into the left ventricle, thereby decreasing LV diastolic compliance (Fig. 64-5).[92] Thus, for the same LV filling pressure, RV dilatation will decrease LV end-diastolic volume and, therefore, cardiac output. This interaction is believed to be the major determinant of the phasic changes in arterial pulse pressure and stroke volume seen in tamponade, referred to as pulsus paradoxus, which can be easily demonstrated during loaded spontaneous inspiration in normal subjects. Spontaneous inspiration increases venous return, causing RV dilatation and decreasing LV end-diastolic compliance. Maintaining a relatively constant rate of venous return, by either volume resuscitation[93] or vasopressor infusion,[1] minimizes this effect. Thus, the presence of pulsus paradoxus can be used as a marker of functional hypovolemia, even if the actual intravascular volume is not reduced.

Mechanical Heart-Lung Interactions

With hyperinflation, the heart may be compressed between the two expanding lungs,[94] increasing juxtacardiac ITP. Because the chest wall and diaphragm can move away from the expanding lungs, whereas the heart is trapped within its cardiac fossa, juxtacardiac ITP may increase more than lateral chest wall or diaphragmatic ITP does.[4,13] This compressive

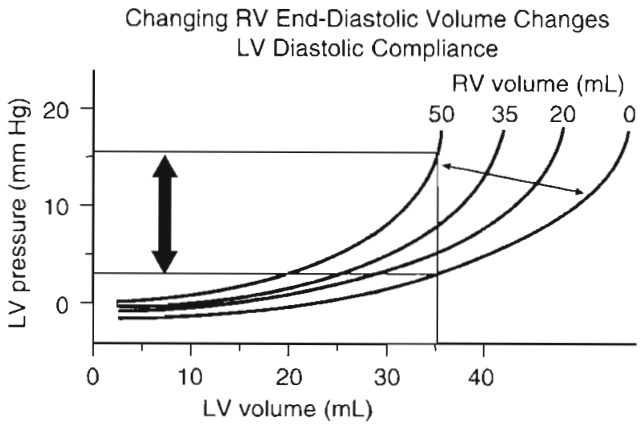

FIGURE 64–5. Schematic diagram of the effect of increasing right ventricular (RV) volumes on the left ventricular (LV) diastolic pressure-volume (filling) relationship. Note that greater RV volumes decrease LV diastolic compliance, such that a higher filling pressure is required to generate a constant end-diastolic volume. (After Taylor RR, Corell JW, Sonnenblick EH, Ross J Jr: Dependence of ventricular distensibility on filling the opposite ventricle. Am J Physiol 1967;213:711-718.)

effect of the inflated lung can be seen with either spontaneous[95] or positive-pressure–induced hyperinflation.[84,85] This decrease in "apparent" LV diastolic compliance[93] was previously misinterpreted as impaired LV contractility, because LV stroke work for a given LV end-diastolic pressure or pulmonary artery occlusion pressure is decreased.[96,97] However, numerous studies have shown that when patients are fluid-resuscitated to return LV end-diastolic volume to its original level, both LV stroke work and cardiac output also return to their original levels,[55,93] despite the continued application of PEEP.[98]

CHANGES IN INTRATHORACIC PRESSURE

The heart within the thorax is a pressure chamber within a pressure chamber. Therefore, changes in ITP affect the pressure gradients for both systemic venous return to the right ventricle and systemic outflow from the left ventricle, independent of the heart itself (Fig. 64-6). Increases in ITP, by increasing right atrial pressure and decreasing transmural LV systolic pressure, reduce the pressure gradients for

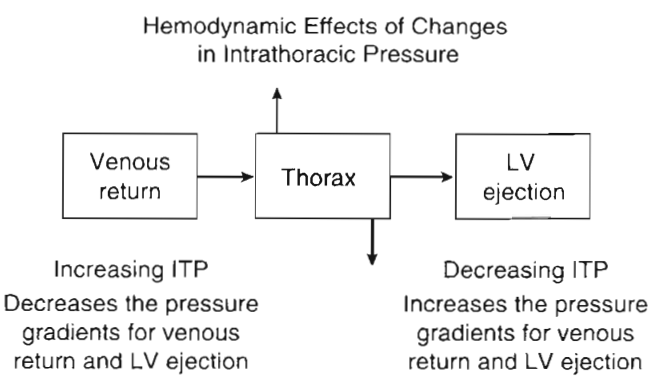

FIGURE 64–6. Schematic diagram of the effect of increasing or decreasing intrathoracic pressure (ITP) on the left ventricular (LV) filling (venous return) and ejection pressure.

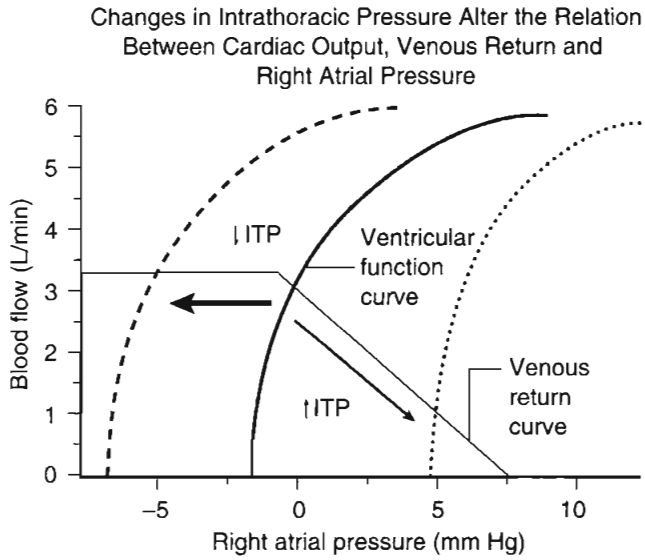

FIGURE 64–7. Schematic representation of the effects of increasing or decreasing intrathoracic pressure (ITP) on steady-state venous return. Note that decreases in ITP that decrease right atrial pressure to below 0 relative to atmospheric pressure increase venous return by only a limited amount, whereas increases in ITP progressively decrease venous return to a complete circulatory standstill.

venous return and LV ejection, decreasing intrathoracic blood volume. Using the same argument, decreases in ITP augment venous return and impede LV ejection and increase intrathoracic blood volume.

Systemic Venous Return

As downstream right atrial pressure varies (as occurs with ventilation), the rate of venous return inversely changes. Pressure in the upstream venous reservoirs is called mean systemic pressure, which is a function of blood volume, peripheral vasomotor tone, and the distribution of blood within the vasculature.[99] Mean systemic pressure does not change rapidly during the ventilatory cycle, whereas right atrial pressure does, owing to concomitant changes in ITP. Accordingly, variations in right atrial pressure are the major determining factor in fluctuations of the pressure gradient for systemic venous return during ventilation.[61,100] Positive-pressure inspiration increases ITP and right atrial pressure, decreasing the pressure gradient for venous return, which decreases venous blood flow,[63] RV filling, and, consequently, RV stroke volume.[61,63,101-108] These long-documented physiologic effects were recently validated in humans using minimally invasive echocardiographic techniques, wherein vena caval flow varies with the phase of the ventilatory cycle (Fig. 64-7).[109] During normal spontaneous inspiration, the converse occurs: with decreases in ITP, right atrial pressure decreases, accelerating venous blood flow and increasing RV filling and RV stroke volume (Fig. 64-8).[1,15,63,66,103,106,110,111]

The decrease in venous return during positive-pressure ventilation is often lower than one might expect based on the increase in right atrial pressure. Because a large proportion of venous blood is in the abdomen, the net effect of PEEP is to increase mean systemic pressure and right atrial pressure. Accordingly, the pressure gradient for venous return may not be reduced by PEEP, especially in patients with hypervolemia. In fact, abdominal pressurization by diaphragmatic descent may be the major mechanism by which the decrease in venous return is minimized during positive-pressure ventilation.[71,112-115] When cardiac output is restored to pre-PEEP levels by fluid resuscitation[71,116] and PEEP is maintained, liver clearance mechanisms increase above pre-PEEP levels.[116-119] These data are consistent with a PEEP-induced alteration in intrahepatic blood flow distribution. Thus, ventilation may have less of an effect on venous return than was originally postulated. Van den Berg and colleagues examined the effects of varying levels of CPAP on right atrial pressure, intra-abdominal pressure, and cardiac output in

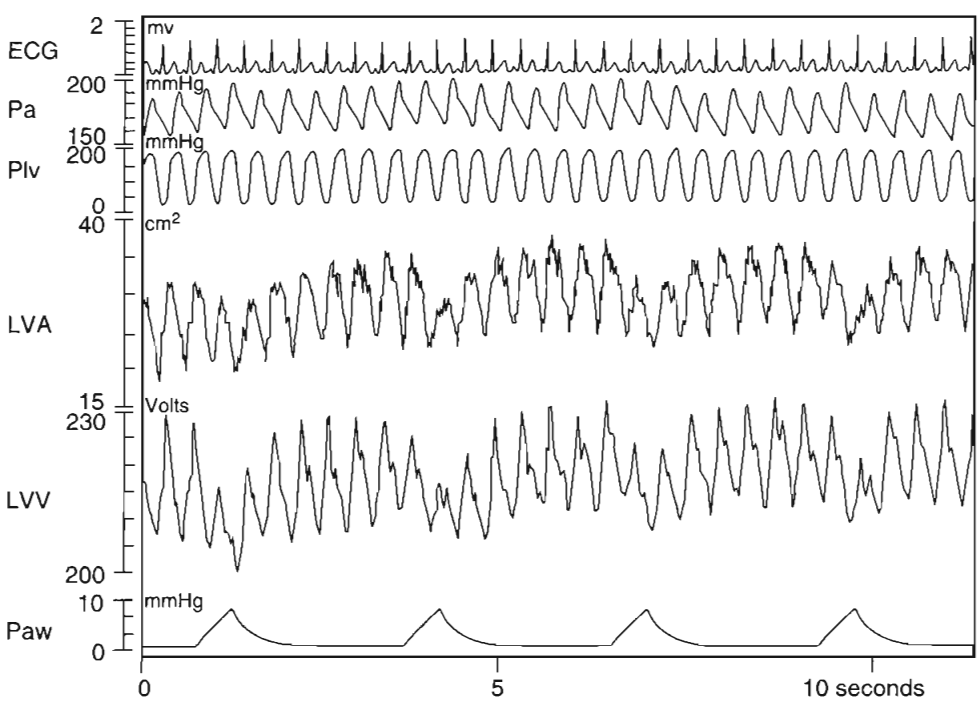

FIGURE 64–8. Effect of positive-pressure ventilation on left ventricular volume (LVV) and related hemodynamic measures in a perioperative intact patient. ECG, electrocardiogram; LVA, left ventricular area; Pa, arterial pressure; Paw, airway pressure; Plv, left ventricular pressure. (From Denault AY, Gasior TA, Gorcsan J 3rd, et al: Determinants of aortic pressure variation during positive-pressure ventilation in man. Chest 1999;116:176-186.)

42 postoperative cardiac surgery patients.[120] Up to 20 cm H_2O, CPAP did not significantly decrease cardiac output, as measured 30 seconds into an inspiratory hold maneuver. The reason for this apparent paradoxical effect became obvious when the investigators compared the associated changes in right atrial pressure, abdominal pressure, and RV end-diastolic volume (Fig. 64-9). They found that only 30% of the increased airway pressure was transmitted to the right atrium; however, and perhaps more important, most of the increase in right atrial pressure was realized by an increase in intra-abdominal pressure. Thus, it was not surprising that RV end-diastolic volume fell by less than 8% from pre-CPAP values. These data demonstrate that in fluid-resuscitated patients, institution of positive-pressure ventilation may not result in a decrease in blood flow. However, if intra-abdominal pressure is allowed to decrease, as would occur with an open laparotomy and decompression of tense ascites, a marked preload-responsive effect of positive-pressure ventilation should occur.

With exaggerated swings in ITP, as occur with obstructed inspiratory efforts, venous return behaves as if abdominal pressure is additive to mean systemic pressure in defining total venous blood flow.[121-124] Recent interest in inverse ratio ventilation has raised questions about its hemodynamic effect, because its application includes a large component of hyperinflation.

Right Ventricular Filling

When RV filling pressure, defined as right atrial pressure minus pericardial pressure, was directly measured in patients undergoing open chest operations, RV filling pressure was unaltered by acute volume loading.[125] Although right atrial pressure increased, pericardial pressure also increased, such that RV filling pressure remained unchanged. Similar data are seen when RV volumes are reduced by the application of PEEP in postoperative cardiac patients.[126] These data suggest that under normal conditions, RV diastolic compliance is very high and that most of the increase in right atrial pressure seen during volume loading reflects pericardial compliance and cardiac fossa stiffness rather than changes in RV distending pressure. Accordingly, changes in right atrial pressure do not follow changes in RV end-diastolic volume.

When cardiac contractility is reduced and intravascular volume is expanded, RV filling pressure increases as a result of decreased RV diastolic compliance, increased pericardial compliance, increased end-diastolic volume, or a combination of all three. In support of this hypothesis, RV filling pressure does not increase until RV volume exceeds a certain threshold value.[179] In postoperative cardiac surgery patients,[10,18,127] PEEP and, by extension, lung expansion compress the heart within the cardiac fossa in a fashion analogous to pericardial tamponade.

Venous return is the primary determinant of cardiac output.[99] The closer right atrial pressure remains to zero relative to atmospheric pressure, the greater is the pressure gradient for systemic venous blood flow.[104,128] For this mechanism to operate efficiently, RV output must equal venous return; otherwise, sustained increases in venous blood flow would overdistend the right ventricle, increasing right atrial pressure. Fortunately, under normal conditions of spontaneous ventilation, the increase in venous return is in phase with inspiration, decreasing again during expiration as ITP increases.[61] Likewise, the pulmonary arterial inflow circuit is highly compliant and can accept large increases in RV stroke volume without changing pressures (Fig. 64-10).[63,69]

This compensatory system rapidly becomes dysfunctional if RV diastolic compliance decreases or if right atrial pressure increases independent of changes in RV end-diastolic volume. An example of decreased RV diastolic compliance is acute RV dilatation or cor pulmonale (pulmonary embolism, hyperinflation, and RV infarction), which induces profound decreases in cardiac output that are not responsive to fluid resuscitation. Dissociation between right atrial pressure and RV end-diastolic volume occurs during either tamponade or positive-pressure ventilation, because right atrial pressure is artificially increased by the increasing ITP. Accordingly, positive-pressure ventilation impairs normal circulatory adaptive processes. Further, even if one restores the coupling of right atrial pressure and RV volume by using partial ventilatory support modes, cardiac output will increase only if the right ventricle can transduce the associated increase in venous return to forward blood flow. Thus, during weaning from mechanical ventilation, occult RV failure may be exposed, manifested by a rapid rise in right atrial pressure and a fall in cardiac output. Because the primary effect of any form of ventilation on cardiovascular function in normal subjects is to alter RV preload by altering venous blood flow, the detrimental effect of positive-pressure ventilation on cardiac output can be minimized either by instituting fluid resuscitation to increase mean systemic pressure[1,101,120,121] or by keeping both mean ITP and swings in lung volume as low as possible. Accordingly, prolonging expiratory time, decreasing tidal volume, and avoiding PEEP all minimize this decrease in systemic venous return to the right ventricle.[17,61,103-107,129,130]

Because spontaneous inspiratory efforts increase lung volume by decreasing ITP, there is an increase in venous return with spontaneous inspiration, owing to the fall in right atrial pressure.[15,53,104-106] This augmentation of venous return is limited,[122,124] however, because if ITP decreases below atmospheric pressure, venous return becomes flow-limited

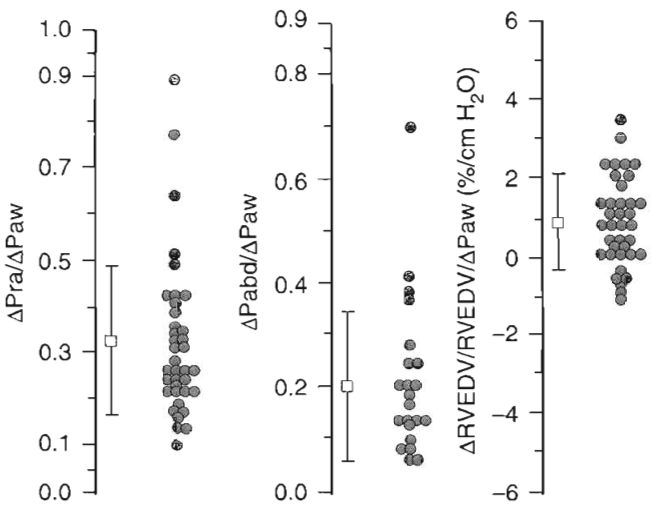

FIGURE 64–9. Effect of increasing levels of continuous positive airway pressure (CPAP) on the relationship between increasing airway pressure (Paw) and right atrial pressure (Pra) (left graph), airway pressure and intra-abdominal pressure (Pabd) (center graph), and airway pressure and changes in right ventricular end-diastolic volume (RVEDV) (right graph) in 43 postoperative fluid-resuscitated cardiac surgery patients. (From data in Van den Berg P, Jansen JRC, Pinsky MR: The effect of positive-pressure inspiration on venous return in volume loaded post-operative surgical patients. J Appl Physiol 2002;92:1223-1231.)

when the large systemic veins collapse as they enter the thorax.[128] This flow limitation is a safety valve for the heart, because ITP can decrease greatly with obstructive inspiratory efforts,[46] and in the absence of flow limitation, the right ventricle could become over distended and fail.[131] Still, in patients with decreased RV compliance, negative swings in ITP can augment RV filling.

Left Ventricular Preload and Ventricular Interdependence

Changes in venous return must eventually result in directionally similar changes in LV preload, because the two ventricles are linked in series. This phase delay in output adjustments from the right ventricle to the left ventricle is exaggerated if tidal volume or respiratory rate is increased and in the setting of hypovolemia.[17,56,58,93,96,97,108,129,132-136] Independent of this series interaction, direct ventricular interdependence can also occur and be clinically significant. Increasing RV volume shifts the intraventricular septum into the left ventricle and simultaneously decreases LV diastolic compliance. During positive-pressure ventilation, RV volumes are usually decreased, minimizing ventricular interdependence.[91,134-137] Echocardiographic studies document that although PEEP results in some degree of right-to-left intraventricular septal shift, the shift is small.[55,56] In fact, increases in lung volume during positive-pressure ventilation primarily compress the two ventricles into each other, decreasing biventricular volumes.[138] The decrease in cardiac output commonly seen during PEEP is due to a decrease in LV end-diastolic volume, and both LV end-diastolic volume and cardiac output are restored by fluid resuscitation,[139,140] without any measurable change in LV diastolic compliance.[93]

During spontaneous inspiration, RV volumes increase transiently, shifting the intraventricular septum into the left ventricle,[92] decreasing LV diastolic compliance and LV end-diastolic volume.[90,137,141] This transient RV dilatation-induced septal shift is the primary cause of inspiration-associated decreases in arterial pulse pressure, which, if greater than 10 mm Hg or 10% of the mean pulse pressure, are referred to as pulsus paradoxus.[15] Because spontaneous inspiratory efforts can occur during positive-pressure ventilation, and especially during partial ventilatory assist, pulsus paradoxus can also be seen in mechanically ventilated patients.

Left Ventricular Afterload

LV afterload can be equated to systolic wall tension, which, by the Laplace equation, is proportional to the product of transmural LV pressure and the radius of curvature of the left ventricle, which itself is proportional to LV volume. Maximal LV wall tension normally occurs at the end of isometric contraction, reflecting both a maximal product of the LV radius of curvature (end-diastolic volume) and aortic pressure (diastolic pressure). When LV dilatation exists, as in congestive heart failure, maximal LV wall stress occurs during LV ejection, because the maximal product of these two variables occurs at this time. Accordingly, LV afterload varies, based on the baseline level of cardiac contractility, arterial pressure, and intravascular volume. LV ejection pressure is the transmural LV systolic pressure, which can be approximated as transmural arterial pressure. Because normal baroreceptor mechanisms located in the carotid body tend to keep arterial pressure constant with respect to atmosphere, if arterial pressure were to remain constant as ITP increased, LV wall tension would decrease as well. Similarly, if transmural arterial pressure were to remain constant as ITP increased but LV end-diastolic volume were to decrease, because of the increased ITP-induced decrease in systemic venous return, LV wall tension would also

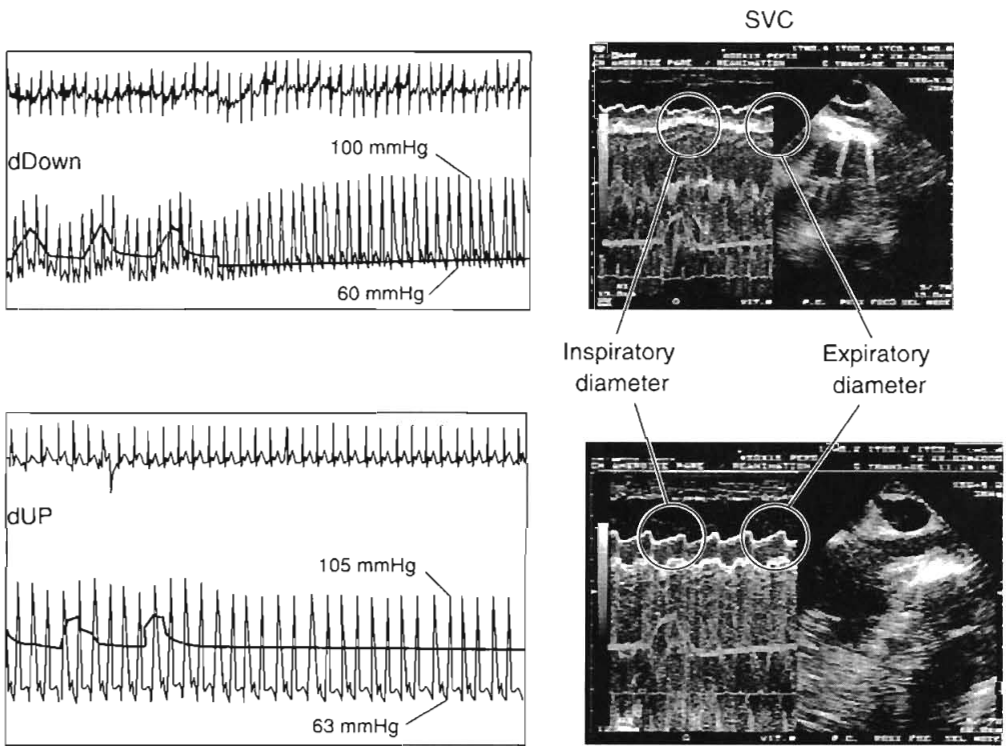

FIGURE 64–10.
Echocardiographic and pulse Doppler images of superior vena cava (SVC) flow patterns during positive-pressure ventilation. Note the inspiratory phase-dependent decrease in venous flow. (From Jardin F, Vieillard-Baron A: Right ventricular function and positive-pressure ventilation in clinical practice: From hemodynamic subsets to respirator settings. Intensive Care Med 2003;29:1426-1434.)

decrease.[142] Thus, by either mechanism, increases in ITP decrease LV afterload. Similarly, decreases in ITP with a constant arterial pressure increase LV transmural pressure, increasing LV afterload.[11,143] These two opposing effects of changes in ITP on LV afterload have profound clinical implications.

First, any process associated with marked decreases in ITP must also be associated with increased LV afterload and myocardial O_2 consumption. Because the transition from positive-pressure ventilation to spontaneous ventilation may result in dramatic ITP swings and changes in the energy requirements of the respiratory muscles, weaning from mechanical ventilation is a cardiovascular stress test.[142,144,145] Interestingly, Jabran and associates demonstrated that all ventilator-dependent patients had increased cardiac output during weaning, but in those who failed to be weaned from mechanical ventilation, venous O_2 saturation decreased, consistent with cardiovascular compromise.[33] A similar argument can be made for the observed improvement in LV systolic function in patients with severe LV failure who are placed on mechanical ventilation.[145]

Pulsus paradoxus occurs during spontaneous inspiration under conditions of marked pericardial restraint. This may occur because of pericardial limitations, such as tamponade and constrictive pericarditis, as well as during loaded spontaneous ventilatory efforts, when RV volumes swell and ITP decreases. In both cases, LV stroke volume decreases.[146-150] Perhaps the most prominent mechanism creating an inspiratory decrease in both LV stroke volume and systolic arterial pressure is the transient decrease in LV diastolic compliance induced by increased venous return, which decreases LV end-diastolic volume. The negative swings in ITP also increase LV ejection pressure (LV pressure minus ITP), increasing LV end-systolic volume.[11] Hypoxia directly reduces LV diastolic compliance, as well as decreasing myocardial contractile function.[151]

Sustained increases in ITP must eventually decrease aortic blood flow and arterial pressure, owing to the associated decrease in venous return.[11] Because normal baroreceptor-based homeostatic mechanisms tend to sustain a constant arterial pressure, to keep organ perfusion constant,[45] if ITP increased arterial pressure without changing transmural arterial pressure, the periphery would reflexively vasodilate to maintain a constant extrathoracic arterial pressure-flow relation.[132] Because coronary perfusion pressure reflects the ITP gradient for blood flow, it is not increased by ITP-induced increases in arterial pressure. However, compression of the coronaries by the expanding lungs may obstruct coronary blood flow. Thus, the combined decrease in coronary blood flow may induce myocardial ischemia.[152-154]

There is little difference in LV energetics between decreasing LV ejection pressure by increasing ITP above atmospheric pressure and increasing ITP from a negative value to atmosphere, if the absolute change in ITP is similar. In both cases, the LV ejection pressure will decrease in proportion to the relative increase in ITP. However, the effect of removing large negative levels of ITP is not similar to that of adding positive ITP on venous return. Relative increases in ITP from very negative values to zero, relative to atmosphere, minimally alter venous return, whereas increases in ITP above atmosphere impede venous return by increasing right atrial pressure. Thus, very negative swings in ITP, as seen with vigorous inspiratory efforts in the setting of airway obstruction (asthma, upper airway obstruction, vocal cord paralysis) or

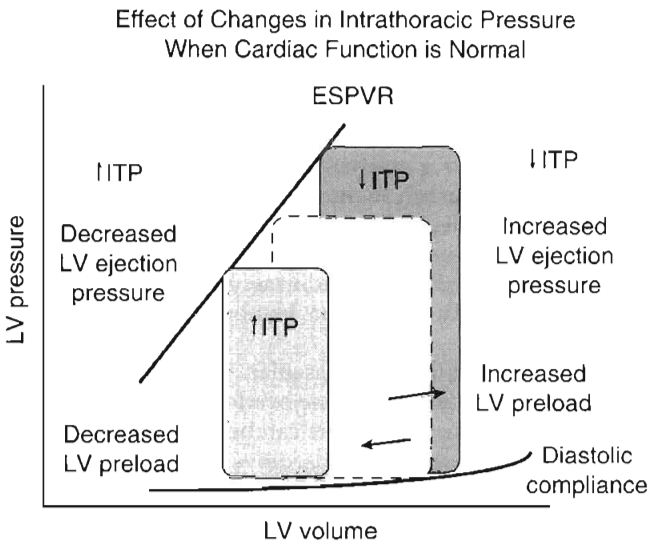

FIGURE 64–11. Schematic representation of the effects of changes in intrathoracic pressure (ITP) on left ventricular (LV) pressure-volume relations when cardiac contractility is normal. ESPVR, end-systolic pressure-volume relation.

stiff lungs (interstitial lung disease, pulmonary edema, ALI), selectively increase LV afterload. Such spontaneous inspiratory efforts may be the cause of the often observed LV failure and pulmonary edema seen in these conditions,[14,46,155,156] especially if LV systolic function is already compromised (see Fig. 64-7).[26,157] Similarly, removing large negative swings in ITP by either bypassing upper airway obstruction (endotracheal intubation) or instituting mechanical ventilation or PEEP-induced loss of spontaneous inspiratory efforts should selectively reduce LV afterload without significantly decreasing either venous return or cardiac output.[1,36,69,128,153,158,159] Reversing this argument, weaning from mechanical ventilation, with its associated increase in both metabolic demand and LV afterload, is a form of cardiac stress testing.[33]

Using Changes in Intrathoracic Pressure to Define Cardiovascular Performance

Sustained increases in airway pressure can be used to measure cardiac contractility, as defined by the end-systolic pressure-volume relation.[160] In a preload-dependent patient, passive inspiratory hold maneuvers that increase airway pressure to 5 to 10 cm H_2O (e.g., CPAP) selectively decrease venous return without greatly altering either pulmonary vascular resistance or LV afterload, because the changes in lung volume and ITP are relatively small. Denault and coworkers documented that, in mechanically ventilated patients undergoing cardiac surgery, LV performance could be measured during ventilation using combined estimates of LV volume and ejection pressure.[161] As shown in Figure 64-8, ventilation induces profound dynamic changes in LV volumes, consistent with rapid changes in LV filling.

HEMODYNAMIC EFFECTS OF VENTILATION BASED ON CARDIOPULMONARY STATUS

Spontaneous and positive-pressure ventilation can have profound hemodynamic consequences. Further, the same

ventilatory maneuver (initiation of or withdrawal from mechanical ventilation) can have opposite effects on cardiovascular stability in different patient populations. Schematic examples of how increasing or decreasing ITP alters the LV pressure-volume relation are depicted for conditions in which LV function is normal (see Fig. 64-11) and depressed (Fig. 64-12). Because the hemodynamic responses to ventilation are highly dependent on the existing cardiovascular state, the specific responses to defined ventilatory maneuvers not only define the baseline cardiovascular state but also allow accurate predictions of what hemodynamic effects will occur.

In patients with cardiovascular insufficiency due to impaired LV ejection or volume overload, the institution of mechanical ventilatory support can be lifesaving because of its ability to support the cardiovascular system while decreasing global O_2 demand. In patients who are predominantly preload dependent or hypovolemic (hemorrhagic shock, loss of vasomotor tone) and in those who may develop RV failure with hyperinflation (anterior chest trauma, spinal cord shock, severe obstructive lung disease), positive-pressure ventilation must be instituted with caution, because profound cardiovascular insufficiency may develop rapidly during intubation and initiation of mechanical ventilation. Similarly, withdrawal of ventilatory support can be considered an exercise stress test, and patients with limited cardiovascular reserve may not be successfully weaned, even if their traditional weaning parameter values are acceptable.[26,157]

MECHANICAL VENTILATION

The hemodynamic differences between different modes of total mechanical ventilation at a constant airway pressure and PEEP can be explained by their differential effects on lung volume and ITP.[162] Importantly, when two different modes of total or partial ventilatory support cause similar changes in ITP and ventilatory effort, their hemodynamic effects are also similar, despite markedly different airway waveforms. Partial ventilatory support with either intermittent mandatory ventilation or pressure-support ventilation results in similar hemodynamic responses when matched for similar tidal volumes.[163] Of note, high-frequency jet ventilation, when delivered at low levels, results in a constant cardiac output in patients with heart failure.[112]

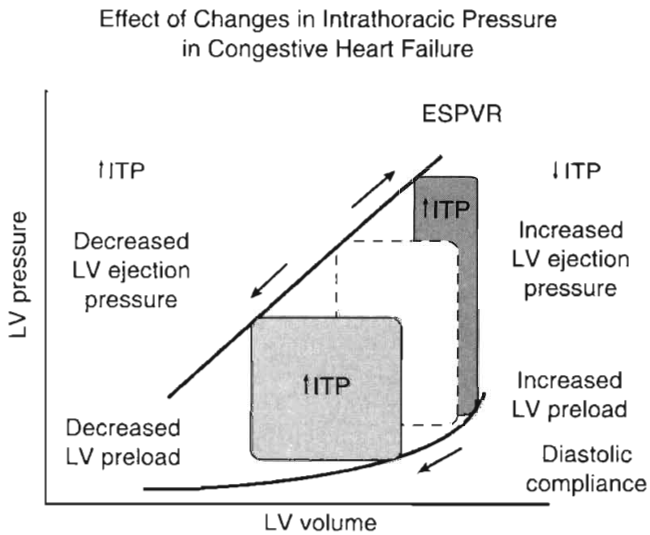

FIGURE 64-12. Schematic representation of the effects of changes in intrathoracic pressure (ITP) on left ventricular (LV) pressure-volume relations when cardiac contractility is impaired and intravascular volume status is expanded. ESPVR, end-systolic pressure-volume relation.

ACUTE LUNG INJURY

Patients with ALI often require PEEP to maintain alveolar distention and arterial oxygenation. Positive-pressure ventilation decreases intrathoracic blood volume,[104] and PEEP decreases it even more[125,126] without altering LV contractile function.[164] However, increases in airway pressure may not reflect increases in ITP, because patients with ALI have varying degrees of increased lung stiffness and decreased chest wall compliance. Further, it is the increase in lung volume, not airway pressure, that determines the degree of increase in ITP during positive-pressure ventilation.[5] Lessard and colleagues, in a study of nine patients with ARDS, found no significant hemodynamic differences among volume-controlled, pressure-controlled, and pressure-controlled inverse ratio ventilation adjusted to keep total PEEP and tidal volume consistent among treatment arms.[165] Davis and associates studied the hemodynamic effects of volume-controlled versus pressure-controlled ventilation in 25 patients with ALI.[166] When matched for the same mean airway pressure, both methods resulted in the same cardiac outputs. However, when airway pressure was increased during volume-controlled ventilation by sine wave to square wave flow pattern, cardiac output fell. Singer and coworkers showed in 18 ventilator-dependent but hemodynamically stable patients that the degree of hyperinflation, not the airway pressure, determined the decrease in cardiac output.[167]

Different modes of mechanical ventilation affect cardiac output to a similar extent for similar increases in lung volume.[112,168] Most of the decrement in cardiac output can be reversed by fluid resuscitation that restores intrathoracic blood volume to pre-PEEP levels.[164,169-171] That the PEEP-induced decrease in cardiac output is due to a decreased pressure gradient for venous return was elegantly shown by Gunter and colleagues,[172] who minimized the decrease in cardiac output in ventilator-dependent septic patients by lowering body compression. Importantly, if cardiac output does not increase with fluid resuscitation, other processes, such as cor pulmonale, increased pulmonary vascular resistance, or cardiac compression, may also be inducing cardiovascular depression.[173]

CONGESTIVE HEART FAILURE

Increases in cardiac output along with increases in airway pressure suggest the presence of congestive heart failure.[36,174] Grace and Greenbaum noted that adding PEEP did not decrease cardiac output in patients with heart failure, and it actually increased cardiac output if pulmonary artery occlusion pressure exceeded 18 mm Hg.[175] Similarly, Calvin and associates[176] noted that patients with cardiogenic pulmonary edema had no decrease in cardiac output when given PEEP.[177] Unfortunately, PEEP may be detrimental in patients with combined heart failure and ALI. Rasanen and coworkers

documented that decreasing levels of ventilatory support in patients with myocardial ischemia and acute LV failure worsened ischemia,[36,178] but this effect could be minimized by preventing spontaneous inspiratory effort–induced negative swings in ITP.[35] Because weaning from mechanical ventilatory support is a form of exercise stress test, withdrawal of ventilatory support can unmask cardiac failure in otherwise stable patients with acute respiratory failure.[26] Such patients may not be weanable from mechanical ventilatory support unless supplemented by positive inotropes.[157]

The cardiovascular benefits of positive airway pressure can be seen with the removal of negative swings in ITP, as created by increasing levels of CPAP.[179,180] Even CPAP levels as low as 5 cm H_2O can increase cardiac output in patients with congestive heart failure; cardiac output decreases with similar levels of CPAP in both normal subjects and those with heart failure without volume overload. Further, these hemodynamic effects of increased airway pressure do not require endotracheal intubation. Patients with congestive heart failure but in whom forced diuresis has induced a relative hypovolemic state, manifested by a pulmonary artery occlusion pressure of 12 mm Hg or less, will decrease their cardiac outputs equally whether they receive CPAP or bilevel positive airway pressure at the same mean airway pressure.[181]

If positive airway pressure augments LV ejection in heart failure states, then systolic arterial pressure should not decrease but should actually increase during inspiration—so-called reverse pulsus paradoxus. This was what Abel and coworkers found in 10 patients after cardiac surgery.[174] Other investigators suggested that the relation between ventilatory effort and systolic arterial pressure can be used to identify which patients may benefit from cardiac assist maneuvers.[182-184] Patients who increase their systolic arterial pressure during ventilation relative to an apneic baseline tend to have a greater degree of volume overload[183] and heart failure,[182] whereas those subjects in whom systolic arterial pressure decreases tend to be volume responsive. This logic has recently been applied to a hemodynamic test, with arterial pulse pressure substituted for systolic pressure. Michard and colleagues found in a series of ventilator-dependent septic patients that the greater the degree of arterial pulse pressure variation during positive-pressure ventilation, the greater the subsequent increase in cardiac output in response to volume expansion therapy.[185]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The primary hemodynamic problem seen in patients with chronic obstructive pulmonary disease (COPD) is related to hyperinflation due to bronchospasm, loss of lung parenchyma, or dynamic hyperinflation. The lungs expand and compress the heart, increasing pulmonary vascular resistance and impeding RV filling. Dynamic hyperinflation is also referred to as intrinsic PEEP. Intrinsic PEEP alters hemodynamic function in a similar fashion to extrinsic PEEP. Matching intrinsic PEEP with externally applied PEEP has no measurable detrimental hemodynamic effect,[186-188] although such matching decreases the work cost of spontaneous breathing. Further, CPAP, like PEEP, has little detrimental effect in patients with COPD when delivered below the intrinsic PEEP level.[189]

Weaning of patients with COPD taxes the cardiovascular system. Patients with severe COPD but adequate ventilatory weaning parameters may go into cardiogenic pulmonary edema during weaning.[26] This probably reflects a combined volume overload and increased LV failure, because LV ejection fraction decreases during such trials[190]; following diuresis, many of these patients can be weaned. Jabran and associates demonstrated that although all ventilator-dependent COPD patients had increased cardiac output during weaning trials, those who failed to wean also had decreased venous O_2 saturation, consistent with an increased metabolic demand in excess of cardiovascular reserve.[33] Thus, occult cardiovascular insufficiency may play a major role in failure to wean in critically ill patients.[191] This theory, though attractive, has not been proved conclusively.

ACKNOWLEDGMENTS

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This study documented for the first time in humans that the cardiac depressive effects of PEEP were due to decreased venous return. When LV volumes were restored, cardiac output returned to baseline, despite continuing PEEP. This stopped the search for the PEEP-induced cardiac depressant.

Jardin F, Vieillard-Baron A: Right ventricular function and positive-pressure ventilation in clinical practice: From hemodynamic subsets to respirator settings. Intensive Care Med 2003;29:1426-1434.

First study in humans to show dynamic and cycle-specific changes in venous return and RV stroke volume during positive-pressure ventilation, as predicted by earlier studies in animals. Although no new information is provided, the illustration are elegant, and there is a web-based video.

Kaneko Y, Floras JS, Usui K, et al: Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med 2003;348:1233-1241.

Good clinical trial documenting the sustained improvement in LV function in patients with heart failure and obstructive sleep apnea who were given nighttime CPAP to relieve the repetitive negative swings in ITP and presumably LV afterload. Good discussion of the mechanisms of interaction in a large outpatient population.

Lemaire F, Teboul JL, Cinoti L, et al: Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. Anesthesiology 1988;69:171-179.

The first study in humans to show that weaning to spontaneous ventilation could induce immediate and severe LV failure and pulmonary edema.

Marini JJ, Culver BN, Butler J: Mechanical effect of lung distention with positive pressure on cardiac function. Am Rev Respir Dis 1980;124:382-386.

Alerted clinicians to the cardiodepressive effects of hyperinflation and auto-PEEP by impeding both venous return and cardiac filling.

Pinsky MR, Matuschak GM, Klain M: Determinants of cardiac augmentation by increases in intrathoracic pressure. J Appl Physiol 1985;58:1189-1198.

The definitive physiologic study of the dynamic effects of positive-pressure ventilation on venous return and LV afterload. Excellent discussion of ventriculoarterial coupling.

Rasanen J, Nikki P, Heikkila J: Acute myocardial infarction complicated by respiratory failure: The effects of mechanical ventilation. Chest 1984;85:21-28.

First study in humans to report the association among negative swings in ITP, LV afterload, and myocardial ischemia, and the reversal of ischemia with the removal of negative swings in ITP. This concept altered the management of cardiogenic pulmonary edema in the setting of ongoing ischemia.

Sharpey-Schaffer EP: Effects of Valsalva maneuver on the normal and failing circulation. BMJ 1955;1:693-699.

Described the arterial pressure response to a Valsalva maneuver in patients with either normal cardiac function or heart failure. First to describe the square wave arterial pressure response of heart failure, now used as a diagnostic tool.

Van den Berg P, Jansen JRC, Pinsky MR: The effect of positive-pressure inspiration on venous return in volume loaded post-operative cardiac surgical patients. J Appl Physiol 2002;92:1223-1231.

The first study in humans to show that positive-pressure inspiration does not reduce the pressure gradient for venous return because it simultaneously increases intra-abdominal pressure. Good discussion of heart-lung interactions.

Chapter 65

ASSIST-CONTROL MECHANICAL VENTILATION

Neil R. MacIntyre

KEY POINTS

1. **Ventilator breath delivery** is characterized by the trigger, target, and cycle variables.
2. The **interaction of a positive-pressure breath and respiratory system mechanics** is summarized by the equation of motion: Driving pressure = (Flow × Resistance) + (Volume/System compliance).
3. **The goal of assist-control ventilation** is to provide adequate gas exchange while protecting the lung from overdistention and recruitment-derecruitment injury.
4. **Assist-control ventilation in obstructive lung disease** poses the additional risk of producing overdistention from air trapping.
5. **High-frequency ventilation** shows promise as a better lung-protective strategy in parenchymal lung injury.

Positive-pressure mechanical ventilatory support provides pressure and flow to the airway in order to effect oxygen (O_2) and carbon dioxide (CO_2) transport between the environment and the pulmonary capillary bed. The goal is to maintain appropriate levels of partial pressure of O_2 and CO_2 in arterial blood while unloading the ventilatory muscles. Conceptually, this mechanical ventilatory support can be either total or partial. With total support, the mechanical device completely unloads the ventilatory muscles and provides virtually all the work of breathing. With partial support, the mechanical device only partially unloads the ventilatory muscles, requiring the patient to provide the remainder of the work of breathing. In general, total support is used in acute respiratory failure when the patient's muscles are clearly overloaded or fatigued or when gas exchange is very unstable or unreliable. Partial support is generally used in less severe forms of respiratory failure (especially during the recovery or weaning phase). Partial support issues are discussed in Chapters 66 and 67. This chapter focuses on positive-pressure ventilation designed to provide total support.

DEVICE DESIGN FEATURES FOR TOTAL VENTILATORY SUPPORT

POSITIVE-PRESSURE BREATH CONTROLLER

Most modern ventilators use piston-bellows systems or high-pressure gas sources to drive gas flow.[1,2] Tidal breaths are generated by this gas flow and can be classified in terms of what initiates the breath (trigger variable), what controls gas delivery during the breath (target or limit variable), and what terminates the breath (cycle variable).[3,4] Trigger variables are either patient effort or a machine timer. During total support, breaths can be initiated by patient effort (assisted breaths) or by the machine timer (controlled breaths). Target or limit variables are generally either a set flow or a set inspiratory pressure. With flow targeting, the ventilator adjusts pressure to maintain a clinician-determined flow pattern; with pressure targeting, the ventilator adjusts flow to maintain a clinician-determined inspiratory pressure. Cycle variables are generally a set volume or a set inspiratory time. Breaths can also be cycled if pressure limits are exceeded.

MODE CONTROLLER

The availability and delivery logic of different breath types define the mode of mechanical ventilatory support.[3,4] The mode controller is an electronic, pneumatic- or microprocessor-based system designed to provide the proper combination of breaths according to set algorithms and feedback data (conditional variables). For total support, the most commonly used modes provide breaths that are either patient or machine initiated (i.e., assisted or controlled) and are either flow or pressure targeted. In addition, the flow-targeted breaths are generally volume cycled, and the pressure-targeted breaths are generally time cycled. Collectively, these approaches are referred to as assist-control modes and are generally divided into volume assist-control and pressure assist-control ventilation. Figure 65-1 depicts the four basic breath types used during assist-control ventilation.

New ventilator designs incorporate advanced monitoring and feedback functions into these controllers to allow continuous adjustments in mode algorithms as the patient's condition changes.[5] The most common of these new feedback designs is the addition of a volume target backup to pressure assist-control, termed pressure-regulated volume control. This feature adjusts the inspiratory pressure level above or below the clinician-set target to achieve the volume target. Other feedback systems adjust the mandatory rate (minimum minute ventilation) or the total minute ventilation being supplied (adaptive support ventilation), according to various criteria.

EFFORT (DEMAND) SENSORS

Assisted breaths require sensors to detect patient effort. These sensors are usually either pressure or flow transducers in the ventilatory circuitry and are characterized by their

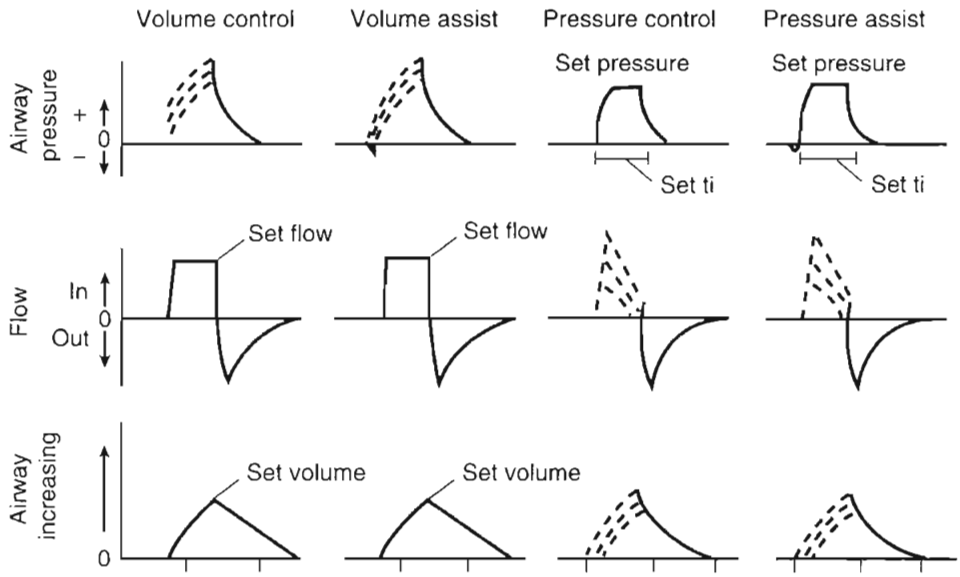

FIGURE 65–1. Airway pressure, flow, and volume tracings over time depicting the four basic breaths available for assist-control ventilation on most modern mechanical ventilators. Breaths are classified by their trigger, target or limit, and cycle variables. Patient-triggered assisted breaths are identified by the small drop in airway pressure before pressure and flow delivery; machine-triggered controlled breaths have no such drop. The target or limit is a clinician-set flow or inspiratory pressure. On most modern ventilators, flow-targeted assist-control breaths are volume cycled; pressure-targeted assist-control breaths are time (ti) cycled.

sensitivity (how much of a circuit pressure or flow change must be generated to initiate a ventilator response) and their responsiveness (the delay in providing this response).[6]

OTHER FEATURES

Blenders mix air and O_2 to produce a delivered inspired O_2 fraction (FIO_2) from 0.21 to 1.0. On newer systems, blenders are also available for other gases such as heliox, nitric oxide, and anesthetic agents. *Humidifiers* adjust blended gas mixtures to approximate body conditions using either passive heat-moisture exchangers in the circuitry or active systems that add heat and moisture directly. *Positive end-expiratory pressure (PEEP)* is usually applied by regulating pressure in the expiratory valve of the ventilator system, but a continuous flow of source gas during the expiratory phase can produce a similar effect. The *gas delivery circuit* consists of flexible tubing that often has pressure or flow sensors and an exhalation valve. It is important to remember that this tubing has measurable compliance (4 mL/cm H_2O is a representative figure), and significant amounts of delivered gas may only distend this circuitry rather than enter the patient's lungs when high airway pressures are encountered.

PHYSIOLOGIC EFFECTS OF POSITIVE-PRESSURE MECHANICAL VENTILATION

EQUATION OF MOTION

Lung inflation during mechanical ventilation occurs when pressure and flow are applied at the airway opening. These applied forces interact with respiratory system compliance (both lung and chest wall components), airway resistance, and, to a lesser extent, respiratory system inertance and lung tissue resistance to effect gas flow.[7,8] For simplicity's sake, because inertance and tissue resistance are relatively small, they can be ignored. Thus, the interactions of pressure, flow, and volume with respiratory system mechanics can be expressed by the simplified equation of motion:

$$\text{Driving pressure} = (\text{Flow} \times \text{Resistance}) + (\text{Volume/System compliance})$$

In a mechanically ventilated patient, this relationship is expressed as:

$$dPAO = (V' \times R) + (VT/CRS)$$

where dPAO is the change in pressure above baseline at the airway opening; V′ is the flow into the patient's lungs; R is the resistance of the circuit, artificial airway, and natural airways; VT is the tidal volume; and CRS is the respiratory system compliance.

By performing an inspiratory hold at end-inspiration (i.e., no-flow conditions: $V' = 0$), the components of dPAO required for flow and for respiratory system distention can be separated. Specifically, when $V' = 0$ at end-inspiration, dPAO is referred to as a "plateau" pressure and reflects the static respiratory system compliance (CRS = VT/dPAOplateau). Adding dPAO to the baseline pressure gives the total respiratory system distending pressure at end-inspiration (dPAOplateau + baseline pressure = PAOplateau). Calculating the difference in dPAO during flow and during no-flow (the "peak to plateau difference") allows the calculation of inspiratory airway resistance (R = dPAOpeak – dPAOplateau/V′).

Separating chest wall and lung compliance (CCW and CL, respectively) during a passive, machine-controlled positive-pressure breath requires an esophageal pressure measurement (Pes) to approximate pleural pressure. With this measurement, the inspiratory change in Pes (dPes) can be used in the following calculations: CCW = VT/dPes, and CL = VT/(dPAO – dPes). In clinical practice, because CCW is usually quite high and dPes is thus quite low, dPAOplateau and PAOplateau are often taken as an approximation of only lung distending pressure. However, in situations in which CCW is reduced (e.g., obesity, anasarca, ascites, surgical dressings), the stiff chest wall can have a significant effect on dPAOplateau and PAOplateau and must therefore be considered when using these measurements to assess lung stretch.

BREATH TARGET AND CYCLE CRITERIA

As noted earlier, there are two basic approaches to delivering positive-pressure breaths during assist-control ventilation: pressure targeting–time cycling and flow targeting–volume

cycling. Although similar ranges of tidal volume and inspiratory time are available with either strategy, these breath characteristics interact differently with changing respiratory system mechanics and patient efforts. Changes in compliance or resistance cause a change in tidal volume (but not in pressure at the airway opening) with a pressure-targeted breath. In contrast, similar changes in compliance or resistance cause a change in pressure at the airway opening (but not in flow or volume) with a flow-targeted breath. Patient effort during a pressure-assist breath causes the ventilator to augment flow (and thus volume) to maintain the inspiratory pressure target; this same effort during a volume-assist breath does not affect delivered flow or volume but instead causes a fall in the measured circuit pressure.

INTRINSIC POSITIVE END-EXPIRATORY PRESSURE AND THE VENTILATORY PATTERN

Intrinsic PEEP develops within the alveoli because of inadequate expiratory time or collapsed airways during expiration (or both). Intrinsic PEEP depends on three factors: minute ventilation, the expiratory time fraction, and the respiratory system's expiratory time constant (the product of resistance and compliance).[9] As minute ventilation increases, expiratory time fraction decreases, or time constant lengthens (i.e., higher resistance or compliance values), the potential for intrinsic PEEP to develop increases.[9]

The development of intrinsic PEEP has different effects on volume assist-control and pressure assist-control ventilation. In volume assist-control, the constant delivered tidal volume (and thus the change in pressure at the airway opening) in the setting of a rising intrinsic PEEP increases both the peak airway opening pressure and the end-inspiratory plateau airway opening pressure. In contrast, in pressure assist-control, the limit on airway opening pressure, coupled with a rising intrinsic PEEP level, decreases the delta pressure at the airway opening and thus the delivered tidal volume (and minute ventilation).

In a passive patient, intrinsic PEEP can be assessed in two ways. First, when an inadequate expiratory time is producing intrinsic PEEP, analysis of the flow graphic will show that expiratory flow has not returned to zero before the next breath is given. Second, intrinsic PEEP in alveolar units with patent airways can be quantified during an expiratory hold maneuver that permits equilibration of the intrinsic PEEP throughout the ventilator circuitry.

DISTRIBUTION OF VENTILATION

A positive-pressure tidal breath must distribute itself among the millions of alveolar units in the lung.[10,11] Factors affecting this distribution include regional resistances, compliances, and functional residual capacities and the delivered flow pattern (including inspiratory pause). In general, positive-pressure breaths tend to distribute more to units with high compliance and low resistance and away from obstructed or stiff units (Fig. 65-2). This creates the potential for regional overdistention of healthier lung units, even in the face of "normal-sized" tidal volumes.

It should be noted that a more uniform ventilation distribution does not necessarily mean better ventilation-perfusion ($\dot{V}/\dot{Q}$) matching (e.g., a more uniform ventilation distribution may actually worsen ($\dot{V}/\dot{Q}$) matching in a lung with inhomogeneous perfusion). Because of all these considerations, predicting which flow pattern will optimize $\dot{V}/\dot{Q}$ matching is difficult and often an empirical trial-and-error exercise.

ALVEOLAR RECRUITMENT

Infiltrative lung disease produces severe ($\dot{V}/\dot{Q}$) mismatching through alveolar flooding and collapse.[12] In many (but not all) of these disease processes, the collapsed alveoli can be recruited during a positive-pressure ventilatory cycle.[13] Three specific techniques to optimize recruitment are the application of PEEP, the use of recruitment maneuvers, and the prolongation of inspiratory time.

PEEP is defined as an elevation of transpulmonary pressures at the end of expiration.[13,14] As noted earlier, PEEP can be produced either by expiratory circuit valves (applied PEEP) or as a consequence of ventilator settings interacting with respiratory system mechanics (intrinsic PEEP). Note that expiratory muscle contraction can also raise intrathoracic pressures at end-expiration; this should not be considered PEEP, however, because it is not a transpulmonary pressure (i.e., alveolar-pleural pressure).

Alveoli that are prevented from "derecruiting" by PEEP provide several potential benefits. First, recruited alveoli improve ($\dot{V}/\dot{Q}$) matching and gas exchange.[13-15] Second, as discussed in more detail later, patent alveoli throughout the ventilatory cycle are not exposed to the risk of injury from the shear stress of repeated opening and closing.[16] Third, PEEP prevents surfactant breakdown in collapsing alveoli and thus improves lung compliance.[17] PEEP, however, can also be detrimental. Because the tidal breath is delivered on top of the baseline PEEP, end-inspiratory pressures are raised by PEEP application. This must be considered if the lung is at risk for stretch injury (see Ventilator-Induced Lung Injury). Moreover, because alveolar injury is often quite heterogeneous, appropriate PEEP in one region may be suboptimal in another region and excessive in another. Optimizing PEEP is thus a balance between recruiting the recruitable alveoli in diseased regions without overdistending already recruited alveoli in healthier regions. Another potential detrimental effect of PEEP is that it raises mean intrathoracic pressure. This can compromise cardiac filling in susceptible patients (see Cardiac Effects).[18]

Recruitment maneuvers are based on the concept that alveolar recruitment occurs throughout a positive-pressure inflation—all the way to total lung capacity.[19] In practice, recruitment maneuvers are performed using sustained inflations (e.g., 30 to 40 cm H_2O for up to 2 minutes).[19,20] An alternative approach is to use frequent "sigh breaths" that briefly take the lung to near total capacity on a frequent basis.[21] It must be pointed out that recruitment maneuvers provide only initial alveolar recruitment; the duration of recruitment almost certainly depends on an appropriate setting of PEEP to prevent subsequent derecruitment.

Prolonging the inspiratory time (generally by adding a pause), often used in conjunction with a rapid decelerating-flow (i.e., pressure-targeted) breath, has several physiologic effects.[22] First, the longer inflation period may recruit more slowly recruitable alveoli. Second, increased gas mixing time may improve ($\dot{V}/\dot{Q}$) matching in infiltrative lung disease. Third, the development of intrinsic PEEP can have similar effects to that of applied PEEP (see earlier). Indeed, much of the improvement in gas exchange associated with long

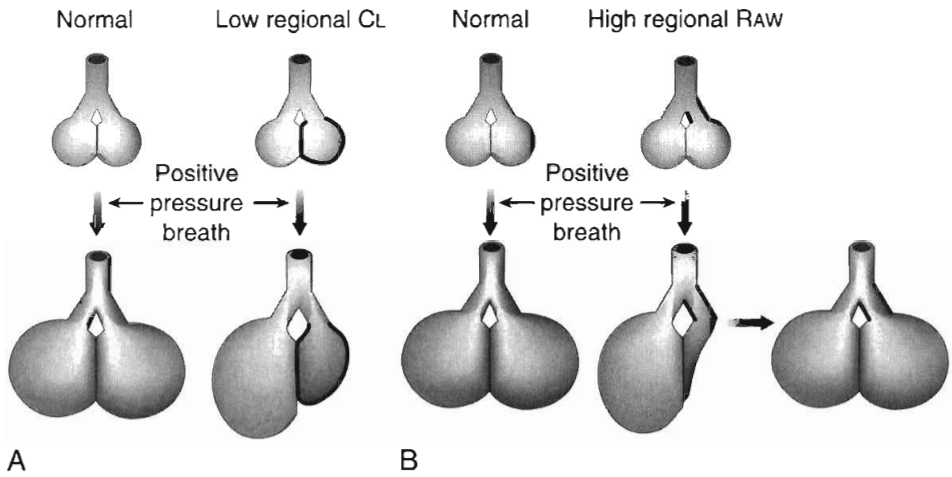

FIGURE 65–2. Schematic effects of the distribution of ventilation in two unit lung models with homogeneous mechanical properties, abnormal compliance distribution, and abnormal resistance distribution. Note that in situations involving inhomogeneous lung mechanics, positive-pressure breaths are preferentially distributed to "healthier" regions of the lung and can produce regional overdistention—even when a normal-sized global tidal volume is delivered. (From MacIntyre NR: Mechanical ventilatory support. In Dantzker D, MacIntyre NR, Bakow E [eds]: Comprehensive Respiratory Care. Philadelphia, WB Saunders, 1995.)

inspiratory time strategies may be merely a PEEP phenomenon.[23] It should be noted, however, that the distribution of intrinsic PEEP (most pronounced in lung units with long time constants) may be different from that of applied PEEP; thus, ($\dot{V}/\dot{Q}$) effects may also be different. Fourth, because these long inspiratory times significantly increase total intrathoracic pressures, cardiac output may be affected (see Cardiac Effects). Finally, inspiratory-expiratory ratios that exceed 1:1 (so-called inverse ratio ventilation [IRV]) are uncomfortable, and patient sedation or paralysis is often required unless a relief mechanism allows spontaneous breathing during the inflation period (airway pressure release ventilation, see below).

ADVERSE EFFECTS OF POSITIVE-PRESSURE VENTILATION

VENTILATOR-INDUCED LUNG INJURY

The lung can be injured when it is stretched excessively by positive-pressure ventilation. The most well-recognized injury is alveolar rupture, presenting as extra-alveolar air in the mediastinum (pneumomediastinum), pericardium (pneumopericardium), subcutaneous tissue (subcutaneous emphysema), pleura (pneumothorax), and vasculature (air emboli).[24] The risk for extra-alveolar air increases as a function of the magnitude and duration of alveolar overdistention. Thus, interactions of respiratory system mechanics and mechanical ventilation strategies (high regional tidal volume and PEEP—both applied and intrinsic) that produce regions of excessive alveolar stretch (i.e., transpulmonary distending pressures in excess of 40+ cm H_2O) for prolonged periods create alveolar units that are at risk for rupture.[24]

A parenchymal lung injury not associated with extra-alveolar air can also be produced by mechanical ventilation strategies that stretch the lungs beyond the normal maximum (i.e., transpulmonary distending pressures >30 to 35 cm H_2O). Pathologically, this manifests as diffuse alveolar damage[25-27] and is associated with cytokine release[28] and bacterial translocation.[29]

In addition to simple overstretching the lung, ventilator-induced lung injury (VILI) appears to be potentiated by a shear stress phenomenon that occurs when injured alveoli are repetitively opened and collapsed during the ventilatory cycle.[16,30,31] VILI may also be worsened by increasing the frequency of excessive lung tidal stretch and from acceleration forces associated with rapid initial gas flow into the lung.[32]

VILI occurs clinically when low resistance–high compliance units receive a disproportionately high regional tidal volume in the setting of high alveolar distending pressures (see Fig. 65-2). Concern about overdistention injury is the rationale for using "lung-protective" ventilator strategies that accept less than normal values for pH and O_2 partial pressure in exchange for lower (and safer) distending pressures.

CARDIAC EFFECTS

In addition to affecting ventilation and ventilation distribution, intrathoracic pressure changes resulting from positive-pressure ventilation can affect cardiovascular function.[18] In general, as mean intrathoracic pressure is increased, right ventricular filling is decreased. This is the rationale for using volume repletion to maintain cardiac output in the setting of high intrathoracic pressure. Conversely, elevations in intrathoracic pressure can actually improve left ventricular function because of an effective reduction in afterload.[33] Indeed, a sudden release of intrathoracic pressure (e.g., during a ventilator disconnect or spontaneous breathing trial) can sometimes precipitate flash pulmonary edema because of the acute increase in afterload coupled with an increased venous return.[34]

Intrathoracic pressures can also influence the distribution of perfusion. The relationship of alveolar pressures to perfusion pressures in the three-zone lung model can help explain this.[35] Specifically, the supine human lung is generally in a zone 3 (distention) state. As intra-alveolar pressures rise, however, zone 2 and zone 1 regions can appear, creating high $\dot{V}/\dot{Q}$ units. Indeed, increases in deadspace (i.e., zone 1 lung) can be a consequence of ventilatory strategies using high ventilatory pressures (e.g., IRV).

Positive-pressure mechanical ventilation can affect other aspects of cardiovascular function. Specifically, dyspnea, anxiety, and discomfort from inadequate ventilatory support can lead to stress-related catechol release, with subsequent increases in myocardial O_2 demands and risk of dysrhythmias. In addition, coronary blood vessel O_2 delivery can be compromised by inadequate gas exchange from the lung injury, coupled with low mixed venous O_2 partial pressure

due to high O_2 consumption demands by the ventilatory muscles.

OTHER ADVERSE EFFECTS

Oxygen concentrations approaching 100% are known to cause oxidant injuries in airways and lung parenchyma.[36] Many of the data supporting this concept, however, have come from animal studies, and animals and humans often have different O_2 tolerances. It is thus not clear what the "safe" O_2 concentration or duration of exposure is in sick humans. Most consensus groups have argued that FIO_2 values less than 0.4 are safe for prolonged periods and that FIO_2 values greater than 0.8 should be avoided if possible.

Mechanically ventilated patients are at risk for pulmonary infections for several reasons.[37] First, the natural protective mechanism of glottic closure is compromised by an endotracheal tube. This permits continuous seepage of oropharyngeal material into the airways. Second, the endotracheal tube itself impairs the cough reflex and serves as a potential portal for pathogens to enter the lungs. This is particularly important if the circuit is contaminated. Third, airway and parenchymal injury from both the underlying disease and management complications make the lung prone to infections. Fourth, the ICU environment itself, with its heavy antibiotic use and the presence of very sick patients in close proximity, poses a risk for a variety of infections.

Preventing ventilator-associated pneumonias is critical, because length of stay and mortality are heavily influenced by their development.[37] Hand washing and carefully chosen antibiotic regimens for other infections can have important beneficial effects. Management strategies that avoid breaking the integrity of the circuit (e.g., circuit changes only when visibly contaminated) also appear to be helpful.[38] Finally, continuous drainage of subglottic secretions may be a simple way of reducing lung contamination with oropharyngeal material.[39]

APPLYING ASSIST-CONTROL MECHANICAL VENTILATORY SUPPORT

TRADEOFFS

To provide adequate support but minimize VILI, mechanical ventilation goals must involve tradeoffs. Specifically, the need for potentially injurious pressures, volumes, and supplemental O_2 must be weighed against the benefits of gas exchange support. To this end, a rethinking of gas exchange goals has occurred over the last decade; pH goals as low as 7.15 to 7.20 and O_2 partial pressure goals as low as 55 mm Hg are now considered acceptable if the lung can be protected from VILI.[40] Ventilator settings are thus selected to provide at least this level of gas exchange support while at the same time meeting two mechanical goals: (1) provision of enough PEEP to recruit the recruitable alveoli, and (2) avoidance of a PEEP–tidal volume combination that unnecessarily overdistends lung regions at end-inspiration. These goals embody the concept of a "lung-protective" mechanical ventilatory strategy, and these principles guide current recommendations for the specific management of parenchymal and obstructive lung disease.[40,41]

PARENCHYMAL LUNG INJURY

Parenchymal lung injury describes disease processes that involve the airspaces and the interstitium of the lung. In general, parenchymal injury produces stiff lungs and reduced lung volumes.[12] Functional residual capacity is thus reduced, and the compliance curve is shifted to the right. It is important to realize, however, that in all but the most diffuse diseases (e.g., diffuse cardiogenic edema), there are often marked regional differences in the degree of inflammation present and thus the degree of mechanical abnormalities that exist. This heterogeneity can have a significant impact on the effects of a particular mechanical ventilation strategy. This is because delivered gases will preferentially go to the regions with the highest compliance and lowest resistance (i.e., the more normal regions) rather than to sicker regions with low compliance (see Fig. 65-2). A "normal-sized" tidal volume may thus be distributed preferentially to the healthier regions, resulting in a much higher regional tidal volume and the potential for regional overdistention injury.

Parenchymal injury can also affect the airways, especially the bronchioles and alveolar ducts.[12] These narrowed and collapsible small airways can contribute to reduced regional ventilation to injured lung units. This can also lead to air trapping, and it may be a factor in subsequent cyst formation during the healing phase.

Gas exchange abnormalities in parenchymal lung injury are a consequence of alveolar flooding or collapse, coupled with a maldistribution of ventilation that results in $\dot{V}/\dot{Q}$ mismatching and shunts. Because deadspace ($\dot{V}/\dot{Q} = \infty$) is not a major manifestation of parenchymal lung disease unless there is severe or end-stage injury, hypoxemia tends to be more of a problem than CO_2 clearance is.

Frequency–tidal volume settings for supporting parenchymal lung injury must focus on limiting end-inspiratory stretch. The importance of this limitation in improving outcome has been suggested by several recent clinical trials[42] but was most convincingly demonstrated by the National Institutes of Health–sponsored trial, which showed a 10% absolute reduction in mortality with a ventilator strategy using a tidal volume of 6 mL/kg compared with 12 mL/kg.[41] Because of this, initial tidal volume settings should start at 6 mL/kg ideal body weight. Moreover, strong consideration should be given to further reducing this setting if end-inspiratory plateau pressures, adjusted for any effects of excessive chest wall stiffness, exceed 30 cm H_2O. Increases in tidal volume settings might be considered if there is marked patient discomfort or suboptimal gas exchange, provided that the subsequent plateau pressures do not exceed 30 cm H_2O. Respiratory rate settings are then adjusted to control pH. Unlike in obstructive diseases (see later), the potential for air trapping in parenchymal lung injury is low if the breathing frequency is less than 35 breaths per minute and may not develop even at frequencies exceeding 50 breaths per minute.

The choice of pressure-targeted or volume-targeted breaths often depends more on clinician familiarity with the two modes than on important clinical differences between them. As noted earlier, both modes provide a comparable range of tidal volumes and inspiratory times. In general, pressure-targeted breaths are preferable when an absolute pressure limit is desired in the circuit or when patient effort is very active, with variable flow demands. In contrast, volume-targeted breaths are preferable when it is critical to maintain a certain level of minute ventilation.

Setting the inspiratory time and the inspiratory-expiratory ratio in parenchymal injury involves several considerations. The normal ratio is roughly 1:2 to 1:4; this produces the most comfort and is the usual initial setting. Assessment of the flow graphic should also be done to ensure that an adequate expiratory time is present to avoid air trapping. As noted earlier, inspiratory-expiratory prolongation beyond the physiologic range of 1:1 (IRV) can be used as an alternative to increasing PEEP to improve $\dot{V}/\dot{Q}$ matching in severe respiratory failure.[22,23] A variation on IRV is airway pressure release ventilation (also known as biphasic or bilevel ventilation).[43] Airway pressure release ventilation incorporates the ability to spontaneously breathe during the long inflation period of a pressure-controlled breath—a feature that may enhance recruitment and comfort.[43]

Generally, IRV strategies are reserved for patients in whom the plateau pressure from the PEEP–tidal volume combination exceeds 30 cm H_2O and potentially toxic concentrations of F_IO_2 are being used without meeting arterial O_2 saturation or O_2 delivery goals. It must be emphasized, however, that although IRV strategies have physiologic appeal, good outcome studies supporting their use do not exist.

There are both mechanical and gas exchange approaches to setting the PEEP-F_IO_2 combination to support oxygenation. Mechanical approaches use either a static pressure-volume plot to set the PEEP–tidal volume combination between the upper and lower inflection points[44] or step increases in PEEP to determine the PEEP level that gives the best compliance.[45] With either of these approaches, a recruitment maneuver could be used to recruit the maximal number of recruitable alveoli before setting the PEEP. F_IO_2 adjustments are then set as low as clinically acceptable. Gas exchange criteria to guide PEEP application generally involve algorithms designed to provide adequate values for arterial partial pressure of O_2 while minimizing F_IO_2 (Table 65-1).[41] Note that constructing a PEEP-F_IO_2 algorithm is usually an empirical exercise in balancing arterial O_2 saturation with F_IO_2 and depends on the clinician's perception of the relative "toxicities" of high thoracic pressures, high F_IO_2, and low arterial O_2 saturation.

OBSTRUCTIVE AIRWAY DISEASE

Respiratory failure from airflow obstruction is a direct consequence of increases in airway resistance. Airway narrowing and increased resistance lead to two important mechanical changes. First, the increased pressures required for airflow may overload ventilatory muscles, producing a "ventilatory pump failure," with spontaneous minute ventilation inadequate for gas exchange. Second, the narrowed airways create regions of lung that cannot properly empty and return to their normal resting volume, and intrinsic PEEP is produced.[9] These regions of overinflation create deadspace and put inspiratory muscles at a substantial mechanical disadvantage, which further worsens muscle function. Overinflated regions may also compress more healthy regions of the lung, impairing $\dot{V}/\dot{Q}$ matching. Regions of air trapping and intrinsic PEEP also function as a threshold load to trigger mechanical breaths.[46]

The gas exchange abnormalities that accompany worsening airflow obstruction are several. First, although there may be transient hyperventilation due to dyspnea in patients with asthma, worsening respiratory failure in those with obstructive lung disease is generally characterized by a falling minute ventilation as respiratory muscles become fatigued in the face of airflow obstruction. The result is termed hypercapneic respiratory failure. Second, as noted earlier, regional lung compression and regional hypoventilation produce $\dot{V}/\dot{Q}$ mismatch, which results in progressive hypoxemia. Alveolar inflammation and flooding, however, are not characteristic features of respiratory failure due to pure airflow obstruction; thus, shunts are less of an issue than in parenchymal lung injury. Third, overdistended regions of the lungs, coupled with underlying emphysematous changes in some patients, result in capillary loss and increasing deadspace. This wasted ventilation further compromises the inspiratory muscles' ability to supply adequate ventilation for alveolar gas exchange. These emphysematous regions also have reduced recoil properties that can worsen air trapping. Fourth, hypoxemic pulmonary vasoconstriction, coupled with chronic pulmonary vascular changes in some airway diseases, overloads the right ventricle, further decreasing blood flow to the lung and making the deadspace worse.

Setting the frequency–tidal volume pattern in obstructive lung disease involves many considerations that are similar to those in parenchymal lung injury. Specifically, tidal volumes should be sufficiently low (e.g., 6 mL/kg ideal body weight) to ensure that plateau pressure is less than 30 cm H_2O.[41] In obstructive disease, however, clinicians should be aware that high *peak* airway pressures, even in the presence of acceptable values for plateau pressure, may transiently subject regions of the lung to overdistention injury because of a pendelluft effect (see Fig. 65-2). As with parenchymal lung injury, tidal volume reductions should be considered to meet plateau pressure goals. Tidal volume increases can be considered for comfort or gas exchange, provided that plateau pressure values do not exceed 30 cm H_2O. The set rate is used to control pH. Unlike parenchymal disease, however, the elevated airway resistance (and often the low recoil pressures of emphysema) greatly increases the potential for air trapping, and this limits the range of breath rates available.

The inspiratory-expiratory ratio in obstructive lung disease is generally set as low as possible to minimize the development of air trapping. For the same reason, approaches using IRV strategies are almost always contraindicated.

Because alveolar recruitment is less of an issue in obstructive lung disease than in parenchymal lung injury, the

TABLE 65-1. PEEP-F_IO_2 ALGORITHM

F_IO_2	.30	.40	.40	.50	.50	.60	.70	.70	.70	.80	.90	.90	.90	1.0	1.0	1.0	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18	20	22	24

This table was used during the National Institutes of Health study.[41] The clinical target is an oxygen partial pressure of 55 to 80 mm Hg or SpO_2 of 88% to 95%. If the patient is below these target values, move up the table to the right. If the patient is above these targets, move down the table to the left.
F_IO_2, inspired oxygen fraction; PEEP, positive end-expiratory pressure.

PEEP-FiO_2 steps in Table 65-1 should probably be shifted to emphasize FiO_2 for oxygenation support. A specific role for PEEP in an obstructed patient occurs when intrinsic PEEP serves as an inspiratory threshold load on the patient's attempting to trigger a breath. Under these conditions, judicious application of circuit PEEP (up to 75% to 85% of intrinsic PEEP) can "balance" expiratory pressure throughout the ventilator circuitry to reduce this triggering load and facilitate the triggering process.[46]

In severe airflow obstruction, use of the low-density gas helium can facilitate ventilator settings. Helium is available as 80:20, 70:30, or 60:40 helium-oxygen breathing gas mixtures and can both reduce patient inspiratory work and facilitate lung emptying (recall that driving pressure decreases and flow increases through a tube as gas density decreases). If using a helium-oxygen gas mixture, it must be remembered that many flow sensors must be recalibrated to account for the change in gas density.

NEUROMUSCULAR RESPIRATORY FAILURE

The risk of VILI is generally less in a patient with neuromuscular failure because lung mechanics are often near normal, making regional overdistention less likely. More "generous" tidal volumes can thus be used to improve comfort, maintain recruitment, and prevent atelectasis. At the same time, however, maximal distending pressures should be monitored and kept as low as possible while still being compatible with the other goals noted earlier. Certainly, plateau pressure should always be kept well below 30 cm H_2O. Low levels of PEEP are often beneficial in preventing derecruitment (atelectasis) in these patients, who are often supine and incapable of secretion clearance or spontaneous sigh breaths.

RECENT INNOVATIONS IN ASSIST-CONTROL MECHANICAL VENTILATORY SUPPORT

TRACHEAL GAS INSUFFLATION

Tracheal gas insufflation involves placing a catheter at the distal end of the endotracheal tube to provide fresh gas to flush the tube of CO_2 during exhalation.[47,48] The rationale is that the next delivered breath will effectively be free of endotracheal tube CO_2 and thus will have a reduced deadspace. This approach has particular appeal during lung-protective ventilatory strategies in which the arterial CO_2 partial pressure is rising. A number of studies have shown that the concept of tracheal gas insufflation accomplishes this physiologic goal (i.e., reduced deadspace), but there is the potential for an inadvertent PEEP buildup.

Tracheal gas insufflation catheters can deliver fresh gas either continuously or only during exhalation. The former approach is easier to implement, but the latter approach reduces the potential for excessive end-inspiratory overinflation. Catheters can also be designed to deliver gas directly into the lung or in a retrograde fashion back up the endotracheal tube. The former enhances gas mixing, but the latter reduces inadvertent PEEP buildup. At present, it is unclear what is the best way to deliver tracheal gas insufflation or whether it can significantly affect outcome. Clearly, however, such systems need to have safeguards to protect the lung from inadvertent overdistention.

HIGH-FREQUENCY VENTILATION

High-frequency ventilation uses very high breathing frequencies (120 to 300 breaths per minute in an adult), coupled with very small tidal volumes (often less than anatomic deadspace) to provide gas exchange in the lungs.[49] Gas transport under these seemingly unphysiologic conditions involves such mechanisms as Taylor dispersion, coaxial flows, and augmented diffusion.[50]

High-frequency ventilation can be supplied by either jets or oscillators. Jets inject high-frequency pulses of gas into the airways. Oscillators vibrate a fresh bias flow of gas delivered at the tip of the endotracheal tube.

The putative advantages to high-frequency ventilation are twofold. First, the high gas flow provides for considerable intrinsic PEEP and thus alveolar recruitment. This is particularly effective following recruitment maneuvers. Second, the very small tidal pressure swings keep the lung well below the overdistention threshold. Because of these features, high-frequency ventilation has sometimes been considered the "ultimate" lung protection strategy.[51]

Clinical experience with high-frequency ventilation has been most extensive in the neonatal and pediatric population. Recent studies suggest that in neonates at risk for overdistention injury, high-frequency ventilation improves outcome.[52] Adult experience is less extensive; only recently have devices become available to adequately support gas exchange in this setting.[53] However, a recent randomized trial comparing high-frequency ventilation with "conventional" ventilation in adults with acute respiratory distress syndrome showed a trend toward improved survival with high-frequency ventilation.[54]

CONCLUSION

Mechanical ventilatory support is a critical component in the management of patients with respiratory failure. It must be remembered, however, that this technology is supportive, not therapeutic; it cannot cure lung injury. Indeed, the best we can hope for is to "buy time" by supporting gas exchange without harming the lungs.

There are exciting innovations on the horizon, but they must be assessed properly. This is particularly important for innovations with significant risks or costs. Only with properly conducted studies of clinically relevant factors such as mortality, ventilator-free days, barotrauma, and cost can we properly assess the sometimes bewildering array of new approaches to this vital life-support technology.

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An excellent report examining mechanical ventilator design and application, including the major features of modern mechanical ventilators, breath delivery features, monitor and alarm strategies, and utility in various settings.

Dreyfuss D, Saumon G: Ventilator induced lung injury: Lessons from experimental studies. Am J Respir Crit Care Med 1998;157:294-323.

An excellent review attempting to link important data from animal studies of ventilator-induced lung injury to the clinical setting, with an emphasis on how ventilator strategies can produce both lung and systemic injury.

NIH ARDS Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-1308.

This landmark study clearly established the link between excessive lung stretch during mechanical ventilation and worse survival in patients with

acute lung injury. The message from this paper is very clear: even though large tidal volumes may improve gas exchange, they ultimately cause harm by overstretching healthier regions of the lung.

Pinsky MR, Guimond JG: The effects of positive end-expiratory pressure on heart-lung interactions. J Crit Care 1991;6:1-15.

An excellent overview of the complex interactions of intrathoracic positive pressure and cardiac function. The fact that the twin effects of decreased right heart filling and decreased left ventricular afterload can have both positive and negative effects is carefully explained.

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Chapter 66

PATIENT-VENTILATOR INTERACTION

Vincenzo Squadrone • Cesare Gregoretti • V. Marco Ranieri

KEY POINTS

1. **Patient-ventilator asynchrony is common,** is often unrecognized and underestimated, and is often inappropriately treated in the clinical setting.
2. **Patient-ventilator asynchrony takes place when the three physiologic variables** of the patient's breathing pattern—ventilatory drive, ventilatory requirements, and duration and ratio of inspiratory time to total breath cycle duration—do not match ventilator trigger, ventilator-delivered flow, and ventilator cycling criteria.
3. **Clinical optimization of patient-ventilator interactions** can be obtained only by continuously matching the triggering, flow delivering, and cycling functions of the ventilator with the patient's physiologic variables.
4. Optimization of patient-ventilator interactions implies **continuous measurement** of physiologic variables and **continuous adaptation** of the ventilator to the spontaneous variations in these physiologic variables.
5. **Future developments in ventilator technology** should be oriented toward a system with the capability to automatically interface between physiologic parameters and ventilator outputs. Such technology will be based on a closed-loop algorithm able to realize total patient-controlled mechanical support.

The clinical management of patients with acute respiratory failure is based on the assumption that significant abnormalities in respiratory mechanics, respiratory muscle performance, and control of breathing are the underlying mechanisms responsible for acute respiratory failure.[1] The effects of mechanical ventilation on gas exchange, respiratory muscle load, and dyspnea depend on the matching between the ventilator settings and the patient's respiratory physiology. However, mechanical ventilation is rarely optimized, which would require that ventilator settings be based on accurate and reproducible measurements of lung and chest wall mechanics, respiratory muscle function, and respiratory drive.[2-5]

RESPIRATORY PHYSIOLOGY

The goal of the ventilatory control system is to generate the timing and intensity of the phrenic nerve signal, integrating inputs from chemoreceptors, pulmonary stretch receptors, variations in metabolic demands, and so forth. Contraction of the respiratory muscles leads to the generation of flow and volume to provide adequate alveolar ventilation with minimal work of breathing.[6] During spontaneous breathing,[7] the respiratory muscles generate pressure (Pmus) to produce flow against the resistive properties (R_{RS}) and volume against the elastic properties (E_{RS}) of the respiratory system and to eventually overcome intrinsic positive end-expiratory pressure (PEEPi). Under these circumstances, the act of spontaneous breathing can be described at any instant as follows:

$$Pmus = Pres + Pel + PEEPi \qquad \text{(Equation 1)}$$

where Pres represents the resistive pressure and is a function of flow ($Pres = Flow \times R_{RS}$), and Pel represents the elastic recoil pressure and is a function of volume ($Pel = Volume \times R_{RS}$). Assuming that R_{RS} and E_{RS} are linear, the equation becomes:

$$Pmus = PEEPi + (Flow \times R_{RS}) + (Volume \times E_{RS}) \qquad \text{(Equation 2)}$$

In patients with acute respiratory failure requiring ventilatory support, pressure generated by the ventilator (Pappl) is added to the pressure generated by the contraction of the respiratory muscles, according to the following equation:

$$Pmus + Pappl = PEEPi + (Flow \times R_{RS}) + (Volume \times E_{RS}) \qquad \text{(Equation 3)}$$

The complex interaction among all the variables in equation 3 can be summarized with the concept of neuroventilatory coupling (Fig. 66-1).[8] Under normal conditions, as well as at the onset of acute respiratory failure, the spontaneous contraction of the respiratory muscles suddenly generates flow and volume; the slope of the relationship between effort and ventilatory output is conditioned by the contractile properties of the respiratory muscles and the impedance of the respiratory system. When positive pressure is applied to assist the action of breathing in most common modes of mechanical ventilation (pressure support or assist mandatory ventilation), the coupling between effort and output is compromised. During assist-mandatory ventilation, flow and volume remain constant, despite changes in muscle contraction; during pressure support ventilation, despite a sort of coupling between inspiratory effort and ventilatory output, any increase in respiratory

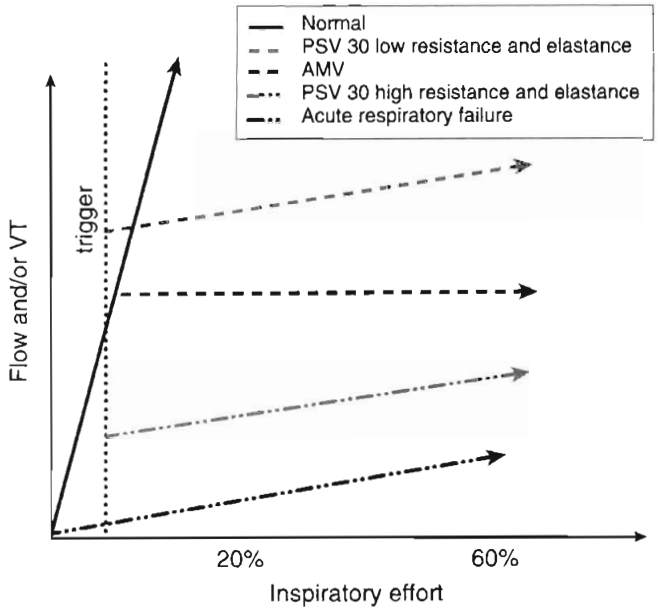

FIGURE 66–1. Neuroventilatory coupling. Under normal conditions, as well as at the onset of acute respiratory failure, the spontaneous contraction of the respiratory muscles suddenly generates flow and volume; the slope of the relationship between effort and ventilatory output is conditioned by the contractile properties of the respiratory muscles and the impedance of the respiratory system. When positive pressure is applied to assist the action of breathing in most common modes of mechanical ventilation, the coupling between effort and output is compromised. During assisted mandatory ventilation (AMV), flow and volume remain constant, despite changes in muscle contraction; during pressure support ventilation (PSV), despite a sort of coupling between inspiratory effort and ventilatory output, any increase in respiratory impedance decreases the amount of delivered flow and volume. VT, tidal volume.

impedance decreases the amount of delivered flow and volume.[8]

PATIENT AND VENTILATOR VARIABLES

PATIENT

The patient interacts with the ventilator based on three physiologic variables[2,9,10]:

1. Ventilatory drive, or when inspiration starts[11]
2. Ventilatory requirements, or how much flow and volume are necessary to satisfy metabolic demands[5]
3. Timing of the integrated circuits generating the respiratory rhythm, as measured by the duration and ratio of inspiratory time to total breath cycle duration[9]

VENTILATOR

The ventilator interfaces with the patient's physiology based on three technologic variables:

1. The inspiratory trigger, or when the ventilator starts to deliver flow, volume, and pressure[12,13]
2. The delivery mechanisms of gas—that is, the algorithm used by the ventilator to assist ventilation through the delivery of flow, volume, or pressure[14-19]
3. The cycling criteria, or when the ventilator stops assisting the inspiratory effort and lets the patient exhale spontaneously[20,21]

Intrinsic manufacturing features of ventilators, such as blowers and inspiratory, expiratory, and PEEP pressure valves, are also important in determining the interaction between patient and ventilator.[22-24]

To unload the respiratory muscles, restore sufficient gas exchange, and relieve the patient from dyspnea, the health care team must establish an interface between patient and ventilator. To do so, there are two options: total ventilator-controlled mechanical support, or partial patient-controlled support.

Total Ventilator-Controlled Mechanical Support. In this method, the patient's breathing pattern is totally controlled by the ventilator. The pressure generated by the respiratory muscles is abolished by paralysis or sedation. Flow, volume, and pressure are imposed by the ventilator, and the patient's breathing pattern is totally replaced by that of the ventilator. The risk of patient-ventilator asynchrony is therefore abolished, but there are potential risks associated with sedation and paralysis,[25] respiratory muscle atrophy,[26] lung damage due to overdistention,[27] patient discomfort,[28] and difficulty weaning after prolonged controlled mechanical ventilation.[1]

Partial Patient-Controlled Mechanical Support. With this method, spontaneous breathing activity is partially preserved.[29] The need for sedation and paralysis may be reduced, disuse atrophy of the respiratory muscles may be minimized, and the weaning process may be accelerated, provided the patient's ventilatory demand and ventilator settings are synchronized.[30] The ability to restore gas exchange, unload respiratory muscles, and relieve patient dyspnea with partial patient-controlled mechanical support therefore depends on the absence of patient-ventilator asynchrony.[31]

Although there are no well-accepted definitions, patient-ventilator asynchrony is common; it is often unrecognized, underestimated, and inappropriately treated.[3-5,19-21,31] The cause of patient-ventilator asynchrony can be described as occurring because of a mismatch between the three physiologic variables characterizing spontaneous breathing (ventilatory drive, ventilatory requirements, and duration and ratio of inspiratory time to total breath cycle duration) and the three technologic variables characterizing ventilator function (trigger function, gas delivery algorithm, and cycling criteria).

RESPIRATORY DRIVE–VENTILATOR TRIGGER ASYNCHRONY

The goal of the ventilator trigger is to track inspiratory effort in order to couple the patient's effort with the delivery of pressure, flow, or volume. The inspiratory effort necessary to trigger a breath may be a significant part of the total inspiratory effort, representing 17% and 12% of the total inspiratory effort during pressure and flow triggering, respectively.[12,22] Aslanian and coworkers found that even though the time required for triggering was 43% shorter and effort during the time of triggering was 62% less with flow triggering than with pressure triggering, effort during the post-triggering phase was equivalent for both pressure and flow triggering.[32] The clinical benefit of flow triggering therefore appears to be much less relevant than commonly stated.[3]

Inspiratory phase asynchrony may be due to problems with inspiratory triggering, and this can be correlated with

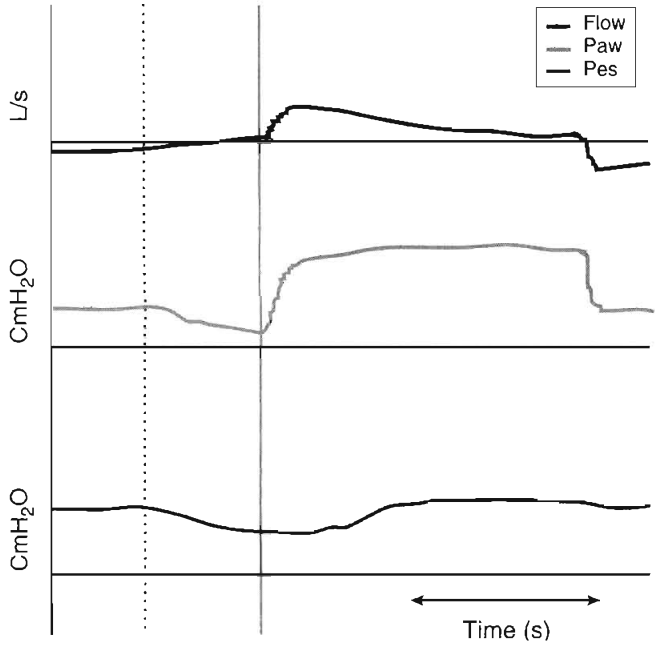

FIGURE 66–2. Representative tracings show the interaction between patient effort and triggering of the ventilator. The delay between the beginning of inspiratory muscle activity *(dotted line)* and the beginning of mechanical inflation *(solid line)* can cause an inspiratory phase asynchrony. Flow, flow generated at the airway opening; Paw, pressure applied at the airway opening; Pes, esophageal pressure.

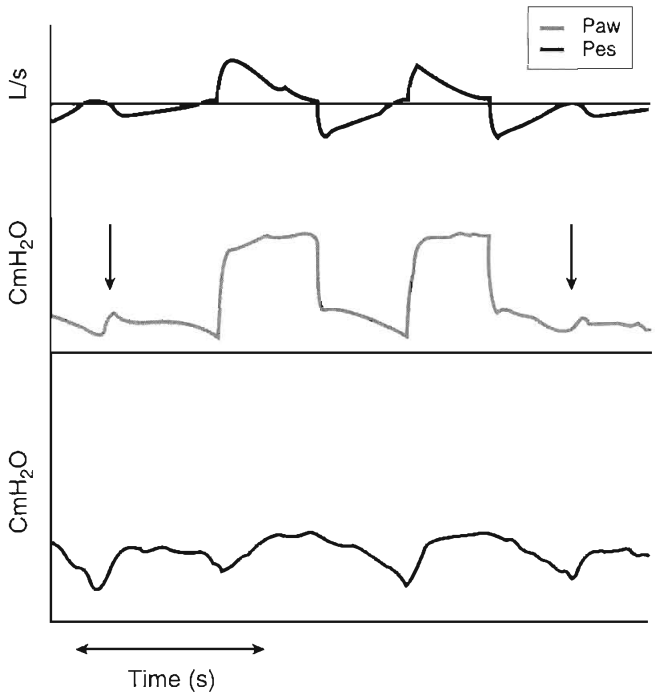

FIGURE 66–3. Representative tracings show ineffective triggering due to the ventilator's inability to detect the patient's "request" for an assisted breath. As indicated by the *arrows,* a substantial inspiratory effort generates only a bump in the flow and pressure tracings, instead of a mandatory assisted breath. Flow, flow generated at the airway opening; Paw, pressure applied at the airway opening; Pes, esophageal pressure.

respiratory drive. Phase lag quantifies the delay between the commencing of inspiratory muscle activity and the beginning of mechanical inflation (Fig. 66-2).[3,9,10] The presence of a threshold load, such as dynamic intrinsic PEEP, may further complicate patient-ventilator interaction during the triggering phase.[12] Giuliani and coworkers suggested that effort during triggering determines patient effort during the remaining portion of inspiration.[33] Leung and coworkers demonstrated that the higher the level of ventilator-applied pressure, the lower the respiratory drive but the longer the time required to trigger the ventilator; as a result, respiratory muscles generate smaller inspiratory swings in intrathoracic pressure, but over a longer inspiratory time.[2] Another problem is related to the fact that pressure is detected on the expiratory limb of the ventilator circuit; therefore, any resistive load (e.g., endotracheal tube or upper airways during noninvasive ventilation) reduces the responsiveness of the gas delivered by the ventilator in response to patient effort.[19]

Ineffective triggering is due to the ventilator's inability to detect the patient's "request" for an assisted breath, despite substantial inspiratory effort (Fig. 66-3). This phenomenon usually occurs with high levels of ventilator assistance and with short expiratory times. Mechanical characteristics that may induce ineffective triggering include low elastance, high resistance, and intrinsic PEEP; ineffective triggering is not correlated to an increase in the patient's inspiratory effort.[2] The application of external PEEP below the intrinsic PEEP level can reduce the patient's inspiratory effort required to trigger the ventilator.[34] Parthasarathy and coworkers demonstrated that prolonging mechanical inflation into neural expiration reduces the time available for unopposed exhalation, resulting in the need for a greater inspiratory effort to trigger the ventilator.[35] Younes and colleagues found that ineffective triggering in ventilator-dependent patients exacerbates dynamic hyperinflation.[36]

VENTILATORY REQUIREMENT–GAS DELIVERY ASYNCHRONY

Gas delivery asynchrony occurs when ventilator-delivered flow, volume, and pressure are insufficient to meet the patient's ventilatory demand. Ward and coworkers demonstrated that increasing the flow rate could be used as a means of reducing the patient's respiratory drive and active respiratory muscle work,[14] although doing so may exert an excitatory effect on respiratory rate and on the rate of rise of inspiratory muscle activity.[3,16,17,37-43] Laghi and colleagues demonstrated that the imposed inspiratory time during mechanical ventilation determines respiratory frequency independent of inspiratory flow and tidal volume.[17] Pressure-targeted breath may better match the patient's ventilatory requirements, because pressure is the independent variable; as a consequence, flow is continuously adjusted by the ventilator to maintain a constant pressure. In addition, the rapid pressurization of the airways is coupled with high inspiratory flow only at the beginning of inspiration, thus reproducing the physiologic flow profile.[44]

INSPIRATORY TIME–VENTILATOR CYCLING ASYNCHRONY

Ventilator-patient asynchrony occurs when the patient is trying to exhale but the ventilator is still delivering gas.[32,35,45] In patients ventilated with a time-cycled breath, expiratory phase asynchrony takes place when the patient's neural inspiratory time is shorter or longer than the ventilator inflation time. For proper cycling off of the ventilator and optimal patient-ventilator synchrony, the patient's inspiratory flow and ratio of inspiratory time to total breath cycle

duration must be tracked. During pressure- or flow-cycled breath, inspiratory time is determined exclusively by the time taken for the exponentially declining flow to reach the flow threshold value (when cycling between inspiration and expiration occurs).[20,46] For proper cycling off and optimal patient-ventilator synchrony, the ventilator needs to track patient's inspiratory flow. The algorithm for the "expiratory trigger" depends on the manufacturer, but most ventilators use a percentage of a drop in inspiratory flow or a preset terminal flow. This expiratory sensitivity can be fixed or can vary from 5% to 90% or from 5 to 25 L/min (Fig. 66-4). Preset terminal flow algorithms can be problematic in patients with chronic obstructive pulmonary disease.[47] The setting of the pressure rise time (pressure slope) can also modify the expiratory threshold by modifying the inspiratory flow.[48,49]

Although there is some evidence that rapid pressure rise times might reduce the patient's work of breathing,[48] a fast pressure increase may lead to particularly high peak inspiratory flow, which may cause premature termination of inspiration when the fixed percentage criterion for expiratory cycling is reached (Fig. 66-5).[19,50] The expiratory sensitivity setting is crucial when ventilators are used to deliver noninvasive ventilation, because air leaks may cause an abnormal prolongation of the inspiratory time; during this time, the patient may make several efforts to exhale against the machine or to inhale, without receiving any ventilatory support (inspiratory hang-up) (Fig. 66-6).[51-54]

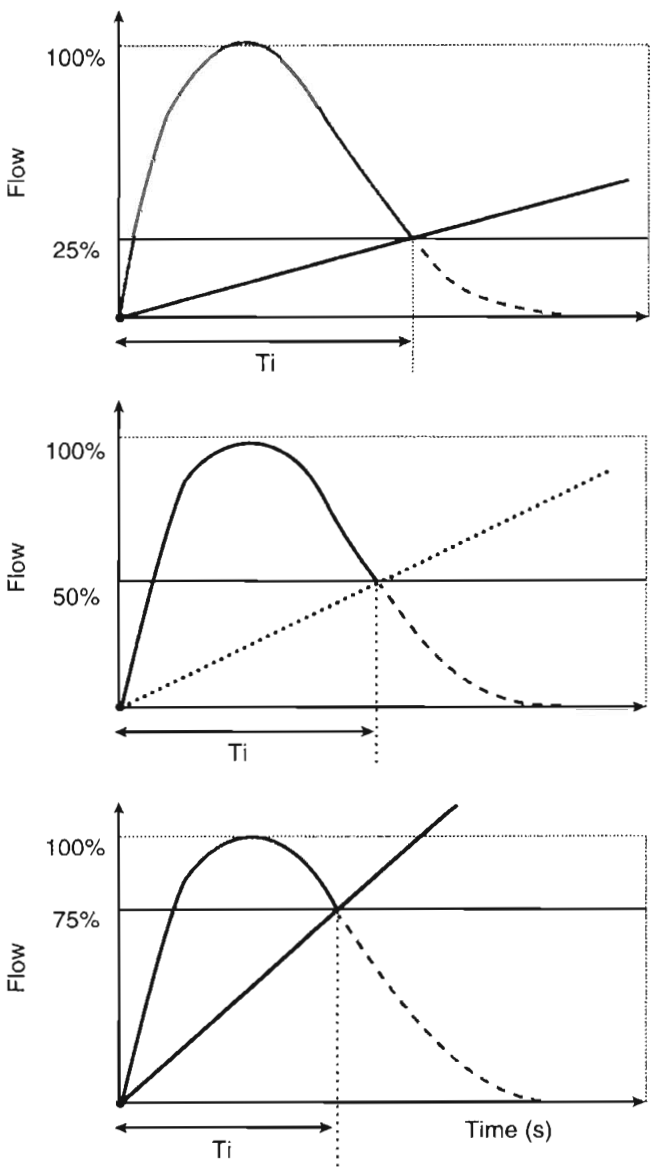

FIGURE 66–4. Representative tracings show different settings for expiratory trigger sensitivity on a flow-time plot. From top to bottom: expiratory trigger set at 25%, 50%, and 75% of peak flow. Ventilator inspiratory time is influenced by the preset flow expiratory trigger sensitivity, at which point the ventilator switches to expiration.

TOTAL PATIENT-CONTROLLED MECHANICAL SUPPORT

Clinical optimization of patient-ventilator interactions can be obtained only by continuous matching between the triggering, flow delivering, and cycling functions of the ventilator and the patient's ventilatory drive, spontaneous inspiratory flow demand, and ratio of inspiratory time to total breath cycle. This implies continuous measurement of physiologic variables and continuous adaptation of the ventilator to the spontaneous variations in these variables. Future development in ventilator technology should be oriented toward systems with the capability to automatically interface between physiologic parameters and ventilator outputs. Such technology will be based on a closed-loop algorithm able to achieve total patient-controlled mechanical support.[4]

The design features of an automatic control system in a mechanical ventilator include (1) what activates the system (the input), (2) what the system produces (the output), (3) the protocol used to link input and output (the controlling algorithm). In a closed-loop system, the output will activate and condition the input. When changes in output are opposite to changes in input, the closed loop is said to be negative. The closed loop is positive when variations in output mirror variations in input. The most common example of a negative closed-loop control system in the clinical setting is the ventilator humidifier. In this case, the input is the temperature inside the chamber, and the output is the temperature of the gas being delivered to the patient. The controlling algorithm is designed to keep the latter constantly above a value set by the operator. If the output (i.e., the temperature of gas delivered to the patient) is lower than the preset level, the algorithm will increase the input (i.e., the temperature in the chamber); if the output is higher than the preset level, the algorithm will decrease the input. Closed-loop systems are hence able to stabilize and limit the performance of a mechanical system. In the case of acute respiratory failure, the patient is unable to provide sufficient output (i.e., minute ventilation). The ventilator should therefore be able to detect the input from the patient and continuously adapt the output to it. If the input is increasing (i.e., ventilatory requirements are increasing), the ventilator will increase the output (i.e., apply more positive pressure); if the input is decreasing (i.e., ventilatory requirements are decreasing), the ventilator will decrease the output (i.e., apply less positive pressure). The controlling closed loop eventually applied by the ventilator must therefore be positive. Positive closed-loop control systems are inherently unstable in the sense that they tend to (1) "run away" with ventilatory assistance—if the pressure generated by the ventilator is higher than the pressure required to offset the passive properties of the respiratory system, the ventilator will continue to deliver flow and volume while the

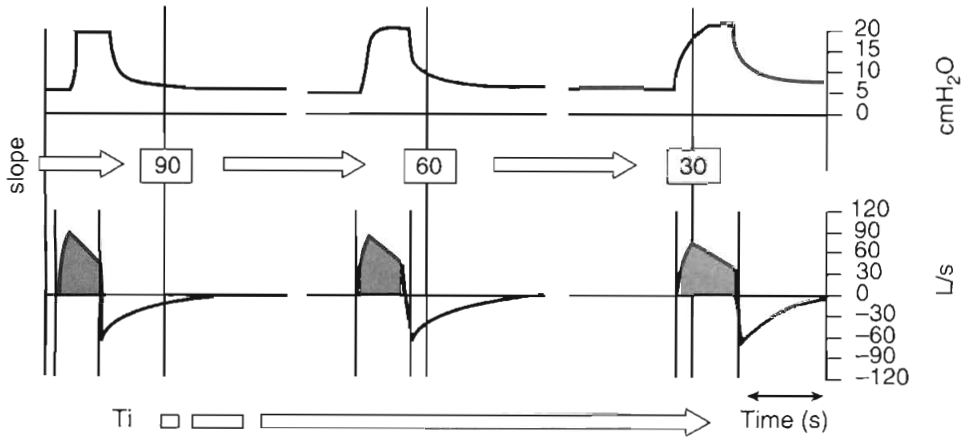

FIGURE 66–5. Representative tracings show different pressure-rise time sensitivities on a flow-time plot. From left to right: pressure-rise time set at 90%, 60%, and 30% of maximal pressurization time. Ventilator inspiratory time *(shaded area)* is influenced by the preset pressure-slope sensitivity that generates a different peak inspiratory flow. Paw, pressure applied at the airway opening.

patient stops his or her inspiratory effort and tries to initiate expiration; and (2) "extinguish" ventilatory assistance—if the patient does not produce any inspiratory effort, the ventilator will not produce any ventilatory support.

Based on a closed-loop algorithm, new modes of mechanical ventilation have been proposed. They represent modifications of pressure support ventilation and are characterized by the patient's ability to control the amount of assistance provided by the ventilator. They are differentiated by the patient-related variable used to close the loop.

PROPORTIONAL ASSISTED VENTILATION AND PROPORTIONAL PRESSURE SUPPORT

During proportional assisted ventilation and proportional pressure support, the ventilator generates pressure in proportion to patient-generated flow and volume; the ventilator amplifies patient effort without imposing any ventilatory or pressure targets. Ventilator-generated pressure rises as long as inspiratory muscle effort is produced by the patient. The preset parameter is not a target pressure but the proportion between pressure applied by the ventilator and flow and volume generated by the patient's inspiratory muscle effort.[55,56] During this type of mechanical support, the clinician adjusts the percentage of flow-assisted or volume-assisted ventilation, after determining the patient's resistance and elastance. In other words, the physician must determine how much to reduce the load imposed by the patient's elastance[57] and resistance.[58,59] Despite the exciting potential of this technique,[59-62] applied either invasively or noninvasively,[63-69] no large-scale studies have demonstrated an improvement in patient outcome compared with other modes of ventilation.

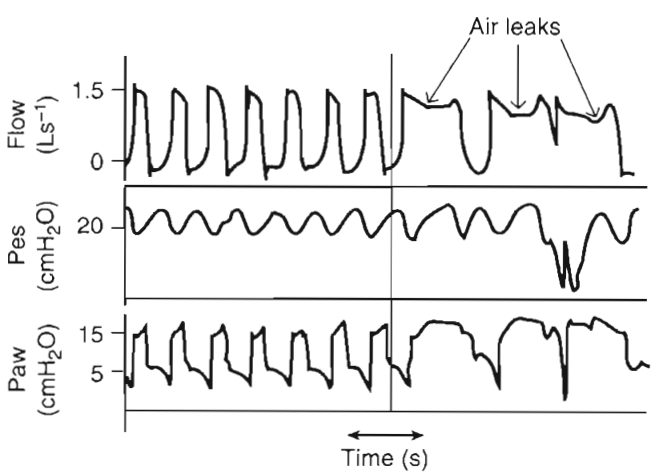

FIGURE 66–6. Representative record of air leaks during noninvasive facemask pressure support ventilation. The presence of air leaks causes a prolonged ventilator inspiratory time *(arrows)*. Flow, flow generated at the airway opening; Paw, pressure applied at the airway opening; Pes, esophageal pressure.

NEURAL-ADJUSTED VENTILATORY ASSISTANCE

With this method, electrical activity of the diaphragm is measured by means of an electrode array inserted into a nasogastric tube and placed in the lower esophagus; this information is then used to control the ventilator to generate flow, volume, and pressure.[8,70,71] Unlike with the proportional method described earlier, estimates of respiratory mechanics are not needed. With neural-adjusted ventilatory assistance, the patient's respiratory center controls the assisted positive breaths in all phases of the ventilation cycle, from triggering to cycling off of inspiration. Any change in patient ventilatory output is matched breath by breath by the ventilator, even in the presence of variations in respiratory mechanics. This system is not yet available, and a number of issues must be sorted out before it can be used routinely.

ADAPTIVE SUPPORT VENTILATION

Adaptive support ventilation is basically an assist time–limited, pressure-targeted mode of ventilation (pressure-controlled ventilation), relying on a negative closed-loop system of regulating ventilator settings in response to changes in both

respiratory impedance (elastance and resistance) and the patient's spontaneous efforts.[72] The basic principle relies on the work of Otis and coworkers[73] and Mead,[6] demonstrating that, for a given level of minute alveolar ventilation, there is a respiratory rate that is least costly in terms of respiratory work. With adaptive support ventilation, the operator enters the patient's body weight and sets the desired percentage of minute ventilation. The expiratory time constant is determined by analysis of the expiratory flow-volume curve,[74] adjusting inspiratory pressure, inspiratory-expiratory time ratio, and respiratory rate to obtain the prescribed minute ventilation. Adaptive support ventilation thus adjusts inspiratory pressure, inspiratory-expiratory time ratio, and mandatory respiratory rate to maintain the target minute ventilation and respiratory rate, within a framework designed to avoid both rapid, shallow breathing and excessive inflation volumes. Spontaneous breathing triggers either a pressure-controlled or a spontaneous breath with inspiratory pressure support, the level of which is adjusted to meet the target respiratory rate–tidal volume combination.

ACKNOWLEDGMENTS

This work was supported by Ministero Università e Ricerca: COFIN 21544 (2002-2004).

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Appendini L, Purro A, Gudjonsdottir M, et al: Physiologic response of ventilator-dependent patients with chronic obstructive pulmonary disease to proportional assist ventilation and continuous positive airway pressure. Am J Respir Crit Care Med 1999;159:1510-1517.

This study found that in difficult-to-wean patients with chronic obstructive pulmonary disease, proportional assisted ventilation improves ventilation and decreases inspiratory muscle effort. It also found that the combination of proportional assisted ventilation and continuous positive airway pressure can unload the inspiratory muscles to values close to those in normal subjects.

Beck J, Sinderby C, Lindström L: Effects of lung volume on diaphragm EMG signal strength during voluntary contractions. J Appl Physiol 1998;85:1123-1134.

These authors found that variations in end-expiratory lung volume between breaths can affect the transformation of respiratory muscle activation into mechanical output (neuromechanical coupling).

Calderini E, Confalonieri M, Puccio PG, et al: Patient-ventilator asynchrony during noninvasive ventilation: The role of the expiratory trigger. Intensive Care Med 1999;25:662-667.

This article describes the loose patient-ventilator synchrony in the presence of air leaks and noninvasive pressure support ventilation.

Laghi F, Karamchandani K, Tobin MJ: Influence of ventilator settings in determining respiratory frequency during mechanical ventilation. Am J Respir Crit Care Med 1999;160:1766-1770.

These authors found that during assist-control mode, ventilator inspiratory time can determine respiratory frequency independently of inspiratory flow and tidal volume.

Leung P, Jubran A, Tobin MJ: Comparison of assisted ventilator modes on triggering, patients' effort, and dyspnea. Am J Respir Crit Care Med 1997;155:1940-1948.

This study found that when receiving assist-control ventilation or high levels of pressure support, one quarter to one third of a patient's inspiratory efforts may fail to open the inspiratory valve triggering the machine. The number of ineffective triggering attempts increases in proportion to the level of ventilatory assistance and is not correlated to the magnitude of inspiratory effort at a given level of assistance.

Parthasarathy S, Jubran A, Tobin MJ: Cycling of inspiratory and expiratory muscle groups with the ventilator in airflow limitation. Am J Respir Crit Care Med 1998;158:1471-1478.

These authors found that the continuation of a mechanical mandatory breath into neural expiration is associated with a waste of inspiratory effort, defined as failure of the subsequent inspiratory attempt to trigger the ventilator.

Parthasarathy S, Tobin JM: Effect of ventilator mode on sleep quality in critically ill patients. Am J Respir Crit Care Med 2002;166:1423-1429.

These authors found that inspiratory assistance during pressure support causes hypocapnia, which, combined with the lack of a backup rate and wakefulness drive, can lead to central apneas and sleep fragmentation, especially in patients with heart failure. A backup rate, as during assist-control volume-targeted ventilation, prevents the development of apneas and perhaps decreases arousals.

Sinderby C, Navalesi P, Beck J, et al: Neural control of mechanical ventilation in respiratory failure. Nat Med 1999;5:1433-1436.

This article describes a completely new mode of detecting inspiratory effort, based on the measurement of electrical activity of the diaphragm by means of an electrode array inserted into a nasogastric tube and placed in the lower esophagus. Output generated from the electrodes, filtered out for, is used to control the ventilator that finally generates the respiratory ouput.

Tobert DG, Simon PM, Stroetz RW, Hubmayr RD: The determinants of respiratory rate during mechanical ventilation. Am J Respir Crit Care Med 1997;155:485-492.

The authors examined the rate response of eight normal volunteers during both quiet wakefulness and non–rapid-eye-movement (non-REM) sleep in the setting of mechanical ventilation through a nasal mask in an assist-control mode with a machine backup rate of 2 breaths per minute. They found that both tidal volume and inspiratory flow settings affect the respiratory rate and can affect carbon dioxide homeostasis. During non-REM sleep, hypocapnia resulted in wasted ventilator trigger efforts. Thus, ventilator settings appropriate for wakefulness may cause ventilatory instability during sleep.

Younes M, Webster K, Kun J, et al: A method for measuring passive elastance during proportional assist ventilation. Am J Respir Crit Care Med 2001;164:50-60.

A noninvasive method to continuously measure elastance of the respiratory system during proportional assisted ventilation is described.

Chapter 67

WEANING FROM MECHANICAL VENTILATION

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KEY POINTS

1. **Liberation from the ventilator is different from extubation.** They are different processes with different pathophysiologic mechanisms that may lead to failure.
2. **Cardiovascular dysfunction may complicate weaning** in a significant number of patients owing to the switch from positive intrathoracic pressure to spontaneous breathing, with a consequent increase in preload and afterload.
3. **The presence of undiagnosed illnesses at the time of extubation** may complicate the subsequent clinical course. Patients with extubation failure have an increased mortality rate that varies based on the specific cause of the failure.
4. **The implementation of weaning protocols improves outcome** in terms of duration of mechanical ventilation and length of stay in the ICU. This effect can be attributed mostly to the fact that patients are checked daily for the ability to maintain spontaneous breathing.
5. **Noninvasive ventilation** may prevent re-intubation and facilitate extubation.

Weaning from mechanical ventilation represents the period of transition from total ventilatory support to spontaneous breathing. The majority of intubated, mechanically ventilated patients (about 75%) are extubated after disconnection from the ventilator or after breathing at low levels of pressure support for a short time, generally 30 to 120 minutes.[1,2] The remaining patients (about 25%) need progressive withdrawal from artificial ventilatory support.

Early liberation from mechanical ventilation (weaning) and removal of the endotracheal tube (extubation) are clinically important. Unnecessary prolongation of mechanical ventilation increases the risk of complications, including infection (particularly of bronchopulmonary origin), barotrauma, cardiovascular compromise, tracheal injury, and muscle deconditioning. Clinicians should take steps to hasten the process that ultimately leads to endotracheal tube removal so as to maximize patient outcomes.[3]

Liberation and extubation are different issues. Once a patient has been weaned from mechanical ventilation and no longer requires ventilatory support, the clinician has to consider a different question: Is the patient able to breathe spontaneously without the endotracheal tube? Recent investigations have clearly determined that liberation and extubation are different entities and that the pathophysiologic mechanisms underlying weaning failure and extubation failure are not the same. In terms of magnitude, the extubation failure rate is variable and ranges from 5% to 20% of extubated patients.

MECHANISMS OF LIBERATION FAILURE

Weaning attempts that are unsuccessful usually indicate incomplete resolution of the illness that generated the need for mechanical ventilation.

RESPIRATORY PUMP FAILURE

The most common mechanism of weaning failure is respiratory pump insufficiency, which is caused by an imbalance between capability and demand.[4-6] During spontaneous breathing, the inspiratory muscles must generate sufficient force to overcome the elasticity of the lungs and chest wall (elastic load), as well as airway and tissue resistance (resistive load). This requires generation of a signal in the respiratory centers of the brainstem, anatomic and functional integrity of the nerves that conduct the signal, unimpaired neuromuscular transmission, and adequate respiratory muscle strength (the aggregate is termed neuromuscular competence). The ability of the respiratory muscles to sustain these loads without fatiguing is called endurance and is determined by the balance between energy supply and energy demand.

Jubran and Tobin investigated the progression of respiratory mechanics during spontaneous breathing trials in patients with chronic obstructive pulmonary disease (COPD).[7] At the beginning of the trials, patients who subsequently failed had slightly higher airway resistance, respiratory system elastance, and intrinsic positive end-expiratory pressure (PEEP) compared with those who succeeded. However, during the course of the trials, respiratory mechanics progressively worsened in patients who failed. They developed rapid, shallow breathing, and most developed an increase in partial pressure of carbon dioxide in arterial blood ($PaCO_2$). Together, these abnormalities resulted in increased inspiratory muscle effort, which in some patients was probably close to the threshold of muscle fatigue.

The issue of fatigue was recently revisited by Laghi and Tobin.[8] They studied 19 intubated patients during weaning from mechanical ventilation; 11 patients failed, and 8 succeeded. Several physiologic indices were measured before

and 30 minutes after a spontaneous breathing trial. Before the trial, the transdiaphragmatic twitch pressure, elicited by magnetic bilateral phrenic stimulation, did not differ between those who failed and those who succeeded, and it did not decrease after the trial in either group. A fall in transdiaphragmatic twitch pressure is a physiologic index of low-frequency fatigue. Patients who failed the spontaneous breathing trial were reconnected to the ventilator because of clinical signs of intolerance. In this study, the ratio of swings in gastric pressure to swings in pleural pressure (an index of rib cage and expiratory muscle contribution to tidal breathing) was significantly higher in the failure group over the course of the trial. These alterations, together with the reinstitution of mechanical ventilation, might defend against the development of low-frequency fatigue. It was concluded that weaning failure was not accompanied by low-frequency diaphragmatic fatigue, although patients who failed to wean exhibited severe diaphragmatic weakness, because twitch pressures were always low.

Disorders That Alter the Balance of Capacity and Load

Reduced Neuromuscular Capacity

Reduced output of the respiratory control centers may occur after the administration of sedatives, narcotics, and anesthetic agents. Central nervous system and brainstem disorders are frequently accompanied by altered levels of consciousness. These disorders are often associated with attenuated cough and upper airway protection reflexes and depressed respiratory drive, all of which can contribute to difficult weaning and, eventually, unsuccessful extubation.

Phrenic nerve dysfunction can occur after traumatic injuries (e.g., high cervical spine lesions) and is also common after cardiac surgery.[9] Diaphragmatic dysfunction may occur after upper abdominal surgery.[10] Critical illness polyneuropathy and myopathy, which are frequent complications of sepsis and multiple organ system failure,[11,12] may impede weaning as well. Finally, neuromuscular blocking agents (with or without concomitant corticosteroids) and aminoglycosides may contribute to weaning failure.[13-17]

Intravenous corticosteroids and prolonged use of neuromuscular blockade have been implicated in ICU-acquired myopathy.[18] In a study of acute asthma requiring mechanical ventilation, Behbehani and colleagues found that the incidence of myopathy was 10.4% among all patients and 30% among patients who received neuromuscular blocking agents.[19] These authors found that the duration of muscle relaxation was the only independent predictor of the development of myopathy. In addition, malnutrition, deconditioning due to prolonged bed rest or mechanical ventilation, and increased muscle catabolism can induce severe muscle dysfunction.

In a multicenter study by De Jonghe and coworkers, a high incidence of ICU-acquired paresis was found in patients without preexisting neuromuscular disorders who had received mechanical ventilation for at least 7 days.[12] In this group of 95 patients, 25% were diagnosed with acquired paresis. The duration of mechanical ventilation after discontinuation of neuromuscular blockade was significantly longer in patients who had paresis compared with those who did not (18.2 versus 7.6 days; $P = 0.03$). In this investigation, the independent predictors of ICU-acquired paresis were female sex, number of days with dysfunction of two or more organs, duration of mechanical ventilation requiring neuromuscular blockade, and administration of corticosteroids. Although the incidence of paresis was elevated, the mortality rate of these patients (4 of 24, 7%) did not significantly differ from the mortality observed in the control group (4 of 71, 6%).

Increased Muscle Load

Increased work of breathing results from increased mechanical loads (elastic, resistive, or both) or from processes that require higher minute ventilation. Increased ventilatory requirements are quite common in critically ill patients, particularly during periods of hyperthermia, overfeeding, and hyperventilation (related to anxiety or pain). An increase in the deadspace–tidal volume ratio is another source of increased ventilatory requirements.

Increased elastic workloads occur when lung or chest wall compliance is reduced (e.g., pulmonary edema, extreme hyperinflation during acute asthma attack, pulmonary fibrosis, abdominal distention, obesity, trauma, thoracic deformities). The presence of intrinsic PEEP is another example of increased elastic workload and is a relatively common phenomenon, especially in patients with COPD. Dynamic pulmonary hyperinflation, apart from generating an elastic threshold load, places the diaphragm in a mechanically disadvantageous position. If lung volume is increased above passive functional residual capacity, the diaphragm flattens and its radius of curvature increases. Consequently, the capacity to generate pressure decreases.

Resistive work of breathing during critical illness may increase because of bronchospasm, excessive secretions, endotracheal tube resistance (which increases with kinking and deposition of secretions), and ventilator valves, circuits, and humidifiers, especially when inspired gases are conditioned with heat and moisture exchangers. The latter also increase deadspace.

CARDIOVASCULAR DYSFUNCTION

The presence of cardiovascular dysfunction can contribute to weaning failure by augmenting loads and reducing neuromuscular capacity. A study by Epstein showed that as many as 33% of weaning failures resulted solely or partly from congestive heart failure,[20] whereas only 14% failed due to cardiovascular reasons in other studies.[21] Cardiovascular dysfunction may result from physiologic changes that occur during the resumption of spontaneous unassisted breathing.[22] When spontaneous breathing resumes, intrathoracic pressure swings during inspiration are negative, which increases left ventricular preload and afterload. Cardiac loading is thus expected to be most marked in patients with large mechanical respiratory muscle loads (e.g., those with severe obstructive or restrictive respiratory diseases), who require relatively large negative pleural pressure swings to inspire. A significant decrease in left ventricular ejection fraction has been described during spontaneous breathing trials in COPD patients without coronary artery disease.[23]

Increased myocardial loading may be sufficient, especially when coupled with left ventricular noncompliance, to precipitate congestive heart failure (which stiffens the lungs and further increases loads). Moreover, increased heart loads augment myocardial oxygen demand and may precipitate myocardial ischemia in patients with coronary artery disease.[24] Myocardial ischemia causes left ventricular dysfunction, which may induce overt acute pulmonary edema and arterial hypoxemia.

Jubran and colleagues examined hemodynamics and mixed venous saturation in patients during weaning trials.[25] Successfully weaned patients demonstrated increases in cardiac index and oxygen transport compared with values during mechanical ventilation. Patients who failed weaning also failed to increase oxygen delivery to the tissues, due in part to elevated right and left ventricular afterloads. Consequently, these abnormalities can jeopardize respiratory muscle function.

MECHANISMS OF EXTUBATION FAILURE

Extubation failure refers to patients who, once extubated, require the reinstitution of ventilatory assistance within 24 to 48 hours. Thus, the extubation failure rate is the number of patients requiring reinstitution of mechanical ventilation divided by the total number of extubated patients. Extubation is performed after the decision to disconnect the patient from mechanical ventilation has been made and after the patient has tolerated a spontaneous breathing trial. The duration of a spontaneous breathing trial is variable, usually 30 to 120 minutes. Patients are subsequently extubated if, during this period of spontaneous breathing, they do not exhibit signs or symptoms of poor clinical tolerance and also show that they are able to cough adequately.[26]

The re-intubation rate may differ according to the cause of respiratory failure. For instance, in a large study including 217 medical and surgical patients, Vallverdú and associates noted that the overall re-intubation rate was 15.5%, ranging from 35.7% (15 of 42) in neurologic patients to 0% (0 of 13) in COPD patients.[27] The re-intubation rate in patients who had acute respiratory failure due to other causes was 8.6% (8 of 93). Data from Esteban and coworkers indicate that good clinical tolerance of a 2-hour trial with low pressure support levels (7 cm H_2O) is as good at predicting extubation success as the classic 2-hour T-piece trial.[28] With this strategy, the re-intubation rate was 18.8% with T-piece and 18.5% with pressure support ventilation (PSV).[28] A study by the same group found that a trial of spontaneous breathing (T-piece) with a target duration of 30 minutes was as effective in identifying patients who could be safely extubated as a trial with a target duration of 120 minutes.[29] In this study, the 48-hour re-intubation rates were also similar (13.5% in the 30-minute group, and 13.4% in the 120-minute group).

Mechanisms explaining extubation failure include physiologic abnormalities not diagnosed at the time of extubation (e.g., pneumonia, ongoing cardiac failure) and an inability to keep the tracheobronchial tree free of copious secretions.[26,27] Finally, intubation can result in laryngotracheal injury, which may explain some episodes of extubation failure; this tends to occur more frequently with a longer duration of intubation and in females.[30]

The majority of investigations indicate that failed extubation is associated with increased hospital mortality.[27-29,31,32] Extubation failure also results in a marked increase in the duration of mechanical ventilation, length of ICU and hospital stay, and need for tracheostomy.[28,29,33] The cause of extubation failure also influences outcome, with mortality being lower for airway problems (upper airway obstruction, aspiration, excess pulmonary secretions) and higher when re-intubation is required for other reasons.[28,29,33,34] Patients requiring re-intubation because of respiratory failure had a mortality rate of 30%, whereas mortality in patients needing re-intubation because of upper airway obstruction was only 7%.[33] In a study by Epstein and Ciubotaru, mortality was lowest for those re-intubated within 12 hours; it increased as the time between extubation and resumption of ventilatory support increased.[33] After controlling for severity of illness, presence of comorbid conditions, organ failure, and cause of re-intubation, time to re-intubation was found to be an independent predictor of outcome. These data suggest that extubation failure is probably a marker of underlying disease severity.

INDICES TO PREDICT WEANING OUTCOME

Many indices have been proposed in an attempt to predict weaning outcome. There are those that assess simple ventilatory parameters, assess oxygenation, assess respiratory muscle strength, assess central respiratory drive, measure respiratory muscle reserve, assess work of breathing, integrate different variables of respiratory function (composite indices), and analyze the pattern of spontaneous breathing in terms of tidal volume (V_T) and respiratory rate (f). In general, except for the f/V_T ratio, these indices have relatively poor positive and negative predictive value. In addition, the performance of these indices is affected by a number of factors. For example, the duration of ventilatory support before weaning is attempted varies widely, and these indices tend to have better predictive capabilities if the duration of mechanical ventilation is short. The time at which the patients are studied is also important, because weaning outcome is likely to be influenced by the different clinician practices from unit to unit (including the use of sedatives, analgesics, and neuromuscular blocking agents). Last, differences in patient populations involving age and disease processes can also strongly influence weaning outcome. Indeed, weaning outcome and respiratory parameters used as weaning predictors vary considerably, depending on the underlying disease.[27]

Yang and Tobin studied the predictive power of several weaning indices and showed that the rapid, shallow breathing index (f/V_T) had the best predictive value.[35] In their study, 95% of patients with f/V_T ratios greater than 105 failed a test of spontaneous breathing. Other studies, however, did not confirm these results. For instance, Epstein and Ciubotaru found that between 27% and 40% of patients with f/V_T ratios greater than 100 could be successfully extubated.[20,30] They also showed that women, especially when breathing through small endotracheal tubes, have higher f/V_T ratios than men.

Vallverdú and associates studied 217 patients receiving mechanical ventilation (33 COPD, 46 neurologic, and 138 acute respiratory failure) who met standard weaning criteria and had undergone a 2-hour T-piece weaning trial.[27] Before starting the T-piece trial, functional respiratory parameters were measured. If the spontaneous breathing trial was clinically well tolerated, the patients were extubated. If clinical tolerance of the T-piece trial was poor, patients were reconnected to ventilatory support. Ventilatory support was resumed because of intolerance in 60.6% of COPD patients. In these patients, the best predictive indices of extubation success were f/V_T and airway occlusion pressure.

For routine care, simple clinical weaning parameters (e.g., the rapid, shallow breathing index) appear to be most useful at the bedside. However, one has to consider that some patients with negative weaning parameters can tolerate disconnection from the ventilator. From a practical standpoint, the information conveyed by weaning indices and

clinical judgment needs to be combined in clinical decision-making.

INDICES TO PREDICT EXTUBATION OUTCOME

In contrast to the discontinuation of mechanical ventilation, indices that reliably predict extubation outcome have not been developed. In two large trials including more than 1000 patients, physiologic parameters such as respiratory rate, heart rate, and systolic blood pressure rapidly deteriorated, usually within the first 15 minutes of spontaneous breathing, in patients who failed the weaning trial.[2,28] However, none of these measurements could discriminate between patients who required re-intubation and those who tolerated extubation.

The frequency of re-intubation and its adverse impact on survival indicate that the accurate prediction of extubation outcome is important. The majority of clinicians assess patient readiness for both weaning and extubation by conducting a spontaneous breathing trial of variable duration. The importance of performing such a trial before deciding to extubate was proved by Zeggwagh and colleagues.[36] These authors proceeded directly to extubation (without performing a spontaneous breathing trial) after medical ICU patients had demonstrated clinical improvement. Of the 119 cases of extubation, 44 (37%) resulted in re-intubation. This rate is much higher than that reported for patients who are extubated after passing a spontaneous breathing test.

Patients incapable of protecting the airway and clearing secretions with an effective cough are at increased risk for extubation failure. Traditional assessment consists of demonstrating the presence of a cough reflex when stimulated with a suction catheter and the absence of excessive secretions, but these criteria have not been standardized. In intubated, mechanically ventilated subjects, a "sawtooth" pattern on the flow-volume curve indicates the presence of excess airway secretions but does not provide quantitative information.[37]

Although tolerance of a spontaneous breathing trial is a good predictor of successful extubation, Vallverdú and associates noted that a high percentage (35.7%) of neurologic patients who passed a 2-hour spontaneous breathing test and were extubated needed subsequent re-intubation.[27] Coplin and coworkers studied the variability in extubating brain-injured patients.[38] Their data provided no justification for delaying extubation in patients whose only indication for prolonged intubation is a depressed level of consciousness. They found that timely extubation of patients who met standard weaning criteria appeared to be safe (no increased risk of re-intubation or subsequent tracheotomy), potentially beneficial (associated with a lower incidence of pneumonia), and less expensive (shorter ICU stay and lower hospital costs). In this study, the re-intubation rate was 18% (24 of 136 patients). Re-intubation for airway or pulmonary dysfunction was not related to extubation delay or to coma at the time of extubation. Only two components of a semiquantitative assessment of the need for airway care were associated with successful extubation: spontaneous cough ($P = 0.01$) and suctioning frequency ($P = 0.001$).

Namen and colleagues evaluated a respiratory-driven weaning protocol (daily screens and spontaneous breathing trial) in 100 neurosurgical patients.[39] Because of concerns about neurologic impairment, the implementation of this classic protocol was limited, and no differences were observed between intervention and control groups. The re-intubation rate was 16%, and multivariate analysis showed that a favorable Glasgow Coma Scale score and PaO_2/FIO_2 ratio were associated with extubation success.

Recently, Smina and coworkers studied a group of 95 patients admitted to a medical ICU who passed a spontaneous breathing test and were ready to be extubated.[40] They hypothesized that the strength of a patient's cough, measured by peak expiratory flow, and the volume of suctioned endotracheal secretions per hour could predict extubation outcome. They found that patients with peak expiratory flows of 60 L/min or lower were five times as likely to have an unsuccessful extubation. In addition, patients with neurologic problems were more likely to have a failed extubation than were those without neurologic problems (risk ratio, 2.7; 95% confidence interval, 1.0 to 7.3). These data emphasize that patients who are incapable of protecting the airways and clearing secretions are at increased risk for unsuccessful extubation.

In an attempt to avoid re-intubation after failed extubation, Keenan and coworkers undertook a randomized, controlled trial in 81 patients.[41] One group ($n = 42$) was allocated to receive standard treatment alone, and the other group ($n = 39$) received the same plus noninvasive ventilation via facemask. The re-intubation rates (69% versus 72%), ICU mortality rates (24% versus 15%), and hospital mortality rates (31% for both groups) were not significantly different. According to these data, noninvasive ventilation is not recommended in patients who require mechanical ventilation for more than 48 hours and who develop respiratory distress within 48 hours after planned extubation. Whether noninvasive ventilation might be useful to avoid re-intubation in certain subgroups of patients is not known.

There is little agreement on what constitutes an acceptable extubation failure rate. Centers reporting very low rates may be keeping patients on mechanical ventilation longer than necessary. In contrast, high failure rates may indicate insufficient assessment before extubation. At present, good clinical tolerance of a spontaneous breathing trial seems to be the best predictor of extubation success.

PROGRESSIVE WITHDRAWAL OF MECHANICAL VENTILATION

Weaning from mechanical ventilation represents the period of transition from total ventilatory support to spontaneous breathing. The most common techniques used to withdraw mechanical ventilation in patients who failed an initial weaning trial are PSV and breathing through a T-piece. Two prospective, multicenter, randomized clinical trials showed that synchronized intermittent mandatory ventilation (SIMV) is less efficacious than the other techniques.[1,2]

ROLE OF PROTOCOLS

A fundamental advance in recent years is the observation that routine screening of patients' ability to breathe spontaneously is the best approach to speeding extubation.[42,43] Saura and colleagues showed that implementation of a weaning protocol based on daily screening of simple clinical weaning parameters dramatically shortened weaning time.[42]

This was attributable mostly to the sharp fall in the number of patients undergoing progressive reduction in ventilatory support because they could be extubated sooner. With this approach, the incidence of re-intubation remained stable (between 14% and 17%), but the length of mechanical ventilation was shortened by an average of 4 days. These data were confirmed by the subsequent randomized, controlled trials of Ely[43] and Kollef[44] and their associates. Both trials focused on monitoring patients' ability to sustain spontaneous breathing. This approach was associated with faster extubation and shorter ICU stay, without increasing the re-intubation rate.

The use of sedative drugs, often administered via continuous intravenous infusion, is common in intubated, mechanically ventilated patients. An important study revealed that regular interruption of these drugs can significantly reduce the duration of mechanical ventilation.[45] Patients randomly allocated to daily interruption were ventilated for a median of 4.9 days, whereas patients treated with the usual approach (interruption of sedatives at the discretion of the clinician) were ventilated for a median of 7.3 days ($P = 0.004$). Moreover, the daily discontinuation strategy allowed for a better assessment of neurologic status, required less diagnostic testing, and was not associated with more complications compared with the usual strategy.

The major impact of protocols to hasten the weaning process was pointed out in a recent study of difficult-to-wean COPD patients requiring invasive mechanical ventilation for more than 15 days.[46] This multicenter study enrolled 26 patients who were weaned with PSV and 26 who were weaned with intermittent spontaneous breathing trials. Weaning success rates (73% versus 77%), duration of ventilatory assistance (180 versus 130 days), and mortality rates (11.5% versus 7.6%) did not differ significantly between the groups. However, when the data obtained in the randomized patients was compared with that from historical controls, it was observed that the weaning success rate was significantly greater (87% versus 70%), and the time spent on mechanical ventilation in surviving weaned patients was significantly shorter (103 versus 170 hours), in protocol patients than in historical controls.

PRESSURE SUPPORT VENTILATION

PSV is a patient-triggered, pressure-limited, flow-cycled mode in which airway pressure is maintained at near constant levels during inspiration. When inspiratory flow reaches a certain threshold level, cycling from inspiration to expiration occurs. This method of ventilatory assistance allows the patient to retain control over respiratory rate and timing, inspiratory flow rate, and tidal volume. During weaning, PSV levels are decreased according to the patient's clinical tolerance, usually by steps of 2 to 4 cm H_2O at least twice a day. In general, adequate clinical tolerance of a PSV level of around 8 cm H_2O is required before extubation is performed, although this level may vary according to individual patient characteristics.

The pressure level, which should be adjusted to begin weaning, is usually determined by letting the patient breathe in a "comfortable" way. However, both previous clinical experience[1,2] and data from clinical research[47,48] suggest that optimal initial levels are those that provide respiratory rates between 25 and 30 breaths per minute. The level of external PEEP to be used in patients with clinically suspected dynamic hyperinflation and dynamic airway collapse should be adjusted with great caution, because measurement of dynamic intrinsic PEEP in spontaneously breathing patients is not easy. To that end, it has been suggested that external PEEP can be titrated according to changes in airway occlusion pressure.[49]

SPONTANEOUS BREATHING WITH A T-TUBE

The T-tube system offers very little resistance to gas flow. No additional work of breathing is imposed, because neither ventilator valves nor circuits are involved. Tolerance of the T-tube is a good way to evaluate a patient's capacity to maintain autonomous spontaneous breathing.[50,51] The optimal duration of the test is at least 30 minutes but no more than 120 minutes.

The main disadvantage of the T-piece trial is related to the lack of a connection to a mechanical ventilator; the patient is not monitored and therefore must be closely supervised, which places great demands on the nursing staff. Additionally, the transition between periods of muscular rest and periods of spontaneous unassisted breathing can be too abrupt for some patients, especially those who have panic reactions after disconnecting from the ventilator and those with latent left ventricular failure and myocardial ischemia.

NONINVASIVE VENTILATION

In Nava and coworkers' prospective randomized trial, patients with COPD who failed an initial spontaneous breathing trial and were extubated to noninvasive PSV were liberated from the ventilator more quickly (10.2 versus 16.6 days), spent less time in the ICU (15.1 versus 24 days), and were more likely to survive (92% versus 72%) than were patients weaned with PSV via endotracheal tube.[52] At 60 days, 88% of patients ventilated noninvasively were successfully weaned, compared with 68% of patients ventilated invasively.

Girault and colleagues prospectively studied 33 COPD patients who failed a 2-hour T-piece trial.[53] Sixteen patients were randomly assigned to conventional invasive PSV weaning, and 17 were randomly assigned to noninvasive PSV weaning immediately after extubation. Although weaning with noninvasive PSV significantly reduced the total duration of invasive mechanical ventilation and the probability of remaining intubated and mechanically ventilated, the total duration of ventilatory support related to weaning was greater in the noninvasive PSV group. The length of ICU and hospital stay and the mortality rate at 3 months were similar in both groups. The contrast between these findings and those in Nava's study may be due to differences in disease severity, selection of patients with regard to timing of extubation, PSV settings, and amount of experience in delivering PSV.

The usefulness of noninvasive ventilation to facilitate early extubation was reanalyzed in a recent randomized multicenter trial.[54] This study was conducted in 43 mechanically ventilated patients with persistent weaning failure. One group of patients ($n = 21$) was extubated and received noninvasive ventilation with pressure support and a full facemask. The other group ($n = 22$) remained intubated and followed a traditional weaning strategy with daily spontaneous breathing trials. The main results of this investigation were a shorter period of invasive ventilation, shorter ICU and hospital length of stay, and increased ICU and 90-day

survival in patients extubated early and treated with noninvasive ventilation, compared with the control group. This study, performed in a nonselected population of ICU patients who met weaning criteria, suggests that early use of noninvasive ventilation may be effective in skilled hands. Another interpretation, however, is that the criteria used to determine failure of a spontaneous breathing trial were too strict and physicians were overzealous in interpreting clinical intolerance (or that some type of bias existed due to the unblinded nature of the study), and that these patients were kept on invasive mechanical ventilation for an unduly prolonged period.

NEW MODALITIES

Intubated and mechanically ventilated patients have varying ventilatory needs and exhibit changes in respiratory mechanics and breathing pattern. These occur during the weaning period as well. Consequently, fixed levels of ventilatory assistance (provided with either volume- or pressure-limited breaths) may be inappropriate when mechanics or demand changes. For this reason, manufacturers have developed new modes with the aim of improving tolerance of assisted ventilation, patient comfort, and patient-ventilator synchrony and avoiding excessive respiratory effort. Some of these modes are closed-loop systems, whereby the ventilator takes into account current physiologic information about the patient (e.g., respiratory rate, end-tidal PCO_2, tidal volume) and adapts its output according to predefined targets.

A number of these systems have been tested extensively, particularly those implementing closed-loop PSV,[55,56] and have the potential to reduce the total duration of mechanical ventilation by continuously adapting the ventilator's assistance to the patient's needs. Such permanent control and adaptation are not feasible even in the best current clinical environment, simply because of the lack of time and sufficient caregivers to undertake these tasks. Whether such systems may further decrease the duration of mechanical ventilation compared with traditional protocols is not known. That question will soon be answered, however, when the results of ongoing clinical trials are known.

UNPLANNED EXTUBATION DURING WEANING

Unexpected removal of the endotracheal tube (unplanned extubation) may be deliberate, as a result of patient agitation or lack of cooperation, or accidental, due to rupture of the endotracheal cuff, nursing procedures, coughing, or other unintentional events. Unplanned extubation is estimated to occur in 8.5% to 13% of intubated, mechanically ventilated patients.[57-63]

In a prospective study carried out during a 32-month period, 59 episodes of unplanned extubation were observed in 55 of 750 patients (frequency, 7.3 %) who required mechanical intubation for more than 48 hours.[61] The extubation was deliberate in 77.9% and accidental in 22.1% of cases. Twenty-seven episodes (45.8%) occurred in patients on full mechanical ventilatory support, and 32 episodes (54.2%) occurred during the weaning period. This parameter had not been studied previously, and it played an important role in determining the subsequent need for re-intubation. The results from this study indicate that the need for re-intubation after an episode of unplanned extubation is dependent on whether the patient is in the weaning phase of mechanical ventilation. Patients who had unplanned extubations during weaning required significantly fewer re-intubations than did those who were not in the weaning phase (odds ratio, 6.6). Only 15.6% of patients (5 of 32) who were being weaned from mechanical ventilation needed re-intubation, whereas re-intubation was necessary in 81.5% of patients (22 of 27) receiving full mechanical ventilatory support ($P < 0.001$). In view of these results, it is conceivable that the process of weaning may be longer than necessary in some patients. Indeed, in this study, at least 15% of the patients being weaned from mechanical ventilation could have been extubated earlier, because they did not require re-intubation.

Epstein and colleagues performed a case-control study involving 75 patients with unplanned extubations and 150 controls matched for Acute Physiology and Chronic Health Evaluation (APACHE II) score, presence of comorbid conditions, age, indication for mechanical ventilation, and gender.[62] They observed that unplanned extubation was not associated with increased mortality, although they noted an increase in total duration of mechanical ventilation, length of ICU and hospital stay, and need for chronic care in the unplanned extubation group. A comparison of mortality between the group that needed re-intubation and the group that did not revealed a higher mortality rate in the former. Finally, these authors reported significant differences regarding re-intubation rates between patients who had an unplanned extubation during weaning trials and those who had one during full ventilatory support (44% in the former; 76% in the latter).

These studies suggest that the incidence of unplanned extubation can be used as an indicator of the quality of nursing and medical care in the ICU. In addition, a high incidence of unplanned extubation and a low incidence of re-intubation in these patients indicate that invasive ventilatory support is being provided for longer than necessary.

SUMMARY

Major advances have been made in the area of weaning from mechanical ventilation. The pathophysiologic mechanisms of weaning failure and extubation failure are better understood. It has been recognized that the vast majority of intubated, mechanically ventilated patients can be successfully liberated from the ventilator after passing a short spontaneous breathing test. Moreover, the best strategy to shorten the total time on mechanical ventilation is based on a simple protocol and a daily clinical approach that determines a patient's ability to sustain spontaneous unassisted breathing. When spontaneous breathing trials fail, techniques for progressive withdrawal of mechanical ventilation (PSV and volume-assisted mechanical ventilation with daily spontaneous breathing trials) seem to be equivalent. This is true as long as the use of these techniques is based on the same criteria used to evaluate tolerance. In the future, new semiautomated ventilatory modalities may be beneficial in difficult-to-wean patients. Noninvasive ventilation may be helpful to hasten weaning in selected populations and when used appropriately. Despite a better understanding of the mechanisms of extubation failure, it still occurs and is associated with increased mortality. Current data show that the employment of noninvasive ventilation in cases of impending extubation failure does not avoid re-intubation any better than a conventional approach does.

ANNOTATED REFERENCES

Brochard L, Rauss A, Benito S, et al: Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med 1994;150:896-903.

This was the first randomized trial comparing three different methods of weaning. The authors concluded that the outcome of weaning is influenced by the modality chosen. The weaning duration was shorter with PSV than with SIMV or T-piece used together.

Ely EW, Baker AM, Dunagan DP, et al: Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med 1996;335:1864-1869.

This randomized, controlled trial demonstrated that daily screening for the ability to sustain spontaneous breathing, followed by a T-piece trial, reduces the duration of mechanical ventilation and ICU costs without increasing the number of complications.

Esteban A, Frutos F, Tobin MJ, et al: A comparison of four methods of weaning patients from mechanical ventilation. N Engl J Med 1995;332: 345-350.

In this randomized, multicenter study comparing four different methods of weaning, the authors found that weaning with a once-daily spontaneous breathing trial was twice as fast as with PSV and three times faster than SIMV. Multiple trials of spontaneous breathing did not reduce the time of weaning compared with a once-a-day trial.

Jubran A, Tobin MJ: Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. Am J Respir Crit Care Med 1997;155:906-915.

This physiologic study determined the mechanisms of acute respiratory distress. COPD patients who failed a spontaneous breathing trial developed rapid, shallow breathing and worsening of pulmonary mechanics, which caused an increase in $PaCO_2$.

Kress J, Pohlman A, O'Connor M, et al: Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342:1471-1477.

This randomized, controlled trial demonstrated that a daily interruption of sedative drugs in intubated and mechanically ventilated patients reduces the duration of mechanical ventilation and length of stay in the ICU.

Chapter 68

NONINVASIVE POSITIVE-PRESSURE VENTILATION

Thomas Rajan • Nicholas S. Hill

KEY POINTS

1. The use of noninvasive positive-pressure ventilation in patients with acute respiratory failure is a recent phenomenon, mainly because of **advances in noninvasive interfaces and ventilator modes**.
2. **Noninvasive positive-pressure ventilation delivered by nasal or oronasal mask** reduces the need for endotracheal intubation, decreases the length of stay in the ICU and hospital, and reduces mortality when used in selected patients with exacerbations of chronic obstructive pulmonary disease (COPD).
3. **The efficacy of noninvasive positive-pressure ventilation has been demonstrated** for acute pulmonary edema, for respiratory failure in immunocompromised patients, and to facilitate extubation in COPD patients.
4. **Patients who develop respiratory failure or who refuse intubation** are potentially good candidates for noninvasive positive-pressure ventilation, but all patients must be selected carefully.
5. **Several factors are vital to the success of noninvasive positive-pressure ventilation:** careful patient selection; properly timed initiation; comfortable, well-fitting interface; coaching and encouragement; and careful monitoring.
6. **Noninvasive ventilation should be used to avert endotracheal intubation rather than as an alternative to it.** One should not persist in the use of noninvasive positive-pressure ventilation if it will lead to a delay in necessary intubation.
7. **A trial of noninvasive ventilation should be instituted in properly selected patients with acute respiratory failure** before respiratory arrest is imminent, to provide ventilatory assistance while the factors responsible for the respiratory failure are aggressively treated.
8. Noninvasive ventilation is an important addition to the methods available to assist patients with acute respiratory failure and, **if properly applied, improves patient outcome in the critical care setting**.

Noninvasive ventilation is defined as the provision of ventilatory assistance to the lungs without an invasive artificial airway. Noninvasive ventilators consist of a variety of devices, including negative- and positive-pressure ventilators. Until the early 1960s, negative-pressure ventilation in the form of tank ventilators was the most common type of mechanical ventilation outside the anesthesia suite.[1] However, during the Copenhagen polio epidemic of 1952, it was observed that the survival rate improved when patients with respiratory paralysis were treated with invasive positive-pressure anesthesia devices. After that, invasive positive-pressure mechanical ventilation gradually became the preferred means of treating acute respiratory failure.[2] Negative-pressure and other so-called body ventilators were the mainstay of ventilatory support for patients with chronic respiratory failure until the mid-1980s.[1]

With the introduction of nasal continuous positive airway pressure (CPAP) to treat obstructive sleep apnea in the early 1980s,[3] and the discovery that nasal masks were a convenient conduit to assist ventilation,[1] noninvasive positive-pressure ventilation rapidly displaced negative-pressure ventilation as the treatment of choice for chronic respiratory failure in patients with neuromuscular and chest wall deformities. Over the past dozen years, noninvasive ventilation has moved from the outpatient to the inpatient setting, where it is used to treat acute respiratory failure. A 1997 survey of medical ICUs in France, Switzerland, and Spain demonstrated that noninvasive ventilation was used in 16% of cases in which mechanical ventilation was required for respiratory failure,[4] and a follow-up survey found that this rate was up to 23% in 2001.[5] This chapter discusses the rationale for the increasing use of noninvasive positive-pressure ventilation in critical care, as well as appropriate indications, practical applications, and monitoring.

RATIONALE

The most important advantage of noninvasive ventilation is the avoidance of complications associated with invasive mechanical ventilation. These include complications related to direct upper airway trauma, bypass of the upper airway defense mechanisms, increased risk of nosocomial pneumonia, and interference with upper airway functions, including the ability to eat and communicate normally.[6] By averting airway intubation, noninvasive ventilation leaves the upper airway intact, preserves airway defenses, and allows patients to eat orally, vocalize normally, and expectorate secretions. Compared with invasive mechanical ventilation, noninvasive ventilation reduces infectious complications, including pneumonia, sinusitis, and sepsis.[7-9] Strengthening the rationale for its use is evidence accumulated over the past decade that noninvasive ventilation lowers morbidity and mortality rates of selected patients with acute respiratory failure and may shorten hospital length of stay, thus reducing costs.

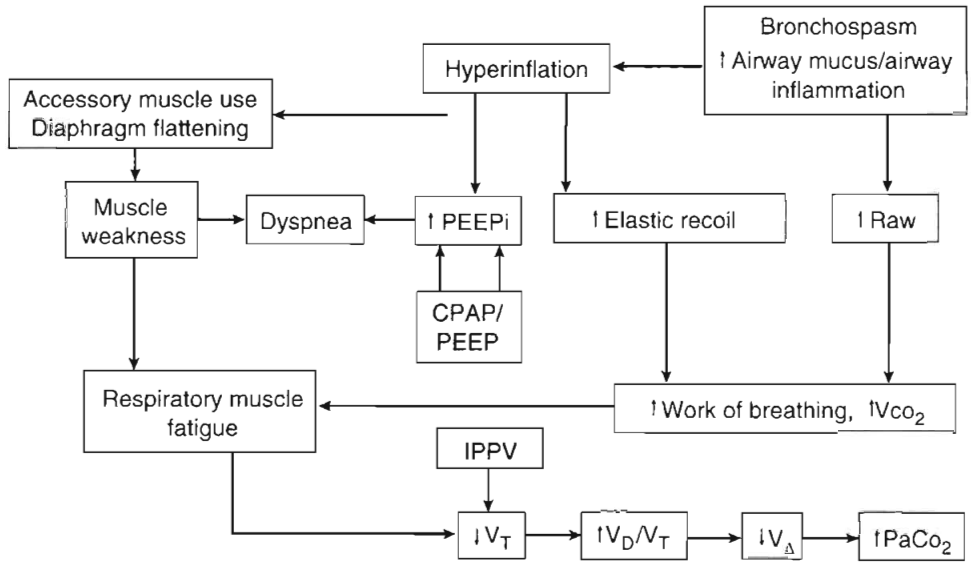

FIGURE 68–1. The pathophysiology of acute hypoxemic respiratory failure, and the points where positive-pressure and oxygen supplementation interrupt the process. Low ventilation-perfusion (V/Q) ratios, shunt, and alveolar hypoventilation cause hypoxemia. Hypoxemia is treated by increasing the inspired oxygen fraction (F_{IO_2}) (limited benefit with shunt) and by applying positive pressure (continuous positive airway pressure [CPAP] or positive end-expiratory pressure [PEEP]) to increase functional residual capacity, open collapsed alveoli and narrowed airways, and enhance compliance. An additional beneficial effect of CPAP may occur in patients with cardiogenic pulmonary edema, because it reduces both venous return and left ventricular (LV) afterload, which may enhance cardiovascular performance in patients with dilated, hypocontractile left ventricles.

The main indication for mechanical ventilatory assistance is to treat respiratory failure, either type 1 (hypoxemic), type 2 (hypercapnic), or both. Figure 68-1 shows that airspace collapse, surfactant abnormalities, and airway narrowing and closure contribute to ventilation-perfusion abnormalities and shunt, which cause hypoxemia. By opening collapsed airspaces and narrowed airways, positive airway pressure reduces shunt and improves ventilation-perfusion relationships, ameliorating hypoxemia. In addition, positive airway pressure can reduce the work of breathing by improving lung compliance as a consequence of opening collapsed airspaces. Another potential benefit of positive airway pressure is enhanced cardiovascular function via the afterload-reducing effect of increased intrathoracic pressure. Conversely, deleterious cardiovascular effects may occur if the preload-reducing effect outweighs the afterload-reducing effect, as may be seen in patients with reduced intravascular fluid volume.

MECHANISMS OF ACTION

Figure 68-2 shows the pathophysiologic mechanisms that contribute to ventilatory failure. Increased airway resistance, reduced respiratory system compliance, and intrinsic positive end-expiratory pressure (PEEP) contribute to increased work of breathing, predisposing to respiratory muscle fatigue. In patients with chronic obstructive pulmonary disease (COPD), the increased radius of the diaphragmatic curvature, which increases muscle tension and thereby increases impedance to blood flow, exacerbates the situation. By counterbalancing intrinsic PEEP with extrinsic PEEP, and by augmenting tidal volume with intermittent positive-pressure ventilation, noninvasive ventilation reduces the work of breathing and averts the vicious circle leading to respiratory failure. Work of breathing measurements, including transdiaphragmatic pressure, diaphragmatic pressure-time product, and diaphragmatic electromyographic amplitude, are all decreased when noninvasive ventilation is delivered to patients with exacerbations of COPD. In such patients, CPAP and pressure support ventilation (PSV) both reduce the work of breathing, but the combination of the two (PSV + PEEP) is more effective than either alone.[10]

INDICATIONS

A number of causes of acute respiratory failure are now considered appropriate for noninvasive ventilation therapy and are listed in Table 68-1. The evidence supporting these indications is rated in the table and briefly discussed here; guidelines for patient selection are discussed later.

AIRWAY OBSTRUCTION

Chronic Obstructive Pulmonary Disease

Starting in 1990, a historically controlled study,[11] a number of subsequent randomized, controlled trials,[12,13] and a meta-analysis[14] have consistently shown that compared with conventional therapy, noninvasive ventilation improves vital signs, gas exchange, and dyspnea scores; reduces the rates of intubation, morbidity, and mortality; and shortens hospital length of stay in patients with moderate to severe exacerbations of COPD. Thus, noninvasive ventilation is considered the ventilatory mode of choice in selected patients with acute exacerbations of COPD. Some studies suggest that the addition of heliox to noninvasive ventilation further improves the work of breathing and gas exchange during COPD exacerbations,[15] but a recent multicenter trial found no improvement in other outcomes compared with noninvasive ventilation alone.[16]

Asthma

Uncontrolled studies have reported improvements in gas exchange and low rates of intubation after the initiation of

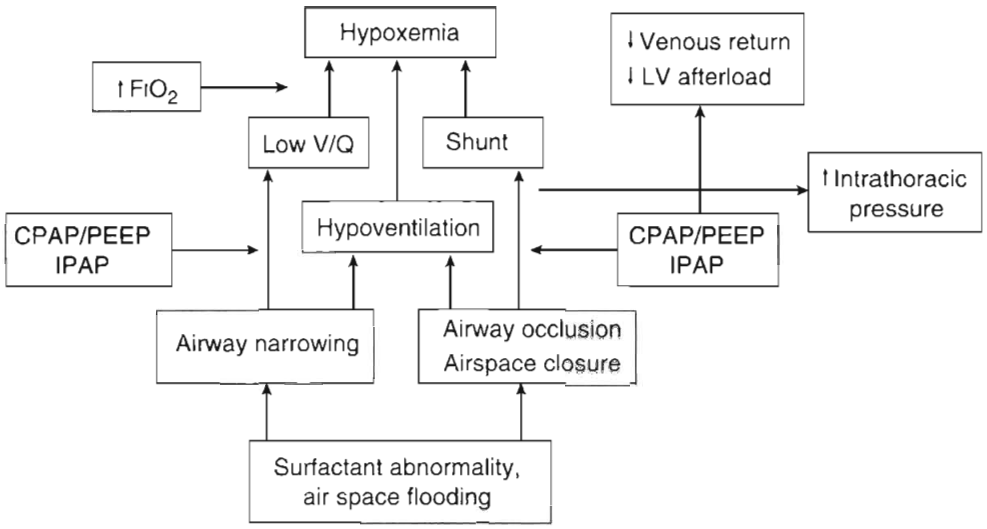

FIGURE 68–2. The pathophysiology of acute hypercapnia, and the points where continuous positive airway pressure (CPAP), positive end-expiratory pressure (PEEP), and pressure support (PS) interrupt the process *(large arrows)*. Hypercapnia (increased partial pressure of carbon dioxide in arterial blood [$PaCO_2$]) occurs when the respiratory muscles fail to adequately ventilate alveoli to maintain homeostasis with carbon dioxide production. Respiratory muscle failure occurs when the work of breathing is normal (e.g., acute or chronic neuromuscular disease) or increased (e.g., patients with chronic obstructive pulmonary disease, asthma, or the obesity hypoventilation syndrome), and presumably because of inadequate oxygen delivery to the respiratory muscles (e.g., approximately one third of patients presenting with cardiogenic pulmonary edema). Strategies to counter these pathophysiologic mechanisms include applying CPAP or PEEP to counterbalance intrinsic PEEP (PEEPi), increasing alveolar ventilation by augmenting tidal volume (V_T), using intermittent positive-pressure ventilation (IPPV), and reducing carbon dioxide production by decreasing the work of breathing.

noninvasive ventilation in patients with severe asthma attacks.[17] A recent controlled trial demonstrated a more rapid improvement in expiratory flow rates and a decreased hospitalization rate in acute asthma patients treated with noninvasive ventilation compared with a sham mask, but it is not clear that aerosolized bronchodilators were effectively delivered in the sham group.[18] Nonetheless, these data support a trial of noninvasive ventilation in asthmatics responding poorly to initial bronchodilator therapy. Noninvasive ventilation can be combined with continuous nebulization and heliox, although the added value of these latter therapies has not been established in controlled trials.

TABLE 68–1. INDICATIONS FOR THE USE OF NONINVASIVE VENTILATION IN THE ACUTE CARE SETTING

Airway Obstruction
COPD (A)*
Asthma (B)
Cystic fibrosis (C)
Obstructive sleep apnea or obesity hypoventilation (C)
Upper airway obstruction (C)
Facilitation of weaning in COPD (A)
Extubation failure in COPD (C)
Hypoxemic Respiratory Failure
ARDS (C)
Pneumonia (C)
Trauma or burns (C)
Acute pulmonary edema (use of CPAP) (A)
Immunocompromised patients (A)
Restrictive thoracic disorders (C)
Postoperative patients (B)
Do-not-intubate patients (C)
During bronchoscopy (C)

*Letters in parentheses indicate the level of evidence supporting the use of noninvasive ventilation: A, multiple randomized, controlled trials—recommended; B, at least one randomized, controlled trial—weaker recommendation; C, case series or reports—can be tried, but with close monitoring.
ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure.

Cystic Fibrosis

Uncontrolled studies indicate that noninvasive ventilation is useful to stabilize gas exchange in the treatment of acute episodes of respiratory failure in end-stage cystic fibrosis patients and can serve as a bridge to transplantation.[19]

Upper Airway Obstruction

Anecdotally, noninvasive ventilation can be used to treat patients with upper airway obstruction such as that caused by glottic edema following extubation. In this situation, noninvasive ventilation can be combined with aerosolized medications or heliox, but no controlled trials have demonstrated the efficacy of this approach. If therapy with noninvasive ventilation is considered, patients should be selected with great caution and monitored closely, because upper airway obstruction can lead to precipitous deterioration. The use of noninvasive ventilation in patients with tight, fixed upper airway obstruction is inappropriate, because it delays the institution of definitive therapy.

HYPOXEMIC RESPIRATORY FAILURE

Hypoxemic respiratory failure is defined as severe hypoxemia (arterial oxygen partial pressure–inspired oxygen fraction ratio <200), combined with a respiratory rate greater than 35 breaths per minute and a non-COPD diagnosis, including acute pneumonia, acute lung injury, acute respiratory distress syndrome (ARDS), pulmonary edema, or trauma.

Controlled trials of noninvasive ventilation to treat patients with acute hypoxemic respiratory failure have shown statistically significant reductions in the rate of intubation, length of hospital stay, and incidence of infectious complications, and a trend toward lower mortality.[6,20] However, because of the heterogeneity of causes, these studies fail to demonstrate that all patient subgroups with hypoxemic respiratory failure benefit equally from noninvasive ventilation. Further, when patients are stratified according to acuity of illness, patients with a simplified acute physiologic score (SAPS II) less than 35 fare considerably better with noninvasive ventilation than do those with higher scores.[21] Thus, the selection of patients with less severe disease is likely to enhance the success of noninvasive ventilation in treating hypoxemic respiratory failure, and studies that examine individual subgroups within the larger category are likely to be more useful clinically.

Pneumonia

One controlled trial showed that noninvasive ventilation in patients with severe community-acquired pneumonia lowers the rate of endotracheal intubation and shortens the length of ICU stay compared with conventional therapy; however, a subgroup analysis revealed that the benefits occurred only in patients with underlying COPD.[22] No benefit was apparent in the non-COPD patients with severe pneumonia. A subsequent uncontrolled trial in non-COPD patients with severe pneumonia found that two thirds of such patients treated with noninvasive ventilation eventually required intubation.[23] Although the latter authors deemed a trial of noninvasive ventilation in non-COPD patients with severe pneumonia to be a reasonable approach, controlled data to support such a recommendation are currently lacking.

Immunocompromised States

The dismal prognosis of invasively ventilated immunocompromised patients makes noninvasive ventilation an appealing ventilatory mode, with its demonstrated ability to decrease the rate of nosocomial infection.[7] In a study of 51 patients undergoing solid organ transplantation who developed acute hypoxemic respiratory failure within 3 weeks, noninvasive ventilation reduced the rate of intubation, frequency of invasive procedures, rate of nosocomial infection, duration of ICU stay, and ICU mortality (but not hospital mortality) compared with conventional therapy.[24] In a subsequent randomized trial of neutropenic patients with pulmonary infiltrates and acute hypoxemic respiratory failure (most of whom had hematologic malignancies), noninvasive ventilation lowered the intubation rate, occurrence of nosocomial infections, and ICU and hospital mortality rates (the latter from 80% to 46%).[25] More recently, noninvasive ventilation has been reported to yield similar benefits in acquired immunodeficiency syndrome (AIDS) patients with *Pneumocystis carinii* pneumonia versus invasive mechanical ventilation in physiologically and demographically matched patients.[26] Thus, whenever possible, noninvasive ventilation should be tried first in immunocompromised patients with hypoxemic respiratory failure because of the potential to avoid the high morbidity and mortality rates associated with invasive mechanical ventilation in these patients.

Acute Respiratory Distress Syndrome

A small retrospective study reported that noninvasive ventilation averted intubation in 50% of patients during the early phase of acute lung injury or ARDS.[27] However, for ARDS patients with severe oxygenation defects and multiple organ system dysfunction, invasive ventilation remains the preferred modality. Noninvasive ventilation may be considered in ARDS patients with relatively mild oxygenation defects (P/F >100), stable hemodynamics, and no other organ involvement, but such patients must be monitored closely to avoid any delay in intubation if deterioration occurs.

Acute Cardiogenic Pulmonary Edema

A meta-analysis of randomized, controlled trials demonstrated that compared with oxygen therapy, CPAP (though not a true mode of ventilatory support) is highly effective at relieving respiratory distress, improving gas exchange, and averting intubation when used to treat patients with acute cardiogenic edema.[28] Inspiratory assistance combined with expiratory pressure can reduce the work of breathing and alleviate respiratory distress more effectively than CPAP alone, and several uncontrolled trials and two controlled trials found that noninvasive ventilation and CPAP are equally effective in improving vital signs and avoiding intubation. One controlled trial demonstrated that noninvasive ventilation lowers arterial carbon dioxide partial pressure ($PaCO_2$) and respiratory rate and improves oxygenation more rapidly than CPAP alone, but the noninvasive ventilation group had an increased rate of myocardial infarction, leading to premature termination of the study.[29] This was a small study, and there were concerns about adequate randomization. A recent preliminary report by the same group using a different "bilevel" ventilator at lower pressures (inspiratory positive airway pressure, 12 cm H_2O; expiratory positive airway pressure, 4 cm H_2O) for delivering noninvasive ventilation showed more rapid improvement in oxygenation and no increased risk of myocardial infarction when compared with CPAP alone.[30] The current recommendation is to use CPAP alone or noninvasive ventilation as initial therapy; if CPAP is used initially, inspiratory pressure support should be added if the patient has persistent hypercapnea or dyspnea.[31]

Postoperative Respiratory Failure

Noninvasive ventilation has been studied in postoperative patients who develop respiratory failure after various kinds of surgery. It reduces extravascular lung water and improves lung mechanics and gas exchange after coronary artery bypass surgery.[32] Controlled trials showed that noninvasive ventilation improves oxygenation, reduces the need for re-intubation, and lowers the mortality rate after lung resectional surgery[33,34] and enhances pulmonary function after gastroplasty.[35] Thus, noninvasive ventilation should be used in selected postoperative patients with respiratory failure, especially in the setting of underlying COPD or pulmonary edema.

Trauma and Burns

Trauma patients develop respiratory failure for a multitude of reasons, but some have chest wall injuries such as flail chest or mild acute lung injury that might respond favorably to noninvasive ventilation. In a retrospective survey of 46 trauma patients with respiratory insufficiency that had been treated with noninvasive ventilation, Beltrame and coworkers found rapid improvements in gas exchange and a 72% success rate; however, patients with burns responded poorly.[36] Despite these promising results, the uncontrolled design of the study limits

the ability to draw conclusions or to make recommendations on the use of noninvasive ventilation in trauma patients.

Restrictive Lung Disease

The use of noninvasive ventilation in patients with underlying restrictive disease and acute deterioration of respiratory status has not been studied extensively because they constitute only a small portion of patients admitted to acute care hospitals. Patients with restriction related to an underlying neuromuscular disease and superimposed acute respiratory failure may benefit from a trial of noninvasive ventilation. Small case series have reported that using noninvasive ventilation in patients with myasthenic crises may avoid intubation.[37] In contrast, patients with end-stage pulmonary fibrosis in respiratory extremis have been reported to do poorly with mechanical ventilation.[38]

Do-Not-Intubate Patients

Although controversial, noninvasive ventilation may be a useful tool in patients with acute respiratory failure who do not wish to be intubated. There are several reports of good outcomes (>50% survival to discharge) with noninvasive ventilation in this subset of patients, especially those with COPD and congestive heart failure.[39] Noninvasive ventilation may also reduce dyspnea, preserve patient autonomy, and provide time for finalization of affairs for some terminal patients.[40] However, there is concern that this may merely prolong the dying process, and patients and their families must be informed that noninvasive ventilation is being used as a form of life support in this setting and should be given the option to refuse it.

Facilitation of Weaning and Extubation

Patients who require invasive mechanical ventilation initially and fail to wean promptly are potential candidates for noninvasive ventilation to facilitate extubation, thus reducing the complications related to prolonged intubation. Several randomized, controlled trials have demonstrated that noninvasive ventilation significantly shortens the duration of invasive mechanical ventilation, reduces the length of ICU stay, and improves survival compared with patients weaned in the routine fashion.[41-43] Another potential application of noninvasive ventilation in the weaning process is to avoid reintubation in patients with extubation failure, a complication of invasive mechanical ventilation associated with a high mortality rate. Earlier studies looking at the role of noninvasive ventilation in this situation showed promise, but more recent randomized studies failed to show improved outcomes.[44] One preliminary study even found that noninvasive ventilation may delay needed intubation in this setting, resulting in an increased mortality rate.[45] Thus, although the use of noninvasive ventilation to facilitate weaning and extubation appears to benefit patients with COPD, its overzealous application could lead to increased extubation failure rates and other adverse consequences.

Bronchoscopy

Both CPAP and noninvasive ventilation have been studied as ways of supporting oxygenation and ventilation during bronchoscopy. Using a specially designed open CPAP system during bronchoscopy in patients with marginal oxygenation, Maitre and colleagues observed maintenance of adequate gas exchange and avoidance of respiratory failure.[46] In a controlled trial, Antonelli and associates demonstrated equivalent oxygenation and complication rates in patients undergoing bronchoscopy and supported with either noninvasive or invasive mechanical ventilation.[47] Thus, noninvasive ventilation is an effective way of providing ventilatory support in patients undergoing bronchoscopy.[48]

PRACTICAL APPLICATION

PATIENT SELECTION

Noninvasive ventilation should be viewed as a "crutch" that assists patients through a period of acute respiratory failure while reversible factors are being treated, helping them avoid invasive mechanical ventilation and its attendant complications. To optimize the chance of success, noninvasive ventilation should be used early, when patients first develop signs of incipient respiratory failure. In addition, predictors of success are useful in identifying patients most likely to benefit (Table 68-2). The selection process might be viewed as taking advantage of a "window of opportunity": the window opens when the patient first needs ventilatory assistance and closes when the patient becomes too unstable.

Based on the predictors of success and criteria used in prior controlled trials, we recommend the following two-step selection process. The first step is to identify patients in need of ventilatory assistance by using clinical and blood gas criteria. Patients with mild respiratory distress and no more than mild gas exchange derangement are likely to do well without ventilatory assistance and should not be considered. Good candidates are those with moderate to severe dyspnea, tachypnea, and impending respiratory muscle fatigue, as indicated by the use of accessory muscles of breathing or abdominal paradox. The level of tachypnea used as a criterion depends on the underlying diagnosis. Those with COPD are considered candidates for noninvasive ventilation when the respiratory rate exceeds 24 breaths per minute; with hypoxemic respiratory failure, higher respiratory rates are used, in the range of 30 to 35 breaths per minute. The second step is to exclude patients for whom noninvasive ventilation would be unsafe. Those with frank or imminent respiratory arrest should be promptly intubated, because the successful initiation of noninvasive ventilation requires some time for adaptation. Patients who are medically unstable with hypotensive shock, uncontrolled upper gastrointestinal bleeding, unstable arrhythmias, or life-threatening ischemia are better managed with invasive mechanical ventilation. Additionally, noninvasive ventilation should not be used for patients who are uncooperative, unable to adequately protect their upper airway or clear

TABLE 68–2. PREDICTORS OF NONINVASIVE VENTILATION SUCCESS IN PATIENTS WITH ACUTE RESPIRATORY FAILURE

Lower acuity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] score)
Ability to cooperate; better neurologic score
Ability to coordinate breathing with ventilator
Less air leakage; intact dentition
Hypercarbia, but not too severe ($PaCO_2$ between 45 and 92 mm Hg)
Acidemia, but not too severe (pH between 7.1 and 7.35)
Improvements in gas exchange and heart and respiratory rates within first 2 h

secretions, or intolerant of masks, or for recipients of recent upper gastrointestinal or airway surgery.

INITIATION OF NONINVASIVE VENTILATION

Once an appropriate candidate for noninvasive ventilation has been selected, a ventilator and interface must be chosen, initial settings must be selected, and the patient must be monitored closely in an appropriate location until stabilized. The roles of physicians, respiratory therapists, and nurses are of paramount importance in explaining the process to and gaining the confidence of the patient. Noninvasive ventilation can be initiated wherever the patient presents with acute respiratory distress, but he or she should be transferred to an ICU or step-down unit that offers adequate continuous monitoring until stabilized. During transfer, ventilatory assistance and monitoring should be continued.

VENTILATOR SELECTION

Selection of a ventilator is based largely on availability, practitioner experience, and patient comfort. Pressure-limited modes, including pressure support and pressure control, are available on most critical care ventilators. Pressure control ventilation delivers time-cycled, preset inspiratory and expiratory pressures, with adjustable inspiratory-expiratory ratios, at a controlled rate. Most such modes also permit patient triggering and selection of a backup rate. PSV delivers preset inspiratory and expiratory pressures to assist spontaneous breathing efforts. Nomenclature and the specific characteristics of these modes may differ among ventilators, and this must be taken into account to avoid errors. For example, with some ventilators, pressure support is the amount of inspiratory assistance added to the preset expiratory pressure. Others require independent selection of inspiratory and expiratory positive airway pressures, with the difference between the two determining the level of pressure support.

PSV is a flow-triggered and -cycled mode, and the patient's effort determines tidal volume and duration of inspiration. Thus, pressure support modes have the potential to match breathing pattern quite closely, and they have been rated by patients as more comfortable for noninvasive ventilation than volume-limited ventilation.[49] However, leaks during noninvasive ventilation can interfere with the detection of reduced inspiratory flow at the termination of inspiration, causing expiratory asynchrony. Noninvasive pressure-limited modes of ventilation are usually administered using either standard critical care ventilators or portable bilevel ventilators. Most bilevel devices have limited pressure-generating capability (≤30 cm H_2O) and lack oxygen blenders or sophisticated alarm or battery backup systems, precluding their use in patients who require high oxygen concentrations or inflation pressures. Newer versions are more appropriate for the acute setting, being equipped with sophisticated alarm and monitoring capabilities, graphic displays, and oxygen blenders. These devices are capable of enhancing synchrony by offering ways to limit inspiratory duration and an adjustable "rise time"—the time to reach the targeted inspiratory pressure. If desired, volume-limited ventilation can be delivered using critical care ventilators, but a higher tidal volume than that commonly used for invasive mechanical ventilation is recommended to compensate for air leakage.

Initial ventilator pressure settings are usually low to facilitate patient acceptance, but they can be set higher if necessary to alleviate respiratory distress. Typical starting pressures are an inspiratory positive airway pressure of 10 to 12 cm H_2O and a PEEP (or expiratory positive airway pressure) of 4 to 5 cm H_2O. For volume ventilation, initial tidal volumes range from 10 to 15 mL/kg. The ventilator is set in a spontaneously triggered mode, with or without a backup rate. Pressures commonly used to deliver CPAP in patients with acute respiratory distress range from 5 to 12.5 cm H_2O. CPAP can be applied using compressed air with a regulator system, blower-based CPAP devices, bilevel devices, or critical care ventilators.

INTERFACES

The major difference between invasive and noninvasive ventilation is that with the latter, pressurized gas is delivered to the airway via a mask rather than via an invasive conduit. The open breathing circuit of noninvasive ventilation permits air leaks around the mask or through the mouth, rendering the success of noninvasive ventilation dependent on ventilators designed to deal effectively with air leaks and to optimize patient comfort and acceptance. Interfaces—the devices that connect the ventilator tubing to the nose, mouth, or both—enable pressurized gas to enter the upper airway during noninvasive ventilation. Commonly used interfaces in the acute setting include nasal masks and full face (or oronasal) masks.

Nasal masks are widely used for the administration of CPAP or noninvasive ventilation, particularly for chronic applications. Nasal masks are usually better tolerated than full face masks for long-term applications, because they cause less claustrophobia and discomfort and allow eating, conversation, and expectoration. The standard nasal mask is a triangular or cone-shaped clear plastic device that fits over the nose and uses a soft cuff that forms an air seal over the skin. The mask exerts pressure over the nasal bridge, often causing skin irritation and redness and occasionally ulceration. Many modifications are available to avoid complications, such as the use of forehead spacers or masks with ultrathin silicon seals or heat-sensitive gels that minimize skin trauma.

Full facemasks cover both the nose and the mouth (Fig. 68-3) and are preferable to nasal masks in the acute setting. The efficacy of both nasal and oronasal masks in lowering $PaCO_2$ and avoiding intubation is similar in the acute setting, but in a recent randomized, controlled trial,[50] patients tolerated the full facemask better because of reduced air leakage through the mouth. Recently, a "total" facemask has become available; it seals around the perimeter of the face and resembles a hockey goalie's mask. Made of optical-grade plastic, it is easy to apply and causes no more claustrophobia than standard facemasks. Mouthpieces are seldom used to administer noninvasive ventilation in the acute setting but are occasionally used during initiation, when the patient holds the mouthpiece in place to adapt to the sensation of positive-pressure ventilation.

Selection of a comfortable mask that fits properly is key to the success of noninvasive ventilation. The full facemask should be tried first in the acute setting, and if possible, the patient should be allowed to hold the mask in place initially. The mask straps are then tightened with the least tension necessary to avoid excessive air leakage. Some leaking is acceptable and is even obligatory with bilevel ventilators, because of the need to flush carbon dioxide from the single-channel ventilator circuit. Bilevel ventilators compensate for air leakage better than critical care ventilators do, but

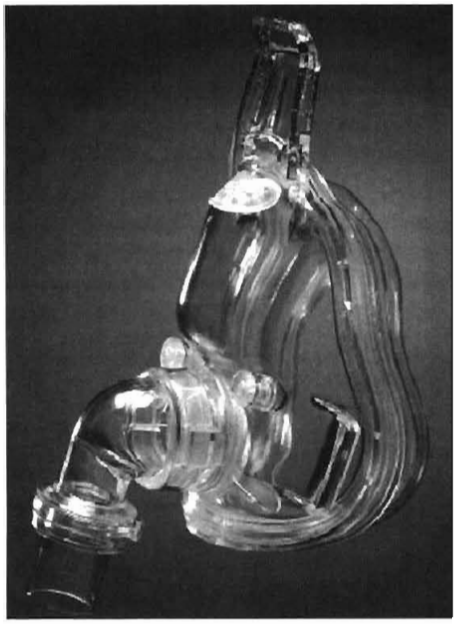

FIGURE 68–3. Full facemask with a soft silicon seal to minimize pressure on the nasal bridge. A disposable version of this mask is widely used in the acute care setting.

excessive air leakage can lead to noninvasive ventilation failure with any ventilator.

Head straps hold the mask in place and are important for patient comfort. Straps attach at two to five points, depending on the type of mask. More points of attachment add to stability.

OXYGENATION AND HUMIDIFICATION

Oxygen is titrated to achieve a desired oxygen saturation, usually greater than 90% to 92%, either by using oxygen blenders on critical care and some bilevel ventilators or by adjusting liter flow (up to 15 L/min, as per manufacturer's recommendations), delivered via oxygen tubing connected directly to the mask or ventilator circuit. Bilevel ventilators have limited oxygenation capabilities (maximal inspired oxygen fraction, 0.45 to 0.5), so ventilators with oxygen blenders should be used for patients with hypoxemic respiratory failure. A heated humidifier should be used to prevent drying of the nasal passage and oropharynx when the duration of application is anticipated to be more than a few hours.

MONITORING

Once noninvasive ventilation is initiated, patients should be closely monitored in a critical care unit or a step-down unit until they are sufficiently stable to be moved to a regular medical floor. The aim of monitoring is to determine whether the main goals are being achieved, including relief of symptoms, reduced work of breathing, improved or stable gas exchange, good patient-ventilator synchrony, and patient comfort (Table 68-3). A drop in the respiratory rate with improved oxygen saturation or improving pH with a lower $PaCO_2$ within the first 1 to 2 hours portends a successful outcome.[51] Abdominal paradox, if present initially, subsides,

TABLE 68–3. MONITORING OF PATIENTS RECEIVING NONINVASIVE VENTILATION IN ACUTE CARE SETTINGS

Location
Critical care or step-down unit
Medical or surgical ward if able to breathe unassisted for >20-30 min
"Eyeball" test
Dyspnea
Comfort (mask, air pressure)
Anxiety
Asynchrony
Leaks
Vital signs
Respiratory and heart rates
Blood pressure
Continuous electrocardiography
Gas exchange
Continuous oximetry
Arterial blood gases (baseline, after 1-2 h, and as clinically indicated)

and the heart rate usually falls. The absence of these propitious signs indicates a poor response to noninvasive ventilation and the need to make further adjustments. Leaks should be sought and corrected, patient-ventilator synchrony should be optimized, and pressures may have to be adjusted upward to relieve respiratory distress and achieve a reduction in $PaCO_2$. If these adjustments fail to improve the response within a few hours, noninvasive ventilation should be considered a failure, and the patient should be promptly intubated if it is still clinically indicated. Excessive delay in intubation may precipitate a respiratory crisis and add to morbidity and mortality.

ADVERSE EFFECTS AND COMPLICATIONS

When applied by experienced caregivers to appropriately selected patients, noninvasive ventilation is usually well tolerated and is associated with minimal complications. The most frequent adverse effects and complications are related to the mask, ventilator airflow or pressure, patient-ventilator interaction, or airway secretions.

Common adverse effects related to the mask include discomfort and erythema or skin ulcers, usually on the nasal bridge, related to pressure from the mask seal. Proper fitting and attachment, consistent use of artificial skin over the nose, and newer masks with softer silicone seals help minimize these problems. Adverse effects related to airflow or pressure include conjunctival irritation caused by air leakage under the mask into the eyes and sinus, or ear pain related to excessive pressure. Refitting the mask or lowering inspiratory pressure may ameliorate these problems. Nasal or oral dryness caused by high airflow is usually indicative of air leaking through the mouth. Measures to minimize leakage may be useful, but nasal saline or emollients and heated humidifiers are often necessary to relieve these complaints. Nasal congestion and discharge are also frequent complaints and can be treated with topical decongestants or steroids and oral antihistamine-decongestant combinations. Gastric insufflation occurs commonly, may respond to simethicone, and is usually tolerated.

Patient-ventilator asynchrony is a common occurrence during noninvasive ventilation. Failure to adequately synchronize compromises the ventilator's ability to reduce the work

of breathing and may contribute to noninvasive ventilation failure. The asynchrony may be related to patient agitation, which can be treated with the judicious use of sedatives. Failure to synchronize can also result from inadequate ventilator triggering or inability to sense the onset of patient expiration because of air leakage. This can be corrected by minimizing air leaks and by using ventilator modes that permit limitation of maximal inspiratory duration. Even with the best efforts to optimize settings and comfort, a minority of patients still fail. This may be partly due to progression of the underlying disease process or the patient's inability to tolerate noninvasive ventilation, but every effort should be made to ascertain that it is not due to technologic problems that could be corrected by mask or ventilator adjustments. Once again, intubation should not be delayed if improvement is not apparent within a few hours.

ANNOTATED REFERENCES

Antonelli M, Conti G, Rocco M, et al: A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. N Engl J Med 1998;329:429-435.

A prospective, randomized study comparing noninvasive positive-pressure ventilation delivered through a facemask with conventional endotracheal intubation and mechanical ventilation in patients with acute respiratory failure. Noninvasive ventilation was as effective as conventional ventilation in improving gas exchange and was associated with fewer serious complications and shorter stays in the ICU.

Brochard L, Isabey D, Piquet J, et al: Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. N Engl J Med 1990;323:1523-1530.

An early landmark study looking at the ability of noninvasive ventilation to provide inspiratory pressure support by means of a facemask in COPD exacerbations. Based on a comparison with historical controls, noninvasive ventilation shortened the duration of mechanical ventilation and ICU stay.

Girou E, Schortgen F, Delclaux C, et al: Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. JAMA 2000;284:2361-2367.

In this matched case-control study in patients with acute exacerbations of COPD or hypercapnic cardiogenic pulmonary edema, noninvasive ventilation was associated with a lower risk of nosocomial infection, less antibiotic use, shorter length of ICU stay, and lower mortality compared with invasive mechanical ventilation.

Hilbert G, Gruson D, Vargas F, et al: Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med 2001;349:481-487.

This study shows that in 52 selected immunosuppressed patients with pneumonitis and acute respiratory failure, early initiation of intermittent noninvasive ventilation significantly reduced the rates of endotracheal intubation and serious complications and improved the likelihood of survival to hospital discharge.

Nava S, Ambrosino N, Clini E, et al: Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease: A randomized, controlled trial. Ann Intern Med 1998;128:721-728.

A multicenter, randomized trial to determine whether noninvasive ventilation improves the outcome of weaning from invasive mechanical ventilation when used to achieve early extubation in patients failing a T-piece trial after 48 hours of invasive ventilation. Patients extubated to noninvasive ventilation had higher 30-day weaning rates, shorter lengths of stay in the ICU, a trend toward decreased nosocomial pneumonia rates, and improved survival at 60 days.

Chapter 69

HIGH-FREQUENCY VENTILATION

Jeffrey M. Singh • Thomas E. Stewart

KEY POINTS

1. **High-frequency ventilation** is a method of mechanical ventilation that uses very small tidal volumes at high frequencies. The most commonly used modes include high-frequency jet ventilation and high-frequency oscillatory ventilation.
2. **Ventilator-induced lung injury** can be a clinically important consequence of mechanical ventilation in patients with respiratory failure, particularly those with underlying acute lung injury. **Volutrauma** from high transpulmonary pressures, **atelectrauma**, and **oxygen toxicity** may all contribute to lung injury, and mechanical ventilation strategies should attempt to mitigate these injurious forces.
3. Despite the recent **clinical success of conventional lung-protective ventilation strategies**, they do not completely prevent lung injury and may be associated with other clinical problems and sequelae, particularly respiratory acidosis.
4. Experimental models suggest that **high-frequency ventilation may mitigate ventilator-induced lung injury**.
5. **In pediatric patients with respiratory distress syndrome, high-frequency oscillatory ventilation is safe and effective** and may be slightly more beneficial than conventional mechanical ventilation when patient selection and clinical conditions are stringently controlled.
6. **In adults, high-frequency oscillatory ventilation has been shown to be safe and effective as salvage therapy** for patients with hypoxic respiratory failure deemed to be failing conventional mechanical ventilation.
7. Despite recent clinical validation of high-frequency ventilation in adults with respiratory distress, **significant research remains to be done to determine the best application of high-frequency ventilation modes**, particularly optimal settings, timing of initiation, and weaning from high-frequency ventilators to conventional ventilators.

High-frequency ventilation is a mode of mechanical ventilation in which small tidal volumes are delivered at high supraphysiologic frequencies. Various types of high-frequency ventilation have been developed over the last 3 decades, including high-frequency positive-pressure ventilation, high-frequency percussive ventilation, high-frequency jet ventilation, and high-frequency oscillatory ventilation. Initially, high-frequency ventilation was mainly of academic interest, with a limited role in rescue and neonatal therapy, but there has recently been renewed enthusiasm for its use as part of a lung-protective ventilation strategy for adult and pediatric patients with acute lung injury and acute respiratory distress syndrome (ARDS).

Over the last 20 years, our understanding of the potential harm of mechanical ventilation has evolved, especially in the case of an injured lung in which normal function is disturbed. Lung damage may occur through injurious mechanical forces generated during mechanical ventilation. This lung injury may contribute to increased systemic inflammation, possibly leading to multiple organ dysfunction and increased morbidity and mortality. Lung-protective mechanical ventilation strategies now aim to reduce these injurious forces and subsequent lung damage while providing adequate ventilation and oxygenation. The mechanics of high-frequency ventilation make it particularly well suited to protecting the lung, and there is growing clinical experience with the use of high-frequency ventilation as an alternative to conventional mechanical ventilation or as salvage therapy in patients failing conventional ventilation strategies.

DESCRIPTION AND CLASSIFICATION

Modes of high-frequency ventilation are characterized by high respiratory rates and lower tidal volumes than those used in conventional mechanical ventilation. Often, the tidal volume is less than anatomic deadspace, and gas exchange is maintained by increasing the respiratory rate to supra-physiologic frequencies. Gas exchange under these conditions may occur through a number of proposed contributory mechanisms (see Mechanisms of Gas Transport). High-frequency positive-pressure ventilation, high-frequency percussive ventilation, high-frequency jet ventilation and high-frequency oscillatory ventilation are described briefly here.

High-Frequency Positive-Pressure Ventilation. High-frequency positive-pressure ventilation delivers small volumes (approximately 3 to 4 mL/kg) of conditioned gas at high frequencies (60 to 100 breaths/min) using a conventional mechanical ventilator. Valves in the inspiratory and expiratory limbs of the ventilator circuit allow control of the inspiratory flow rate (which is generally high) and positive

end-expiratory pressure (PEEP), respectively. Expiration is passive and relies on the elastic recoil of the patient's respiratory system. The clinician controls the respiratory rate, inspiratory flow rate, diving pressure, and PEEP. Because high respiratory rates leave little time for passive expiration, there is a risk of gas trapping, with hyperinflation and resultant overdistention injury.

High-Frequency Percussive Ventilation. High-frequency percussive ventilation is a hybrid that attempts to combine the principles of high-frequency and conventional ventilation using a proprietary mechanical ventilator.[1] A conventional ventilation circuit is fitted with a gas-driven piston at the end of the endotracheal tube. The reciprocating piston generates pressure oscillations at 3 to 15 Hz with short expiratory times, which are superimposed on the conventional inspiratory-expiratory pressure waves. The high-frequency beats are delivered in bursts to generate auto-PEEP through breath stacking, then stopped to allow alveolar pressure to fall back to baseline. It has been hypothesized that the auto-PEEP generated may improve alveolar recruitment without exposing the alveoli to the high peak airway pressures that would be generated with comparable conventional mechanical ventilation. The high-frequency percussion also provides some internal mucokinesis, improving pulmonary toilet and reducing endotracheal suctioning requirements. Although the high-frequency pressure oscillations are driven actively in both directions, the bulk of exhalation from the underlying conventional mechanical ventilation breaths is passive. Clinicians have control of all aspects of these underlying breaths, as well as the frequency and pressure of the high-frequency beats.

High-Frequency Jet Ventilation. High-frequency jet ventilation employs a small-aperture nozzle to direct a high-pressure stream of gas into the lung (Fig. 69-1). Flow of gas through the nozzle is controlled by a solenoid valve, allowing control of frequency and inspiratory time. During inspiration, a high-pressure jet streams into the proximal airways, entraining air from the circuit. Tidal volumes are largely dependent on the momentum of the jet and the entrainment of gas from the surrounding circuit. Expiration is passive, relying on respiratory system recoil. PEEP is determined by changing the flow of fresh gas through the circuit and the resistance to flow through the expiratory limb. The small size of the injector nozzle (2 to 3 mm) allows it to be placed in the endotracheal tube or proximal trachea, which not only decreases deadspace but also allows better visualization and access during surgical procedures involving the upper airway.

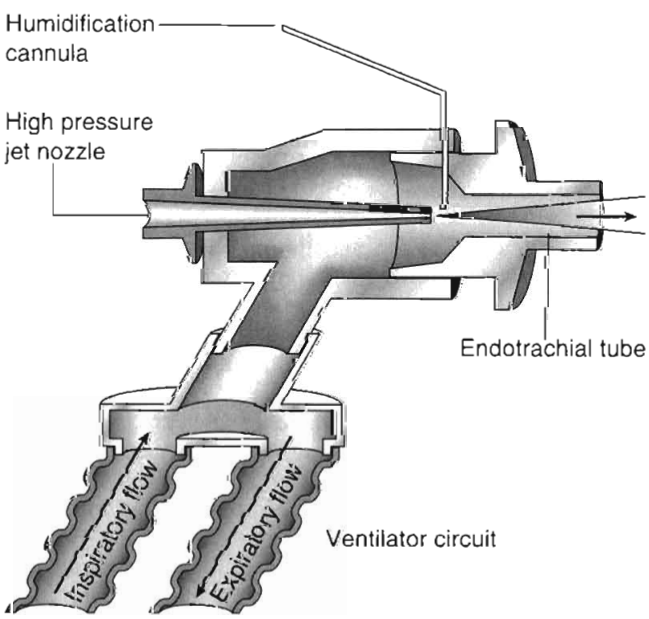

FIGURE 69–1. Typical high-pressure jet cannula and humidification system used in high-frequency jet ventilation. Note that the gas jet is directed down the endotracheal tube, entraining gas from the proximal ventilator circuit.

The clinician has control over frequency, inspiratory time, jet drive pressure, and mean airway pressure applied through the ventilator circuit. Larger tidal volumes can be delivered by increasing jet drive pressure and inspiratory time. Larger jet catheters and endotracheal tubes also augment tidal volume by increasing jet flow and gas entrainment, respectively. Because expiration is passive, gas trapping with intrinsic PEEP may occur at high frequencies when expiration is limited by progressively shorter expiratory times.

Complications specific to high-frequency jet ventilation include traumatic upper airway injury. The high-velocity inspiratory jet may cause direct trauma to the proximal airways, and necrotizing tracheobronchitits is a well-established complication of high-frequency jet ventilation in both infants and adults.[2,3] Gas conditioning in high-frequency jet ventilation, particularly humidification and warming, is also problematic. Although the gas entrained from the proximal circuit is warmed and humidified, the gas projecting from the jet nozzle expands and cools, compromising the overall conditioning of the inspired gas. It has also been hypothesized that high gas flow rates and rapid increases in lung volume could cause lung injury through the generation of shear forces at the interface of adjacent compliant and atelectatic lung units.

High-Frequency Oscillatory Ventilation. In high-frequency oscillatory ventilation, an oscillating diaphragm creates pressure waves in the ventilator circuit (Fig. 69-2). Because the diaphragm is actively driven in both directions, the ventilator creates both inspiratory and expiratory pressure waves, meaning that expiration is active. This distinguishes high-frequency oscillatory ventilation from other forms of high-frequency ventilation, in which expiration is passive and dependent on the elastic recoil of the respiratory system. Active expiration may be advantageous in controlling lung volumes and preventing hyperinflation. Although all modes of high-frequency ventilation may generate some degree of auto-PEEP, which may be beneficial in increasing alveolar recruitment, high levels of auto-PEEP can cause hyperinflation and lung injury. High-frequency oscillatory ventilation has been shown to be associated with less gas trapping than other forms of high-frequency ventilation.[4] Mean airway pressure is determined by adjusting the resistance to the flow of fresh gas (bias flow) across the circuit.

Clinicians set the bias flow rate, mean airway pressure, frequency, inspiratory-expiratory ratio, and energy applied to the oscillating diaphragm. The generation of pressure oscillations is controlled in part by the frequency and the energy applied to the moving diaphragm (power). The excursion of the diaphragm (and presumably the delivered tidal volume) is inversely related to the frequency. High frequencies result in a short inspiratory period that limits the time during which the diaphragm can move. This can be overcome in part by increasing power, which increases its excursion at a given frequency.

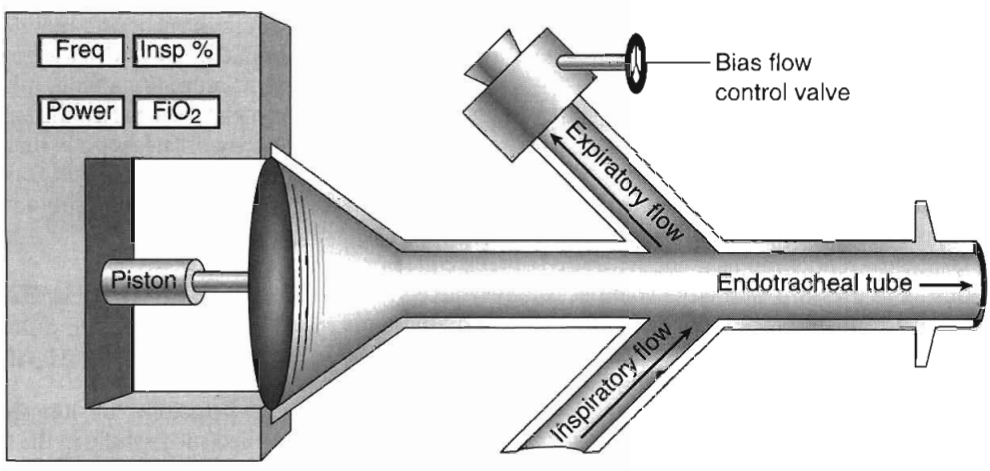

FIGURE 69–2. Schematic of high-frequency oscillatory ventilator. A computer allows precise control over the piston driving the oscillating diaphragm. Adjustment of the bias flow of conditioned gas allows control of mean airway pressure.

MECHANISMS OF GAS TRANSPORT

During conventional mechanical ventilation, when tidal volumes are larger than anatomic deadspace, gas exchange is largely related to bulk flow of gas to the alveoli. High-frequency ventilation is thought to generate tidal volumes smaller than anatomic deadspace, and adequate ventilation under these conditions must rely on alternative gas exchange mechanisms. A number of proposed mechanisms may contribute to gas transport during high-frequency ventilation.[5]

When tidal volume approximates anatomic deadspace, the leading edge of the gas front may actually reach a number of proximal alveoli and thus contribute to some gas exchange through bulk flow.[5] Although it is thought that high-frequency ventilation modes generally generate tidal volumes that are lower than anatomic deadspace, recent experimental data suggest that larger tidal volumes may be generated under some conditions. High-frequency oscillatory ventilation, which is usually considered to have the smallest tidal volumes among high-frequency modes, was found in one animal model to deliver tidal volumes significantly greater than anatomic deadspace when applied using settings similar to those traditionally used in adults (frequency, 3 to 6 Hz; ΔP, 60 to 90 cm H_2O).[6] The in vitro characteristics of pediatric high-frequency oscillatory ventilators have been studied, revealing a tidal volume of 3 to 11 mL.[7] Thus, bulk flow may still contribute to gas exchange during high-frequency ventilation, although to a much lesser degree than during conventional mechanical ventilation.

Pendelluft is a phenomenon of regional gas movement that occurs as a result of heterogeneity in alveolar filling rates. The filling rate of a lung unit is dependent on its time constant (τ), a property related to the product of compliance and resistance.[8] Adjacent lung units with different time constants may fill at different rates during inspiration. Following inspiration, there is redistribution of inspired gas from full, fast-filling units to slower-filling units, augmenting gas exchange.[9]

Convective streaming occurs as a result of the asymmetrical velocity profile of the inspired gas front as it moves through the bronchial tree. When inspired gas flows down the bifurcating bronchial tree, the gas front is skewed, such that inspired gas streams down the inside wall of distal airways. During exhalation, the velocity profile of the gas front is flat across the airway cross section. The asymmetry in gas velocity between the inspiratory and expiratory phases of breathing results in a net streaming of fresh gas down the inside walls of distal airways and of carbon dioxide (CO_2)–laden gas back along the outside walls.[10,11] The asymmetrical streaming of fresh gas down airways creates a radial concentration gradient (augmented diffusion), which may contribute significantly to gas mixing.[12] In addition, the beating heart may enhance gas exchange through agitation of surrounding lung tissue (cardiogenic mixing) in these lung units and molecular diffusion.

The extent to which each of these mechanisms contributes to gas exchange at any one moment in a given patient is unknown and may be of questionable clinical relevance, beyond the fact that adequate gas exchange can be achieved with high-frequency ventilation. Experimental models have shown that CO_2 elimination is a product of the frequency and the square of the tidal volume ($V_{CO_2} \alpha = f \times V_T^2$),[13] suggesting that adequate CO_2 elimination may become problematic as tidal volumes decrease, unless accompanied by proportionately larger increases in frequency. Regardless, clinical experience has demonstrated that adequate gas exchange can be achieved with mechanical ventilation using tidal volumes that are less than anatomic deadspace.

RATIONALE FOR HIGH-FREQUENCY VENTILATION

More than 3 decades after its first description, high-frequency ventilation remains an "alternative" mode of mechanical ventilation, with the exception of a few specialized indications (e.g., airway control during laryngeal surgery, ventilation of patients with bronchopleural fistula). The mechanical characteristics of high-frequency ventilation, however, make it well suited for use in the injured lung. There has recently been a resurgence of interest in high-frequency ventilation, particularly high-frequency oscillatory ventilation, as part of a lung-protective strategy in patients with severe lung injury and ARDS. Appreciation of the potential advantages of high-frequency ventilation, particularly with respect to lung protection, requires an understanding of the mechanics of high-frequency ventilation, the proposed mechanisms of gas exchange in high-frequency

ventilation, and current concepts of ventilator-induced lung injury (VILI).

VENTILATOR-INDUCED LUNG INJURY AND LUNG PROTECTION

The last 20 years have witnessed a greater appreciation of the potential lung injury caused by mechanical ventilation itself. Mechanical ventilation using high inspired oxygen concentrations, high pressure, and large volumes is largely accepted as being harmful, but recent research has shed light on the some of the pathogenic mechanisms of VILI. The pathogenesis of VILI is complex and remains incompletely elucidated, although current data support several mechanisms, including volutrauma, atelectrauma, barotrauma, and biotrauma.

Mechanical ventilation with large tidal volumes can overdistend alveoli and result in lung injury. Animal studies suggest that high transpulmonary pressures (with resultant large lung volumes and overdistention), rather than high inflation pressures alone, are the cause of lung injury.[14-16] Supporting evidence shows that animals ventilated with large volumes develop pathologic abnormalities similar to those seen in ARDS, even using negative-pressure ventilators.[14] Mechanical restriction of lung volume in the same animal model mitigates this damage, even when extremely high inflation pressures are applied.[14] This understanding has led to adoption of the term "volutrauma." The exact mechanism by which large volumes cause lung injury is not clear but may be related to alveolar wall stretch, stress failure of the lung ultrastructure, and cellular mechanotransduction leading to the release of inflammatory mediators.[17]

Although high-volume ventilation can be harmful, mechanical ventilation at low end-expiratory volumes can also be injurious. "Atelectrauma" occurs when end-expiratory volume is insufficient to maintain inflation of lung units throughout the respiratory cycle. Under these conditions, lung units collapse at end-expiration, only to be forced open during inspiration. Shear forces generated during this cyclic collapse and re-inflation injure the alveolar walls, contributing to VILI.[18] Similar forces may also be generated at the interface between aerated and atelectatic lung units during the respiratory cycle, stressing the connecting alveolar walls.[19] Further, underlying lung pathology may predispose or exacerbate atelectrauma-type injury. Although cyclic collapse can be tolerated for short periods in healthy lungs,[20] the shear forces are intensified when lung mechanics are altered by surfactant depletion and underlying lung injury.[21]

The end-organ effects of VILI are not isolated to the lung. "Biotrauma" refers to the contribution of VILI to systemic inflammation.[22] Injurious mechanical ventilation is associated with increases in circulating inflammatory mediators, and this increase can be attenuated through the use of mechanical ventilation strategies that avoid these injurious forces.[23] The production of systemic inflammatory mediators may contribute to multiple organ dysfunction and mortality. The potential benefit of reducing biotrauma becomes more obvious when it is noted that the majority of deaths among patients with ARDS are due not to oxygenation failure but to multiple organ failure.

Mechanical ventilation strategies designed to reduce VILI have been termed "lung-protective." The current goals of lung protection are threefold: (1) prevention of overdistention-related lung injury through the reduction of tidal volumes and the avoidance of high transpulmonary pressures; (2) recruitment and maintenance of lung volume (the "open lung" concept), with the goal of preventing cyclic collapse and atelectrauma-type lung injury; and (3) reduction of inspired oxygen fraction requirements, thereby reducing oxygen toxicity.[24] The hope is that the reduction of these injurious mechanical forces will translate into a decrease in systemic inflammation and subsequent end-organ dysfunction and mortality.

SUCCESSES AND LIMITATIONS OF LUNG-PROTECTIVE CONVENTIONAL MECHANICAL VENTILATION

The principles of lung-protective ventilation have been applied successfully in the clinical setting using conventional mechanical ventilation. Approaches to minimize VILI include limiting tidal volumes to prevent volutrauma and using PEEP and recruitment maneuvers to maintain end-expiratory lung volume, thereby preventing cyclic collapse. One study evaluating a lung-protective strategy in adults with ARDS demonstrated improved survival at 28 days, although this benefit did not persist to hospital discharge.[25] Although criticized for a high mortality rate in the control arm, this study demonstrated conclusively that changes in ventilatory management can contribute to mortality. In another randomized clinical trial that evaluated a lung-protective strategy based on low tidal volumes and reduced airway pressures, a 9% absolute reduction in mortality was observed.[26] Lung-protective conventional mechanical ventilation is also associated with lower levels of circulating inflammatory mediators, supporting the hypothesis that mitigating the injurious forces during mechanical ventilation may help decrease biotrauma and its contribution to multisystem organ failure.[23,26]

The clinical application of these ventilation protocols, however, is often complicated by impaired ventilation. The use of lower tidal volumes may lead to a decrease in alveolar ventilation that may not be completely offset by increases in respiratory rate. Consequently, clinicians may be forced to accept hypoventilation and respiratory acidosis, so-called permissive hypercapnia, if they wish to maintain low tidal volumes. In addition, even the best possible lung-protective strategy may contribute to the injury of some lung units. Computed tomography studies have demonstrated that lung injury in ARDS is heterogeneous,[27] resulting in local differences in lung mechanics and variable susceptibility to VILI. Relatively healthy lung units may have higher compliance and lower time constants than their more severely injured neighbors, making them more prone to volutrauma-type injury. Conversely, relatively noncompliant lung units may be more prone to atelectrauma-type injury if allowed to collapse at end-expiration. Thus, even when conventional mechanical ventilation is applied with low, lung-protective tidal volumes (4 to 6 mL/kg), patients may still suffer atelectrauma-type injury in diseased, noncompliant lung units while adjacent healthy lung units are injured by overdistention. Further, determining the ideal level of PEEP to prevent end-expiratory collapse may be difficult. One study found that alveolar recruitment occurred progressively over the entire inflation limb of the pressure-volume curve, making reliable identification of the lower inflection point difficult.[28]

Thus, although lung-protective conventional mechanical ventilation has been found to decrease mortality in well-designed clinical trials, it may be possible to further optimize

lung protection. Currently, other adjuncts and alternative ventilator modes, including high-frequency ventilation, are under investigation. Finally, despite the best use of conventional mechanical ventilation, some patients fail to be adequately oxygenated and ventilated, and alternative salvage therapies may be needed.

THEORETICAL ADVANTAGES TO HIGH-FREQUENCY VENTILATION

High-frequency ventilation may be well suited to accomplish all the goals of lung protection. By nature of its low tidal volumes, high-frequency ventilation may decrease the risk of overdistention injury, even to relatively healthy, compliant lung units. In addition, because these tidal volumes are delivered using relatively small pressure swings at high rates, mean airway pressure can be maintained at higher levels than are generally used during conventional mechanical ventilation (Fig. 69-3). This high mean airway pressure may optimize end-expiratory lung volume, leading to improved oxygenation and prevention of cyclic collapse and resultant atelectrauma.

The ideal application of high-frequency ventilation might involve "opening" the lung using sustained inflation maneuvers and appropriate levels of PEEP and mean airway pressure, pushing the lung onto the expiratory limb of the pressure-volume curve and optimizing oxygenation and lung compliance (Fig. 69-4). The open lung is then ventilated using small tidal volumes and pressure swings, minimizing alveolar overdistention and collapse throughout the respiratory cycle. In animal models comparing high-frequency oscillatory ventilation to lung-protective conventional mechanical ventilation, such a strategy has been found to decrease pulmonary inflammation and attenuate the increase in systemic inflammatory mediators observed during conventional mechanical ventilation.[29,30]

CLINICAL EXPERIENCE WITH HIGH-FREQUENCY VENTILATION

High-frequency ventilation is largely considered an alternative mode of mechanical ventilation and traditionally has been used only in specialized situations or as salvage therapy when conventional mechanical ventilation fails. Although clinical experience with high-frequency ventilation in pediatric and neonatal populations is sizable, published experience with high-frequency ventilation modes in adults remains modest, with the largest experience involving high-frequency oscillatory ventilation and high-frequency jet ventilation. There has been renewed interest in the use of high-frequency ventilation in adults, however, as greater understanding of VILI has spurred the search for more lung-protective ventilation strategies. This section reviews the existing clinical experience with the various modes of high-frequency ventilation.

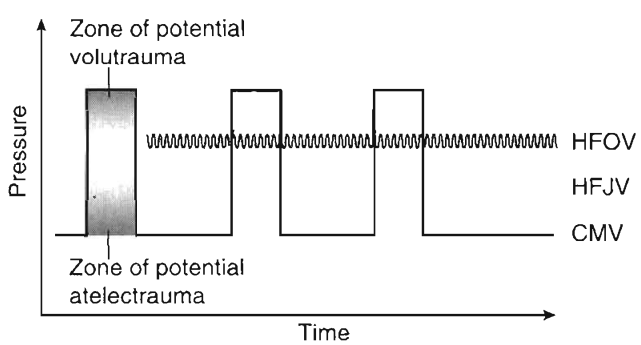

FIGURE 69–3. Comparative pressure-time diagram depicting the pressure-time swings for the most common modes of high-frequency ventilation compared with conventional mechanical ventilation (CMV). HFJV, high-frequency jet ventilation; HFOV, high-frequency oscillatory ventilation.

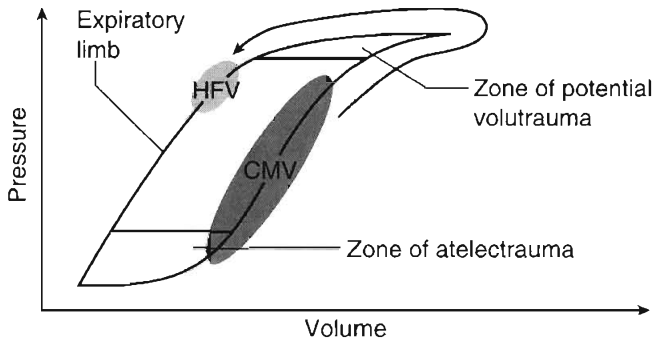

FIGURE 69–4. Pressure-volume curve depicting the "open lung" concept using high-frequency ventilation (HFV). Potential lung injury is reduced when ventilation of the lung is shifted onto the expiratory portion of the curve using aggressive lung recruitment. Lung volume is then maintained using high mean airway pressures and small tidal volumes. CMV, conventional mechanical ventilation.

HIGH-FREQUENCY POSITIVE-PRESSURE VENTILATION

First described in 1969 as an experimental technique,[31] high-frequency positive-pressure ventilation has found limited clinical use in specialized upper airway surgical procedures and bronchoscopy.[32] Published clinical experience with high-frequency positive-pressure ventilation is largely limited to neonatal populations. One meta-analysis found that synchronized mechanical ventilation delivered as high-frequency positive-pressure ventilation was associated with decreased barotrauma and shorter length of hospital stay compared with conventional mechanical ventilation.[33] The effect of high-frequency positive-pressure ventilation on mortality and chronic oxygen dependency was not clear after analysis of the published studies. In adult patients, high-frequency positive-pressure ventilation has been used only in specialized applications.[34-36]

HIGH-FREQUENCY PERCUSSIVE VENTILATION

The existing literature evaluating high-frequency percussive ventilation in patients with acute respiratory failure is limited to one case series in pediatric patients[37] and several case reports and case series in adults.[38-43] In most of these series, the investigators observed improvements in oxygenation after switching from conventional mechanical ventilation to high-frequency percussive ventilation, without a significant rise in peak or mean airway pressure. These uncontrolled series were small, however, and did not detect differences in mortality or other clinical outcomes.

HIGH-FREQUENCY JET VENTILATION

High-frequency jet ventilation is commonly used in specific clinical settings, particularly pulmonary air leak syndromes, when the ability to achieve adequate gas exchange with lower peak airway pressures may be advantageous.[44] Additionally, the decreased reliance on bulk flow when using high-frequency jet ventilation may improve gas distribution and gas exchange in the presence of large air leaks. High-frequency jet ventilation has also been used intraoperatively during surgical procedures involving the airway and upper trachea; the small tidal volumes minimize movement of the proximal airways, and the small jet catheter and lack of a cuffed endotracheal tube improve visualization of the operative field. High-frequency jet ventilation has also been used in acute respiratory failure in both adults and infants, where it was generally found to improve gas exchange while decreasing peak airway pressures. The published clinical experience with high-frequency jet ventilation in acute respiratory failure remains small compared with that of conventional mechanical ventilation, and to date, the greatest clinical experience is in the neonatal and pediatric populations.

Several studies comparing high-frequency jet ventilation with conventional mechanical ventilation in premature infants with respiratory distress syndrome and pulmonary interstitial emphysema showed that the former is safe and provides improved ventilation at lower peak airway pressures. Although one study demonstrated improved outcomes (decreased incidence of bronchopulmonary dysplasia and home oxygen use at 36 weeks),[45] the majority of studies did not demonstrate a significant advantage of high-frequency jet ventilation over conventional mechanical ventilation with respect to long-term outcome or mortality, despite short-term improvements in gas exchange and respiratory parameters.[46-48] One study evaluating the early use of high-frequency jet ventilation in 73 premature infants found that infants receiving high-frequency jet ventilation were more likely to suffer adverse outcomes (cystic periventricular leukomalacia, intraventricular hemorrhage, death) than were infants receiving conventional mechanical ventilation.[49]

The published experience with high-frequency jet ventilation in adult respiratory failure is limited, although many ICUs have sizable anecdotal experience. Comparative clinical trials have shown that high-frequency jet ventilation is safe and offers improved oxygenation and ventilation compared with conventional mechanical ventilation, while improving respiratory parameters and decreasing required peak pressures.[50-52] None of these trials, however, demonstrated a significant clinical advantage.

HIGH-FREQUENCY OSCILLATORY VENTILATION

High-frequency oscillatory ventilation has recently been the subject of renewed interest for use in acute respiratory failure. It has the potential to achieve all the goals of lung protection; the small, high-frequency pressure oscillations allow the application of high mean airway pressures to optimize lung volume recruitment and prevent end-expiratory collapse, without exposing the lung to injurious peak airway pressures during inflation. In addition, the circuit allows optimal gas conditioning, reducing the likelihood of airway trauma and inspissation of secretions.

The most extensive published clinical evaluation of high-frequency oscillatory ventilation has been in the neonatal and pediatric populations.[53-62] In neonates, the safe and effective application of high-frequency oscillatory ventilation appears to require lung volume recruitment maneuvers and possibly exogenous surfactant. The majority of studies using high-frequency oscillatory ventilation in this manner have demonstrated that it is safe, improves oxygenation, and may reduce the risk of air leak and barotrauma.[54-58] Although the efficacy of high-frequency oscillatory ventilation in reducing infant mortality and morbidity is contentious, two studies suggest that in carefully controlled clinical settings, it is beneficial.[57,61]

A meta-analysis of the existing trials evaluating pediatric high-frequency oscillatory ventilation found no difference in mortality between it and conventional mechanical ventilation, although high-frequency oscillatory ventilation may have been associated with a modest reduction in chronic lung disease compared with conventional ventilation.[63]

Because the cause and pathophysiology of respiratory failure in preterm neonates and adults are different, the results of trials of neonatal high-frequency oscillatory ventilation are inadequately extrapolated to adult populations. Clinical application of high-frequency oscillatory ventilation in adult subjects was initially hampered by technical failures and a lack of adequately powered ventilators. With the development of more robust ventilators that could generate sufficient power to oscillate an adult patient, there has been a resurgence of interest in high-frequency oscillatory ventilation as part of a lung-protective strategy in patients with ARDS. Two published case series described patients with ARDS who were ventilated with high-frequency oscillatory ventilation after failing conventional mechanical ventilation and found improved oxygenation and decreased inspired oxygen fraction requirements.[64,65] The mortality rate in these uncontrolled series was high (32% to 53%), but this is not surprising, given that high-frequency oscillatory ventilation was used as salvage therapy, preselecting patients with high mortality rates. Other small case series have described the use of high-frequency oscillatory ventilation in burn and trauma patients, both with similar improvements in oxygenation.[66,67]

The best evidence for the use of high-frequency oscillatory ventilation in ARDS comes from two prospective series[68,69] and a prospective clinical trial.[70] Both Mehta and David and their respective colleagues reported experience with high-frequency oscillatory ventilation in patients failing conventional mechanical ventilation and found significant improvements in oxygenation compared with baseline.[68,69] High-frequency oscillatory ventilation was safe and well tolerated, without causing significant hemodynamic compromise. Although the series by Mehta and colleagues had a very high mortality rate, their patient population included very high-risk patients (hematologic malignancy and burn victims). Derdak and colleagues published the first prospective, randomized trial comparing high-frequency oscillatory ventilation with conventional mechanical ventilation in early ARDS and found that the former was safe and improved oxygenation.[70] Although not statistically significant, there was a trend toward decreased mortality in the patients receiving high-frequency oscillatory ventilation. Of interest, all three of these prospective studies found that a longer duration of conventional mechanical ventilation before instituting high-frequency oscillatory ventilation was predictive of a poor outcome, which led some investigators to propose early application of high-frequency oscillatory

ventilation in an attempt to attenuate VILI and possible mortality.

In summary, high-frequency oscillatory ventilation is safe and effective in pediatric patients with hypoxic respiratory failure and in adult patients failing conventional mechanical ventilation. In carefully selected children, high-frequency oscillatory ventilation may be superior to conventional mechanical ventilation. Despite the paucity of published experience in adults, there is a suggestion that the early use of high-frequency oscillatory ventilation may be of additional benefit, although this has yet to be established by rigorous clinical trials.

FUTURE OF HIGH-FREQUENCY VENTILATION

Despite several decades of research into the principles and clinical application of high-frequency ventilation, many important issues remain unresolved, particularly regarding its use in adults. In fact, even the mechanical characteristics of high-frequency ventilation (tidal volumes, gas exchange mechanisms) are still incompletely understood. The optimal settings to maximize lung protection and gas exchange are not clear for many modes of high-frequency ventilation. It has been theorized that optimization of such modes would involve minimizing tidal volumes to reduce the risk of overdistention injury and cyclic lung unit collapse and maximizing alternative gas transport mechanisms. Further, the best time to initiate high-frequency ventilation is not clear; for example, do the benefits of early application outweigh the risks of the increased sedation and paralysis necessary?

These issues must be resolved, because the inappropriate use of high-frequency ventilation may be associated with increased morbidity. The early negative results in trials of high-frequency oscillatory ventilation in neonatal populations without the use of aggressive lung volume recruitment are testament to the importance of the proper ventilation protocol. It is important that these questions be answered before embarking on comparative trials, lest high-frequency ventilation be dismissed not because of lack of benefit but because of inappropriate application. Despite these unknowns, however, high-frequency ventilation possesses many theoretical advantages over conventional mechanical ventilation of the injured lung, especially in upholding the principles of lung protection.

CONCLUSION

All high-frequency ventilation modes are characterized by small tidal volumes delivered at high frequencies, and they take advantage of alternative mechanisms to achieve adequate gas exchange when tidal volumes are less than anatomic deadspace. Evolving understanding of VILI has prompted clinicians to apply mechanical ventilators in a way that minimizes such injury—so-called lung-protective ventilation. The mechanical characteristics of high-frequency ventilation make it well suited to use in the injured lung, because it may reduce volutrauma-type injury while achieving higher mean airway pressures and maintaining end-expiratory lung volume, reducing cyclic collapse. Clinical experience with high-frequency ventilation, particularly high-frequency oscillatory ventilation, has found it to be safe and effective for improving oxygenation in neonatal and adult populations failing conventional mechanical ventilation. It may also be advantageous to apply high-frequency oscillatory ventilation early in the course of ARDS to avoid VILI related to aggressive conventional mechanical ventilator settings. Despite these initial promising results, however, more research is needed to determine the optimal settings and timing of initiation of high-frequency ventilation, as well as its role in the evolving armamentarium of lung-protective ventilation strategies.

ANNOTATED REFERENCES

Courtney SE, Durand DJ, Asselin JM, et al: High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. N Engl J Med 2002;347:643-652.

This large, multicenter trial (along with that of Johnson and colleagues) represents the most recent evaluation of high-frequency oscillatory ventilation in neonates at high risk for bronchopulmonary dysplasia. These authors found a small but significant clinical benefit from high-frequency oscillatory ventilation when it was applied under rigorously controlled conditions.

Derdak S, Mehta S, Stewart TE, et al: High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: A randomized, controlled trial. Am J Respir Crit Care Med 2002;166:801-808.

This trial represents the first prospective, randomized clinical trial comparing conventional mechanical ventilation and high-frequency oscillatory ventilation early in the course of ARDS. It found high-frequency oscillatory ventilation to be effective and safe, with a trend toward decreased mortality in patients randomized to receive it. Of note, pre-enrollment conventional ventilation for more than 5 days was predictive of mortality.

Imai Y, Nakagawa S, Ito Y, et al: Comparison of lung protection strategies using conventional and high-frequency oscillatory ventilation. J Appl Physiol 2001;91:1836-1844.

This laboratory study suggested the superiority of high-frequency oscillatory ventilation over conventional mechanical ventilation in an animal model. The authors found decreased systemic and local inflammatory mediators and histologic lung damage in the animals ventilated with high-frequency oscillatory ventilation.

Johnson AH, Peacock JL, Greenough A, et al: High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity. N Engl J Med 2002;347:633-642.

In contrast to the study by Courtney and colleagues, these authors found no advantage to high-frequency oscillatory ventilation over conventional mechanical ventilation.

Mehta S, Lapinsky SE, Hallett DC, et al: Prospective trial of high-frequency oscillation in adults with acute respiratory distress syndrome. Crit Care Med 2001;29:1360-1369.

This prospective clinical study established the safety and efficacy of high-frequency oscillatory ventilation as salvage therapy in adults with ARDS failing conventional mechanical ventilation. High-frequency oscillatory ventilation was safe and effective at improving oxygenation, and prolonged conventional ventilation before switching to the high-frequency mode was predictive of death, suggesting the need for further investigation into the timing of high-frequency ventilation.

Rotta AT, Gunnarsson B, Fuhrman BP, et al: Comparison of lung protective ventilation strategies in a rabbit model of acute lung injury. Crit Care Med 2001;29:2176-2184.

Like the report by Imai and colleagues, this laboratory study suggested the superiority of high-frequency oscillatory ventilation over conventional mechanical ventilation in an animal model.

Chapter 70
EXTRACORPOREAL LIFE SUPPORT

Stephen A. Rowe • Robert H. Bartlett

KEY POINTS

1. **Extracorporeal life support should be instituted early**, before significant ventilator trauma.
2. **The main complication of extracorporeal life support is hemorrhage.**
3. **Venovenous support is the primary mode for respiratory failure.** Venoarterial bypass provides full support for both respiratory and cardiovascular failure.
4. **Extracorporeal life support is not active treatment but allows time** for the native organs to regain function.

Extracorporeal life support, also known as extracorporeal membrane oxygenation, is the use of a cardiopulmonary bypass device to prolong the life of a critically ill patient who has inadequate pulmonary or cardiac function. Extracorporeal life support was first used successfully in 1972 in a patient who developed acute respiratory distress syndrome (ARDS) after a motorcycle crash.[1] The basis for extracorporeal life support was the development of cardiopulmonary bypass devices for open heart surgery. The original devices used a direct blood-gas interface and were used for only a few hours[2]; however, the development of membrane blood-gas interfaces by Kolobow and others initiated the laboratory study and clinical application of prolonged extracorporeal circulation.[3-5] In 1976, the first successful neonatal extracorporeal life support was reported.[6] Currently, extracorporeal life support is used for pulmonary and cardiac failure in all age groups, with an overall survival rate ranging from 30% in cardiac arrest to 90% in neonatal respiratory failure.

INDICATIONS

Extracorporeal life support is used for patients with severe (predicted mortality 80%) but potentially reversible cardiopulmonary failure. It is invasive and expensive and requires anticoagulation; therefore, it is reserved for patients who have failed simpler treatment regimens. Extracorporeal life support provides rest from high ventilator settings, high inspired oxygen fractions (FIO_2), and high doses of pressors. It is best used early in the treatment of cardiopulmonary failure rather than as a "rescue" treatment.[7]

Neonates must be at least 32 weeks' gestation and have an oxygenation index greater than 25. The presence of intraventricular hemorrhage or coagulopathy precludes extracorporeal life support. Major genetic abnormalities are also a relative contraindication. Common neonatal conditions for which extracorporeal life support is used are meconium aspiration syndrome, persistent pulmonary hypertension, congenital diaphragmatic hernia, pneumonia, and respiratory distress syndrome.[8,9]

Adult and pediatric patients have similar criteria. High mortality risk in adults and children with hypoxic respiratory failure is identified by a partial pressure of arterial oxygen (PaO_2)/FIO_2 ratio less than 100, compliance less than 0.5 mL/cm H_2O per kilogram, or shunt fraction greater than 30% in the setting of maximal medical therapy. High mortality risk in cardiac failure is identified by low cardiac index despite optimal pharmacologic support, increasing lactic acidosis, failure to wean from cardiopulmonary bypass postoperatively, and persistent hypotension.[10-14] Absolute contraindications are incurable disease, poor neurologic status, and active bleeding. Relative contraindications are advanced age and duration of positive-pressure ventilation. Pulmonary fibrosis increases with time on the ventilator and is usually irreversible when pulmonary artery pressures are two thirds of systolic pressures or if the patient has been on high ventilator settings for more than 7 days. Common diagnoses leading to extracorporeal life support are pneumonia; ARDS following surgery, trauma, or sepsis; status asthmaticus; aspiration; and pulmonary embolism.[15-17] Sepsis and septic shock were previously considered to be contraindications to extracorporeal life support; however, septic patients are now commonly treated successfully.[18,19]

Specific indications and contraindications for neonates and for children and adults are summarized in Tables 70-1 and 70-2, respectively.

TECHNIQUE

Extracorporeal life support involves the continuous drainage of venous blood to a pump and membrane oxygenator and re-infusion to a major vein or artery. Venoarterial bypass was originally the standard method of access but is now reserved for patients who require hemodynamic support or neonates whose veins are too small to accommodate an adequate double-lumen cannula. Cannulation and management techniques are described in detail elsewhere.[20]

Venoarterial bypass is performed by accessing the right atrium or inferior vena cava for venous drainage and infusion into the carotid or femoral artery. Access to all vessels except the carotid can usually be performed by percutaneous Seldinger technique.[21,22] Because arterial flow is antegrade and directed to the proximal aorta, there is hypothetically

TABLE 70–1. CRITERIA FOR NEONATAL EXTRACORPOREAL LIFE SUPPORT

Age >32 wk
Weight >1.5 kg
No intracranial hemorrhage (>grade 1); recent head ultrasonography needed
No coagulopathy
Ventilation <10-14 days
AaDO >605-620 for not more than 4-12 h
$AaDO_2 = 713$
Oxygenation index >25

TABLE 70–2. CRITERIA FOR ADULT AND PEDIATRIC EXTRACORPOREAL LIFE SUPPORT

Indications	Contraindications
Poor gas exchange	>7 days on high ventilator settings (adult) >14 days on high ventilator settings (pediatric)
Compliance <0.5 mL/cm H_2O/kg	Incurable disease (e.g., malignancy)
PaO_2/FiO_2 <100	Age >70 yr
Shunt fraction >30%	Pulmonary artery pressures >(2/3) systolic pressures
	Poor neurologic status
	Active bleeding or unresolved surgical issues

better perfusion to the brain, coronary vessels, and viscera. However, the incidence of cerebrovascular accident is as high as 15%. In children weighing less than 25 kg, cannulation through the neck is the only option for venoarterial bypass, because the femoral artery cannot be adequately cannulated. The advantage of cannulating the femoral vessels is that it can be performed completely percutaneously. The disadvantages of femoral artery cannulation are retrograde flow and the possibility of rendering the cannulated leg ischemic. However, the ischemia can be treated by placing a third cannula in the ipsilateral leg and "Y-ing" it to the arterial side of the extracorporeal life support circuit. Figure 70-1 displays a typical venoarterial extracorporeal life support setup.

Venovenous access is the most common route of extracorporeal support for respiratory failure.[23] In adults, the right atrium and inferior vena cava are cannulated via the internal jugular and femoral veins. In neonates and small children, double-lumen cannulas can be inserted into the internal jugular vein. Venovenous support has several advantages: percutaneous techniques can be used, the risk of cerebrovascular accident is greatly reduced, normal hemodynamics are maintained, and there is no risk of ischemia to the lower extremity. A typical venovenous setup is displayed in Figure 70-2.

Once bypass is initiated, flow is begun at around 50 to 60 mL/kg per minute. The extracorporeal life support circuit provides the majority of support, and the ventilator settings are minimized to decrease pulmonary trauma.[24] Typical ventilator settings with extracorporeal life support are pressure of 30/10, frequency of 5, and FiO_2 of 0.40. Systemic heparinization is maintained and titrated to activated clotting time, which should range from 160 to 220 seconds. Extracorporeal life support provides full life support in the absence of cardiac or pulmonary function, but it is not active treatment. It affords time to treat the primary condition without reliance on native heart or lung function. Patients with respiratory failure undergo diuresis or hemofiltration to their dry weights and are benefited by intermittent prone positioning. Any underlying cause of ARDS, such as pneumonia or sepsis, is treated. The ventilator is gradually resumed until native lung function is adequate to wean the patient off of extracorporeal life support. Patients with cardiac failure may

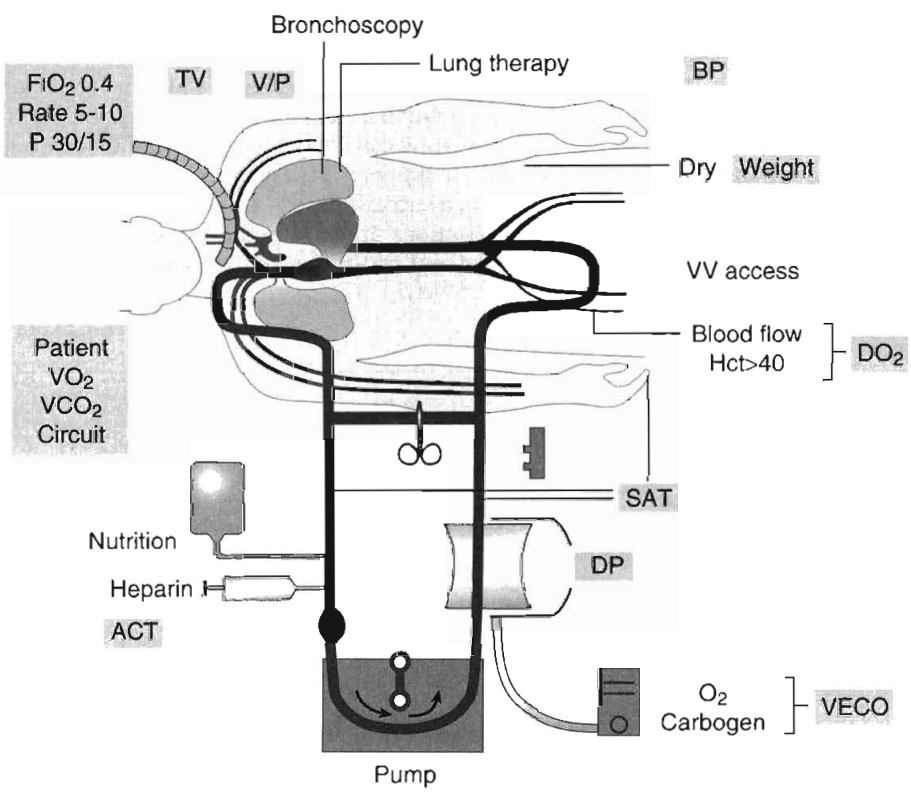

FIGURE 70–1. Typical venoarterial bypass setup. ACT, activated clotting time; BP, blood pressure; Hct, hematocrit.

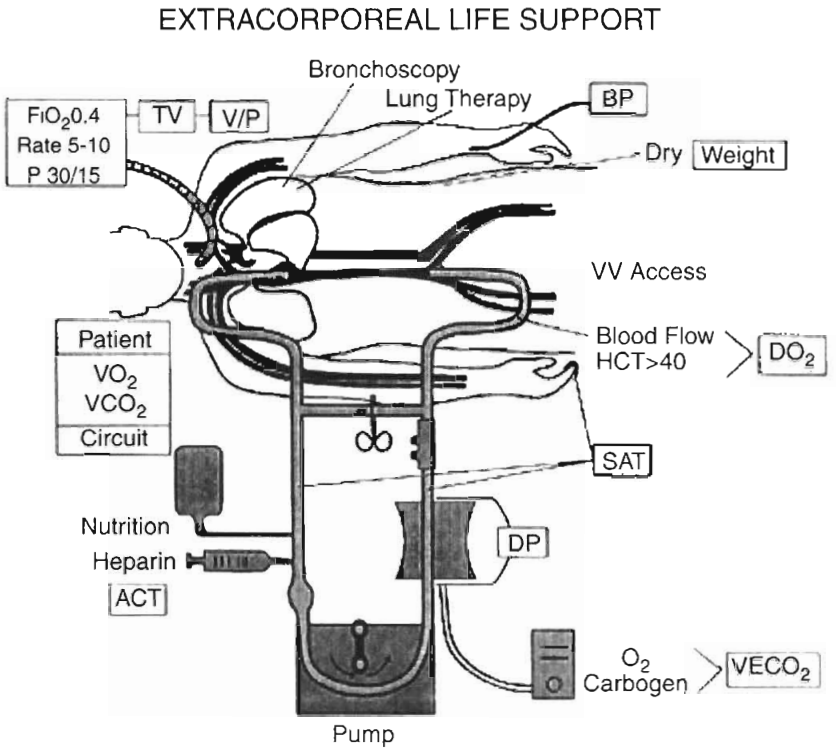

FIGURE 70–2. Typical venovenous bypass setup. ACT, activated clotting time; BP, blood pressure; Hct, hematocrit.

improve with time, but some cardiac patients require ventricular assist devices and transplant evaluations.

Because of the complexity of the extracorporeal life support circuit, a bedside specialist monitors the equipment at all times. In addition to titrating the heparin, the specialist maintains the circuit and repairs any malfunction, oxygenator failure, or tube rupture. The patient's dependence on the extracorporeal life support circuit dictates that these repairs occur within a few minutes. In experienced centers, extracorporeal life support can be maintained for weeks without major complications.

OUTCOME

Extracorporeal life support is a viable and effective treatment. Patients who are placed on extracorporeal life support typically have a 20% predicted survival rate without bypass. In the 1970s, trials failed to show improved survival with extracorporeal life support. However, since that time, there have been improvements in technology, technique, and understanding of the involved pathophysiology. A randomized, controlled trial is currently under way in the United Kingdom to assess the outcome with current extracorporeal life support protocols.[25]

The Extracorporeal Life Support Organization maintains a registry of patients treated with extracorporeal life support. As of July 2003, 27,219 patients had undergone extracorporeal life support, with 76% surviving to decannulation and 67% surviving to discharge. Neonates cannulated for respiratory failure have by far the best success rate, with 77% surviving to discharge. A summary of survival outcomes is listed in Table 70-3.[26] Table 70-4 summarizes several major studies on survival of ARDS with and without extracorporeal life support.[11,24,27-39]

Given the complexity of extracorporeal life support, it should be no surprise that the complication rate is as high as 24%.[26] The most common complication is bleeding, which is reported in 15% to 20% of patients. Premature infants are at risk for intracranial bleeding; adults are

TABLE 70–3. SURVIVAL OUTCOME OF PATIENTS ENTERED IN THE EXTRACORPOREAL LIFE SUPPORT ORGANIZATION REGISTRY AS OF JULY 2003

	Group	Total	Number Surviving to Decannulation (%)	Number Surviving to Discharge (%)
Neonatal	Respiratory	18,283	15,644 (86)	14,156 (77)
	Cardiac	1,965	1,098 (56)	733 (37)
	ECPR	107	66 (62)	42 (39)
Pediatric	Respiratory	2,548	1,620 (64)	1,410 (55)
	Cardiac	2,684	1,505 (56)	1,130 (42)
	ECPR	218	105 (48)	85 (39)
Adult	Respiratory	891	518 (58)	462 (52)
	Cardiac	419	193 (46)	138 (33)
	ECPR	104	49 (47)	34 (33)

TABLE 70–4. SURVIVAL IN ACUTE RESPIRATORY DISTRESS SYNDROME WITH AND WITHOUT EXTRACORPOREAL LIFE SUPPORT

Author	Year	Treatment	Number of Patients (% Survived)			
			All ARDS	*Severe ARDS*	*Severe ARDS with ECLS*	*ECLS Only*
Zapol	1991	General	635 (58)	149 (15)	—	—
Artigas	1991	General	583 (41)	403 (31)	—	—
Sloane	1992	General	153 (46)	—	—	—
Vasilyev	1995	General	1426 (56)	311 (18)	—	—
Weg	1998	Surfactant	725 (55)	—	—	—
Luhr	1999	General	221 (58)	—	—	—
Zapol	1979	NIH-ECMO	686 (34)	48 (8)	—	42 (10)
Gattinoni	1986	ECCOR	—	—	—	43 (49)
Morris	1994	Randomized	—	19 (42)	—	21 (33)
Brunet	1993	ECCOR	—	—	—	23 (50)
Macha	1996	ECLS	—	—	—	33 (39)
Kolla	1997	ECLS	—	—	—	100 (54)
Peek	1997	ECLS	—	—	—	50 (66)
Lewandowski	1997	Algorithm & ECLS	—	—	122 (75)	49 (55)
Rich	1998	Algorithm & ECLS	—	—	141 (62)	100 (54)
Ullrich	1999	Algorithm & ECLS	84 (80)	—	—	13 (62)

ARDS, acute respiratory distress syndrome; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; NIH, National Institutes of Health.

susceptible to gastrointestinal hemorrhage. Bleeding on extracorporeal life support is managed by decreasing the activated clotting time to 160 to 180 seconds and correcting the platelet count to 150,000.[39] Mechanical complications include oxygenator failure, clotting, and rupture of the tubing. Mechanical complications are addressed immediately by the bedside specialist and are rarely fatal.

TRANSPORT ON EXTRACORPOREAL LIFE SUPPORT

In some cases, patients at referring facilities are too unstable to be transported on conventional ventilation. The University of Michigan recently reported 100 patients transported on extracorporeal life support. Overall survival to discharge was 66%, and the complication rate during transport was 17%, with no deaths in transit.[40,41] Currently, the technology exists to transport any patient by ground. Technical issues preclude the transport of patients weighing less than 10 kg by air. Although it is possible to transport patients on extracorporeal life support, it is preferable to refer severe cardiac or pulmonary failure patients to an extracorporeal life support center on conventional support.

SUMMARY

Extracorporeal life support provides a means of keeping patients alive following cardiopulmonary collapse that is refractory to conventional means of support. Additionally, these patients are afforded time for the treatment and improvement of native cardiopulmonary function while avoiding the detrimental effects of high ventilator settings. The last decade has seen improvements in extracorporeal life support technology and refinements in the techniques used to manage patients with severe cardiopulmonary failure. In children and neonates, the utility of extracorporeal life support has been proved by prospective, randomized trials. In adults, retrospective data suggest that survival might be increased with extracorporeal life support.

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This is the first description of the use of extracorporeal life support in neonatal patients.

Bartlett RH, Roloff DW, Custer JR, et al: Extracorporeal life support: The University of Michigan experience. JAMA 2000;283:904-908.

The largest single-center report of extracorporeal life support.

Hill JD, O'Brien TG, Murray JJ, et al: Extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome): Use of the Bramson membrane lung. N Engl J Med 1972; 286:629-634.

This is the first description of successful long-term use of extracorporeal life support.

Kolla S, et al: Extracorporeal life support for 100 adult patients with severe respiratory failure. Ann Surg 1997;226:544-564; discussion 565-566.

In addition to summarizing survival data in a large series of patients, this paper provides details on criteria for the use of extracorporeal life support.

Rich PB, Awad SS, Kolla S, et al: An approach to the treatment of severe adult respiratory failure. J Crit Care 1998;13:26-36.

Provides guidelines for the development of clinical protocols to treat patients with severe ARDS who are on extracorporeal life support.

Chapter 71
ADJUNCTIVE RESPIRATORY THERAPY

Sanjay Manocha • Keith R. Walley

KEY POINTS

1. Inability to effectively clear secretions is common in critically ill patients, increasing the risk of aspiration, atelectasis, and pneumonia.
2. Chest physiotherapy and positional therapy should be considered in all critically ill patients.
3. Other adjunctive forms of respiratory therapy should be considered on an individual basis based on the underlying clinical condition.
4. Aerosolization of medications is an effective way of delivering medications directly to the lungs.
5. Metered-dose inhalers (MDIs) are preferred over nebulization for the delivery of bronchodilators in both the spontaneously breathing and mechanically ventilated patient.
6. Inhaled nitric oxide can be safely administered in the critically ill patient with proper monitoring.
7. Inhaled nitric oxide is associated with improved pulmonary and cardiac physiologic parameters when administered in a variety of clinical conditions encountered in the ICU.

Most critically ill patients are unable to effectively clear secretions that accumulate in the central and peripheral airways. This can be due to factors such as increased secretion production, impaired cough reflex, weakness, and pain. The presence of an endotracheal tube prevents closure of the glottis to generate the high expiratory pressures needed for an effective cough, thereby promoting the retention of secretions. In addition, in critically ill patients, cilia in the pulmonary tree are impaired in function and reduced in number.[1,2] This leads to an increased risk of aspiration, atelectasis, and pneumonia, which is detrimental in the critically ill patient.

Adjunctive respiratory therapy addresses many of these concerns to prevent and treat respiratory complications that are encountered in the critically ill patient. As highlighted in Table 71-1, they range from simple measures such as proper body positioning and suctioning to more complex interventions such as chest physiotherapy, bronchoscopy, and use of aerosolized/inhaled medications that act directly on the pulmonary system.

METHODS TO IMPROVE PULMONARY MUCOCILIARY CLEARANCE

PERCUSSION

Percussion of the chest can aid in secretion clearance. It is performed by clapping cupped hands over regions of the thorax that are affected in a rhythmic fashion or using mechanical devices that mimic the same action. The energy of the force generated by the cupped hands is transmitted through the thorax to dislodge secretions. When used in conjunction with postural drainage to maximize secretion movement, this is an effective method to mobilize secretions from the pulmonary tract. It is a technique often used in the daily management of cystic fibrosis patients[3] and those with severe bronchiectasis.

HIGH-FREQUENCY CHEST COMPRESSION

High-frequency chest compression (HFCC) relies on rapid pressure changes to the respiratory system during expiration to enhance movement of mucus in the peripheral airways to the central airways for clearance. This method employs a vest worn by the patient that is attached to an air-pulse generator. Small volumes of gas are introduced into the vest at a rapid rate ranging from 5 to 25 Hz producing pressures up to 50 cm H_2O. This technique is mainly used in cystic fibrosis patients and is equivalent to conventional chest physiotherapy techniques of percussion and postural drainage.[4-6] One study examined the use of HFCC in nine long-term mechanically ventilated patients.[7] In this observational study, the HFCC was compared with percussion and postural drainage. No difference was seen in the amount of sputum production, oxygen saturation, or patient comfort between the two methods. In this small study, HFCC was determined to be safe and believed to save staff time. It is difficult to apply this technique to most critically ill patients because the size of the vest covering the thorax may prevent adequate monitoring.

MANUAL HYPERINFLATION

Manual hyperinflation with a manual inflation bag using high tidal volumes involves disconnecting the patient from the ventilator. Typically, the lungs are inflated slowly to one and one-half to two times the tidal volume or peak airway pressures of 40 cm H_2O as measured by a manometer. It is held at end inspiration with an inspiratory pause to allow for filling of alveoli with slow time constants. This is followed by a quick release to allow for rapid expiration. The goal of

TABLE 71–1. ADJUNCTIVE RESPIRATORY THERAPIES

Methods to Improve Pulmonary Mucociliary Clearance
Chest physiotherapy
Percussion
Postural drainage
Chest vibration
Suctioning
Oropharyngeal suctioning
Nasopharyngeal suctioning
Endotracheal suctioning
Continuous lateral rotation
Positive expiratory pressure devices
Forced expiration
Closed chest oscillation
Bronchoscopy
Manual hyperinflation
Bronchodilators
Mucoactive agents
Methods to Improve Lung Expansion
Deep breathing
Incentive spirometry
Intermittent positive ventilation
Optimum body position
Methods to Improve Oxygenation and Ventilation
Inhaled vasodilators
Nitric oxide
Prostaglandins
Helium-oxygen (heliox)

manual hyperinflation is to recruit atelectatic lung regions to improve oxygenation and improve clearance of secretions. Similar to recruitment maneuvers described with mechanical ventilators, manual hyperinflation only leads to transient improvements in oxygenation without any long-term clinically significant improvement on outcomes.[8-11] It also has the disadvantage of requiring a ventilator disconnect, and this method can be mimicked by a mechanical ventilator.

Contraindications include hemodynamic compromise and high intracranial pressure. There is also a risk of barotrauma because of preferential inflation of open lung regions that are highly compliant compared with collapsed regions.

POSITIONING AND MOBILIZATION

Mobilization of patients in the ICU either through active or passive limb exercises may improve overall patient well-being and in the long term may lead to better patient outcomes. Positioning also plays an important role. Position of the patient with the head of the bed elevated at least 30 degrees significantly reduces the risk of aspiration and ventilator-associated pneumonia.[12] Upright positioning of patients in whom there is no contraindication improves lung volumes and therefore gas exchange and work of breathing, especially in those in whom the supine or semi-recumbent position leads to an increased work of breathing. Positioning of selected individuals with unilateral lung disease on their side with the affected side up can lead to improved ventilation-perfusion ($\dot{V}/\dot{Q}$) matching (by gravitational increased perfusion to the dependent "good" side).[13,14] If atelectasis secondary to retained secretions is the cause, having the affected side up leads to postural drainage.

Postural drainage involves positioning the body to allow gravity to assist in the movement of secretions. Postural drainage is indicated in patients with a sputum production of more than 25 to 30 mL/day and in those who have difficulty clearing their secretions.[15] In cystic fibrosis, postural drainage with percussion is an effective method to clear pulmonary secretions and is associated with improved lung function.[16,17]

TRACHEAL SUCTION

Used in conjunction with other techniques to mobilize secretions from the peripheral airways to the central airways, suctioning is an effective way of removing secretions to improve bronchial hygiene. It can be performed using open methods where the patient is disconnected from the ventilator and a disposable suction catheter is placed. The closed system involves a closed circuit with the suction catheter placed in a protective sheath and directly connected to the ventilator circuit. No disconnect is required, and the risk of environmental cross contamination is less. Routine changes of in-line suction catheters are not required, and the procedure is cost-effective.[18,19] But, overall, the risk of nosocomial pneumonia between open and closed systems is not different.[20,21]

Because of the anatomic arrangement of the large central airways, the suction catheter most often enters the right mainstem bronchus compared with the left mainstem bronchus. Specially designed curved-tipped "left-sided" suction catheters increase the likelihood of suctioning from the left mainstem bronchus.

Nasotracheal suctioning has fallen out of favor over direct tracheal suctioning and should only be considered in patients who are able to protect their airway and used in conjunction with assisted coughs and other forms of chest physiotherapy.

Complications with suctioning include hypoxemia, especially in the setting of a ventilator disconnect, increased intracranial pressure with vigorous stimulation of the airways, mechanical trauma to the trachea, and bacterial contamination. All patients should be preoxygenated with 100% oxygen for 1 to 2 minutes before suctioning. To reduce the risk of agitation, the patient should be informed before tracheal suctioning is performed. The suctioning should be limited to 15 to 20 seconds. The suction port on the catheter should be opened and closed intermittently and not closed for more than 5 seconds at a time.

CONTINUOUS ROTATION THERAPY

Continuous rotational or kinetic therapy extends the practice of regular 2 hourly repositioning of patients from one side to the other by placing the patient on a bed that moves to pre-programmed angles on a more frequent basis or through the use of air mattresses that deflate alternatively from side to side to provide the continuous postural position changes. Most studies on various patient populations demonstrate a lower incidence of nosocomial pneumonia or atelectasis but no overall improvement in other clinically significant outcomes such as duration of mechanical ventilation, length of stay in the ICU, or mortality.[22-28]

COUGHING

Assisted coughing is often required in spontaneously breathing patients because of an ineffective cough for a variety of reasons, as previously highlighted. Techniques include "huffing" in the setting of an open glottis where in expiration the

patient forcibly exhales quickly several times. Other maneuvers include abdominal or thoracic compression on expiration to generate high intrathoracic pressures mimicking a cough.

POSITIVE EXPIRATORY PRESSURE THERAPY

Positive expiratory pressure therapy (PEP) involves the use of a facemask or mouthpiece that provides a resistance to airflow of 10 to 20 cm H_2O on expiration. After repeating this maneuver a number of times, mucus in the peripheral airways is mobilized and moved toward the larger airways to be coughed or expelled with other techniques. Its use in critically ill patients who are spontaneously breathing is likely limited by the coordination required for slow expirations. Other methods may be easier to perform in this patient population to aid in secretion clearance.

BRONCHOSCOPY

Fiberoptic bronchoscopy has the advantage of providing direct visualization of the airways and permits suctioning of specific segments where secretions may be retained, causing problems such as atelectasis. Bronchoscopy can be considered as an adjunctive therapy for the treatment of atelectasis or removal of secretions. As highlighted in one review,[29] bronchoscopy is a moderately effective technique for the treatment of atelectasis in the critically ill patient, with success rates ranging from 19% to 89% depending on the extent of the atelectasis (lobar atelectasis responds better than subsegmental atelectasis). But when compared with aggressive multimodal chest physiotherapy, in the only randomized trial, no difference in the rate of resolution was seen between the two methods.[30] Being an invasive procedure, bronchoscopy is not without risks, including complications associated with sedation required for the procedure, transient increases in ICP, hypoxemia, and hemodynamic consequences/arrhythmias. Therefore, it cannot be recommended as first-line therapy except in certain situations such as extensive unilateral atelectasis leading to significant difficulties in oxygenating or ventilating that have not resolved with other methods such as suctioning.

CHEST PHYSIOTHERAPY

Chest physiotherapy is a multimodal therapy with the goals of improving pulmonary function (gas exchange, improved lung compliance, and improved pulmonary mucus clearance). Techniques include percussive therapies (manual or mechanical chest percussion), postural drainage, chest vibration, manual hyperinflation, mobilization, suctioning, and rotational therapy. Overall, chest physiotherapy provides transient improvements in oxygenation and lung compliance likely secondary to airway clearance and recruitment of atelectatic regions. Chest physiotherapy may, in specific situations, improve outcome and clinical course such as in the prevention of ventilator-associated pneumonia[31] or acute lobar atelectasis.[32]

AEROSOL THERAPIES

AEROSOLIZATION

The aerosolization of medications is an effective method for drug delivery directly to lungs. The two most common methods of delivery are via nebulization or via metered-dose inhalers (MDIs). The theoretical advantage of this form of therapy includes direct delivery and activity at the site of pathology and the ability to deliver high concentrations with minimal systemic absorption and toxicity. The most common aerosolized therapy is the administration of bronchodilators. Other medications that can be administered directly to the lungs include corticosteroids, antibiotics, antifungal agents, surfactant, mucolytic agents, and saline.

Nebulization is the process of using a high flow of gas (usually 6 to 8 L/min) to produce small respirable particles of the liquid medium containing the medication of interest. The most common nebulizer is the pneumatic (jet) nebulizer. In the spontaneously breathing patient, approximately 50% of the nebulized liquid is in the respirable range of a mass median aerodynamic diameter (MMAD) of 1 to 5 μm, with approximately 10% reaching the lower respiratory tract/small airways. In mechanically ventilated patients, 1% to 15% is delivered to the lower respiratory tract. Ultrasonic nebulization uses high-frequency ultrasonic waves on the surface of the liquid medium to generate respirable particles. Its use is limited by the expense of the equipment involved.

MDIs are pressurized canisters with the drug suspended in a mix of propellants, preservatives, and surfactants. On activation, particles ranging from 1 to 2 μm are produced. The MDI in conjunction with a chamber/spacer device significantly increases drug delivery in both spontaneously breathing patients and when attached to the ventilator circuit either directly to the endotracheal tube or as part of an in-line device in the inspiratory limb of the Y-piece.

Factors that influence the efficacy of aerosol delivery in the mechanically ventilated patient include[33]:

1. *Position of administration in the circuit:* the MDI should be closer to the endotracheal tube at the Y-piece with a chamber, compared with a pneumatic nebulizer, which should be at least 30 cm from the Y-piece.
2. *Humidification:* this can decrease aerosol delivery to the respiratory tract because of greater deposition in the ventilator circuit. Higher doses may be required to achieve the desired effect.
3. *Timing of delivery:* the aerosol should be delivered during the inspiratory phase to maximize drug delivery.
4. *Flow rates:* slower inspiratory flow rates (and therefore longer inspiratory time) increase delivery of nebulized medications. A decelerating flow pattern can also increase delivery to the lower airways.
5. *Tidal volumes:* larger tidal volumes greater than 500 mL ensure optimal delivery.
6. *Endotracheal tube size:* tube sizes less than 7.0 mm reduce delivery.
7. *Density of inhaled gas:* low-density gases such as helium-oxygen mixtures increase deposition to the lower airways by increasing laminar flow and producing smaller respirable particle size.

BRONCHODILATORS

Bronchodilators are the most frequently administered aerosolized therapy in the critically ill patient. Inhaled $beta_2$ agonists such as albuterol or fenoterol are generally well tolerated in the critically ill patient. Adverse effects such as arrhythmias and hypokalemia can occur in those receiving

excessive doses in which significant systemic absorption is likely. Other bronchodilators such as ipratropium bromide are also effective, especially when used in conjunction with a $beta_2$ agonist. Bronchodilators administered via MDI are equally as effective as a nebulizer in spontaneously breathing patients.[33] In mechanically ventilated patients, the use of nebulization is either equally as good as[34] or less effective[35,36] than an MDI with a spacer. MDI administration has the advantage of easier use without the risk of bacterial contamination and need for adjustment of flow rates.[33]

ANTIBIOTICS

Aerosolization of antibiotics as a form of topical treatment for pulmonary infections has been studied for over 20 years. Theoretical advantages of aerosolized antibiotics include direct therapy at the site of infection at higher concentrations with a lower risk of systemic absorption and side effects. In chronic pulmonary infective states such as cystic fibrosis and severe bronchiectasis,[37-39] inhaled aerosolized antibiotics have a role in reducing bacterial concentration in the sputum but only provide a long-term clinical benefit in cystic fibrosis.[37] In the acute infective state with an exacerbation of the disease, they have no additional benefit to parenteral antibiotics.[40,41]

In the intubated or tracheostomy patient, colonization of the airway frequently occurs with a significant increase in the risk for nosocomial pneumonia. In an observational study of six chronically ventilated patients, aerosolized aminoglycosides (tobramycin or amikacin) eradicated the colonizing bacteria 67% of the time with a significant reduction in inflammatory markers within the sputum.[42] As a preventive measure for ventilator-associated pneumonia, one small randomized trial in a cohort of trauma patients showed a reduction in the frequency of pneumonia with aerosolized ceftazidime.[43] But as an adjuvant for treatment of ventilator-associated pneumonia, the instillation of tobramycin through the endotracheal tube, although eradicating the causative pathogen more frequently than did placebo, did not result in any clinically significant improvement in outcomes.[40] Concerns of bacterial resistance must be considered in any preventive form of therapy with antibiotics. Side effects reported in spontaneously breathing patients treated with inhaled tobramycin include increased cough, dyspnea, and chest pain.[38]

The role for aerosolized or instilled (via the endotracheal tube) antibiotics as an adjuvant for the prevention or treatment of pulmonary infections in the ICU remains to be defined with better clinical studies.

MUCOACTIVE AGENTS

In chronic inflammatory lung states (e.g., chronic obstructive pulmonary disease [COPD], cystic fibrosis, bronchiectasis, intubation/tracheostomy), overproduction of mucus and impaired clearance result in complications commonly encountered in critical care patients, such as airflow obstruction, atelectasis, and infection. The mucus is primarily composed of water, mucin glycoprotein, cellular debris, neutrophil-derived filamentous actin and DNA, and bacteria.[44] Mucoactive agents can help improve the clearance of mucus secretions.

Expectorant methods such as simple hydration and oral expectorant medications such as guaifenesin or bromhexine that act via the vagal-mediated increase in airway secretion to decrease mucus viscosity have not been shown to be effective methods of clearance of secretions.[45,46] Oral iodine preparations (e.g., saturated solution of potassium iodine), although described as a mucoactive agent, similarly are not effective and may be associated with significant side effects such as hypothyroidism or hyperkalemia.[44]

Mucolytic agents reduce the viscosity by breaking down the mucin glycoprotein network or free DNA strands, thereby improving mucus rheology to improve clearance. Aerosolized *N*-acetylcysteine (NAC) breaks down the disulfide bonds of the mucin glycoprotein network and is associated with improved mucus clearance. However, because of the increased risk of bronchospasm, its use is limited, but it may be used in conjunction with an inhaled bronchodilator.[44] Free DNA can significantly increase the viscosity of mucus and therefore impede clearance from the airways. Recombinant human DNase (rhDNase, dornase alfa) improves pulmonary function in the chronic management of cystic fibrosis patients but without any significant effect in acute exacerbations of cystic fibrosis.[47,48] In non–cystic fibrosis bronchiectasis, rhDNase is not effective and may potentially be harmful.[49]

RACEMIC EPINEPHRINE

Racemic epinephrine has been used as a therapy for acute upper airway obstruction secondary to inflammation, corticosteroids, and surfactant.

METHODS TO IMPROVE LUNG EXPANSION

Atelectasis is a common complication encountered in the critically ill patient. This is often secondary to prolonged supine body position and retained secretions obstructing airways. Lung expansion techniques mimic normal sigh maneuvers to help reverse and prevent atelectasis. These techniques are often used in postoperative patients at high risk for pulmonary complications such as those undergoing thoracic and upper abdominal surgery and patients with neuromuscular or chest wall disorders.

Deep breathing and incentive spirometry involve coached inspiratory maneuvers to voluntarily increase lung volumes to greater than the vital capacity of the patient. It requires an awake, cooperative patient who is able to tolerate the maneuver. The only advantage of using an incentive spirometer is that it provides visual feedback and a reminder to the patient to continue these maneuvers. Both incentive spirometry and deep breathing are equally effective in reducing postoperative pulmonary complications compared with no forms of chest physiotherapy.[50]

Intermittent positive-pressure breathing is a method to improve lung expansion that has fallen out of favor as a preventive measure in postoperative patients because of the expense, lack of difference in outcomes compared with deep breathing or incentive spirometry, and complications such as abdominal distention.[50,51]

METHODS TO IMPROVE OXYGENATION AND VENTILATION

NITRIC OXIDE

The effects of nitric oxide (NO) have been known for over 20 years. Since the initial discovery of NO as the "endothelial

derived relaxing factor," it has grown to a potential therapeutic agent in the care of the critically ill patient.

Nitric oxide was first described as a vascular-derived relaxing factor that caused vasodilation via vascular smooth muscle relaxation. It is a highly lipid-soluble gas that allows for rapid diffusion through the alveoli-blood barrier into the pulmonary circulation and smooth muscle cells of the vasculature. The main action of NO is mediated by activating guanylate cyclase and increasing intracellular cyclic guanylate monophosphate, thereby causing smooth muscle and subsequent vasomotor relaxation.[52] The beneficial effects observed with inhaled NO are mediated primarily through this action on the pulmonary vascular smooth muscle. Pulmonary blood flow is specifically increased in well-ventilated regions, which improves matching of perfusion to ventilation. A reduction in pulmonary vascular resistance from arteriolar and venous vasodilation leads to a reduced intravascular pressure at the level of the capillaries with the potential benefit of a reduced fluid leak into the alveolus. Additional benefits observed include a reduction in platelet aggregation and neutrophil adhesion/sequestration in the lungs.[53-55] NO is rapidly inactivated by binding to the heme moiety of hemoglobin. Because of this short half-life, it does not enter the systemic circulation, making it an ideal selective pulmonary vasodilator.

The most common use of NO in the ICU is in the setting of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Numerous clinical observational studies in ALI/ARDS have demonstrated improvements in oxygenation by improving $\dot{V}/\dot{Q}$ mismatch as demonstrated by a 10% to 20% increase in PaO_2/FiO_2 ratio and a reduction on pulmonary vascular resistance and mean pulmonary arterial pressures by at least 5 to 8 mm Hg.[56]

These physiologic benefits from both animal and clinical observational studies suggest that clinical use will be beneficial. Randomized controlled trials of varying sample size and design had similar findings.[57-60] Typically, NO improved the PaO_2 and PaO_2/FiO_2 ratios acutely, but by 24 to 72 hours those in the control group achieved the same level of improvement. Similarly, although a reduction in mean pulmonary artery pressure was also observed in these trials with the use of NO, this did not translate into clinically meaningful outcomes of a decrease in mortality, less organ failure, or days free of mechanical ventilation. A trend toward a benefit was seen in a post-hoc analysis in one trial in the more severe forms of ARDS but further studies are needed.[57] Only 60% of ALI/ARDS patients respond to inhaled NO.[57] No clear predictors of who will respond to NO exist. Given that doses below 40 ppm were safe without any significant adverse effects, it can be considered a "rescue" therapy to possibly allow for more protective forms of ventilation with decreases in FiO_2 and mean airway pressures to maintain acceptable oxygenation or in situations in which secondary pulmonary hypertension leads to compromised hemodynamic function from right ventricular failure, especially in more severe cases.

Almitrine bismesylate enhances pulmonary vasoconstriction in areas of hypoxic vasoconstriction, thereby enhancing redistribution of blood flow from shunt areas to lung units with normal $\dot{V}/\dot{Q}$ ratios.[61,62] This therefore potentiates the response of gas exchange to inhaled NO. Almitrine is not readily available in North America and requires further study to define its role in combination with NO.

In addition to ALI/ARDS, other clinical conditions in which the use of NO may be beneficial are listed in Table 71-2.

TABLE 71–2. CLINICAL CONDITIONS IN WHICH INHALED NITRIC OXIDE MAY BE USED

Acute respiratory distress syndrome
Severe primary and secondary pulmonary hypertension[79]
Congenital cardiac syndromes[80,81]
Right ventricular failure in acute pulmonary embolism or after cardiac surgery[82-85]
Pulmonary ischemic-reperfusion injury after a heart-lung or lung transplant[63,85]
Sickle cell crisis[86,87]

Inhaled NO has been used after heart and lung transplants as a method to reduce right ventricular afterload in the setting of high pulmonary pressures.[63] In lung transplants, NO has been described to reduce the risk of ischemic-reperfusion injury, but this was not supported by one randomized clinical trial early in the course of lung transplants.[64] Further studies are necessary.

Inhaled NO is typically started at low doses ranging from 1 to 2 ppm and gradually increased until the desired effect is achieved. One method, as recommended from the U.K. Consensus conference on NO use, is to perform a dose response test starting at 20 ppm and reducing the doses to 10, 5, and 0 ppm to find the lowest effective dose.[65] A significant response should be considered as a 20% increase in the PaO_2/FiO_2 ratio or at least a 5 mm Hg decrease in the mean pulmonary artery pressure. The improvement in gas exchange is usually seen at lower doses. The dose required to reduce mean pulmonary artery pressure is usually higher. The usual dose ranges from 10 to 40 ppm. Doses greater than 80 ppm are associated with a higher risk for adverse effects. From the clinical trials, longer administration is generally safe with no evidence of the effect wearing off. However, the patient should be weaned from inhaled NO as soon as improvement occurs.

Adverse effects of NO include the formation of methemoglobin and the spontaneous oxidation to nitrogen dioxide (NO_2). NO_2 is known to be toxic to the respiratory system with maximal exposure limited to 5 ppm. Complications from NO_2 exposure include airway irritation and hyperreactivity with levels as low as 1.5 ppm, pulmonary edema, and pulmonary fibrosis when exposed to higher levels. Despite these adverse effects, the development of methemoglobinemia or other toxicities related to NO_2 during acute or prolonged NO inhalation has been unusual, especially when NO is administered at doses less than 80 ppm.[66]

To reduce the risk of exposure to NO_2, NO should be stored at concentrations no higher than 1000 ppm in a pure nitrogen environment and only exposed to oxygen at the time of administration. NO should be delivered into the ventilator circuit as close to the patient as possible. NO and NO_2 levels should be monitored closely on the inspiratory side of the Y-piece when using doses greater than 2 ppm. Care should be taken to prevent abrupt discontinuation of NO. Rebound pulmonary vasoconstriction can occur with sudden discontinuation leading to rapid worsening of $\dot{V}/\dot{Q}$ mismatch and pulmonary hypertension with significant hemodynamic collapse.[67] Backup supplies of NO and delivery systems should be readily available.

An absolute contraindication to NO therapy is methemoglobinemia reductase deficiency (congenital or acquired). Relative contraindications include bleeding diathesis (secondary to reports of alteration in platelet function and bleeding time with inhaled NO), intracranial hemorrhage,

and severe left ventricular failure (New York Heart Association grade III or IV).[65]

INHALED PROSTAGLANDINS

Inhaled prostaglandins I_2 (PGI_2) and E_1 (PGE_1) are alternative medications that have effects similar to inhaled nitric oxide with minimal systemic effects. For PGI_2, doses ranging from 1 to 25 ng/kg/min are favorably tolerated with similar reductions in pulmonary artery pressures and improvements in oxygenation as inhaled NO.[68,69] PGE_1 has the advantage of a more rapid degradation by the pulmonary endothelial cells, providing a selective advantage over PGI_2 at higher doses.[70] Additional studies are required to define a role for these agents, but they can be considered as alternatives for rescue therapy for similar conditions treated with inhaled NO.

HELIOX

Helium is an inert gas with a significantly lower density than room air (1.42 g/L for oxygen versus 0.17 g/L for helium). By substituting helium for nitrogen in a helium-oxygen mix (heliox), the degree of reduction in density of the gas is directly proportional to the fraction of the inspired helium concentration in the mix. The higher the concentration of helium, the lower the density from 100% oxygen. Heliox reduces the Reynolds number and thereby results in more laminar flow, therefore reducing airflow resistance, work of breathing, and dynamic hyperinflation associated with a high resistance. Clinical situations in which heliox may be used include conditions with high airflow resistance such as severe acute exacerbations of asthma or COPD, bronchiolitis, bronchopulmonary dysplasia, and extrathoracic or tracheal obstruction. It may also be used during noninvasive ventilation in patients with exacerbations of COPD to improve compliance, reduce work of breathing, and avoid intubation[71,72] and to improve aerosolized drug delivery.[73] In the management of moderate-to-severe exacerbations of asthma, routine use is not supported by two systematic reviews of the literature but can be considered as an adjuvant in severe cases.[74,75] In COPD exacerbation, researchers in one multicenter trial did not find any difference in intubation rate or length of stay in the ICU with the addition of heliox but there was an overall cost benefit from a shorter hospital length of stay.[76] Heliox is generally well tolerated without any significant adverse effects. Disadvantages of using heliox in critically ill patients include the cost of therapy and the high concentrations of helium required. Most studies utilize helium:oxygen mixes of 80:20 or 70:30 to achieve a therapeutic benefit. At higher concentrations of oxygen, the effect of helium is less and therefore is limited in use to those not requiring high FiO_2. When used in conjunction with nebulized medications, higher flows may be required to ensure adequate delivery of the medication, although this may be offset by the smaller particle size generated in a heliox mixture.[73,77] Ventilators also require recalibration for measured FiO_2, flows, and tidal volumes when using heliox.[78]

CONCLUSION

Pulmonary disease and complications are common in the critically ill patient, especially those undergoing mechanical ventilation. It is important for the clinician to recognize these potential complications and the many forms of adjunctive respiratory therapies available to prevent further morbidity. Simple therapies such as chest physiotherapy, suctioning, and positioning should be utilized in most patients, whereas more advanced procedures and therapies should be used on a selective basis based on the underlying clinical condition.

ANNOTATED REFERENCES

Dellinger RP, Zimmerman JL, Taylor RW, et al: Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: Results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. Crit Care Med 1998;26:15-23.

A multicentered, randomized, blinded, controlled trial of 177 patients within 72 hours of developing acute respiratory distress syndrome. In this patient population, inhaled nitric oxide was associated with a transient improvement in oxygenation and mean pulmonary artery pressures but this did not translate into differences in 28-day mortality or days alive and free of mechanical ventilation.

Jolliet P, Tassaux D, Roeseler J, et al: Helium-oxygen versus air-oxygen noninvasive pressure support in decompensated chronic obstructive disease: A prospective, multicenter study. Crit Care Med 2003;31:878-884.

In this well-conducted, randomized, multicentered study, the addition of heliox to noninvasive positive-pressure ventilation in patients with acute exacerbations of COPD did not demonstrate a beneficial effect with respect to intubation rate, ICU length of stay, or mortality. The use of heliox was associated with a significantly lower post-ICU hospital length of stay and hospital costs.

Kollef MH, Prentice D, Shapiro SD, et al. Mechanical ventilation with or without daily changes of in-line suction catheters. Am J Respir Crit Care Med 1997;156(2 pt 1):466-472.

A randomized trial comparing daily versus as-needed in-line suction catheter change. This study demonstrated that the rate of ventilator-associated pneumonia and hospital mortality was not different between the two groups and that an "as-needed" approach was highly cost-effective. This provides good evidence that routine changes of in-line suction catheters are not necessary.

Meade MO, Granton JT, Matte-Martyn A, et al: A randomized trial of inhaled nitric oxide to prevent ischemia-reperfusion injury after lung transplantation. Am J Respir Crit Care Med 2003;167:1483-1489.

A small randomized, placebo-controlled trial that did not demonstrate a protective effect of inhaled nitric oxide therapy on the risk of developing ischemia-reperfusion injury after a lung transplantation when given soon after reperfusion of the transplanted lung.

Ntoumenopoulos G, Presneill JJ, McElholum M, Cade JF: Chest physiotherapy for the prevention of ventilator-associated pneumonia. Intensive Care Med 2002;28:850-856.

A small prospective clinical trial examined the benefit of a common adjunctive respiratory therapy—chest physiotherapy—on a common clinical complication of mechanical ventilation—ventilator-associated pneumonia (VAP). In this study, routine, twice-daily chest physiotherapy was associated with a lower occurrence of VAP compared with standard therapy, supporting its role as a simple preventive measure for VAP.

Chapter 72

INDICATIONS FOR AND MANAGEMENT OF TRACHEOSTOMY

Bradley D. Freeman • Timothy G. Buchman

KEY POINTS

1. Patients requiring prolonged mechanical ventilation should undergo tracheostomy in an effort to facilitate ventilator weaning, diminish the incidence of infectious complications, promote oral hygiene and pulmonary toilet, enhance patient comfort, provide airway security, and, in selected patients, allow oral nutrition and speech.
2. The presence of a "difficult airway" in a patient requiring prolonged mechanical ventilation is an absolute indication for tracheostomy.
3. The optimal timing of tracheostomy for most patients remains debated. General guidelines for timing of tracheostomy are as follows. For patients in whom the need for ventilatory support is anticipated to be less than 10 days, translaryngeal intubation is preferred. If the need for ventilatory support is anticipated to exceed 21 days, a tracheostomy is preferred. When the anticipated need for mechanical ventilation is unclear, daily assessment is required to determine when conversion to tracheostomy is indicated.
4. For appropriately selected patients, there may be advantages of percutaneous dilational tracheostomy compared with conventional surgical tracheostomies. These include cost savings, a lower incidence of selected perioperative and postoperative complications, and ease of performance. Percutaneous dilational tracheostomy should not be used on an emergent basis.
5. A variety of tracheostomy tube designs are commercially available, including cuffed tracheostomy tubes, cuffless tracheostomy tubes, fenestrated tracheostomy tubes, and metal tracheostomy tubes. Intensivists should have a working knowledge of the indications and rationales for these standard tracheostomy tube designs.
6. Tracheostomy cuff pressures should be monitored on a regular basis to prevent cuff-related complications such as tracheomalacia and tracheal stenosis.
7. Before tracheostomy tube removal (or decannulation), the patient should have tolerated liberation from mechanical ventilation for at least 24 to 48 hours and should be able to breathe without difficulty with an occluded and deflated tracheostomy tube in place. Inability to do this may indicate the presence of tracheal stenosis. Such patients should undergo further evaluation before decannulation.
8. Intensivists should be able to recognize and manage complications associated with tracheostomy use. These include cuff leak, tracheostomy tube occlusion, tracheostomy tube dislodgment, and tracheoinnominate artery fistula formation.

Tracheostomy is one of the most commonly performed surgical procedures in critically ill patients requiring prolonged mechanical ventilation.[1] Although a large body of literature has accumulated in recent years regarding benefits, risks, and technical aspects of this procedure, little consensus exists as to what constitutes optimal tracheostomy practice in the critically ill patient.[2] It is our goal in this chapter to review basic aspects of tracheostomy management in the intensive care setting, particularly focusing on indications, timing, techniques, and management of complications.

INDICATIONS FOR TRACHEOSTOMY

The presence of a "difficult airway" in a patient requiring prolonged mechanical ventilation is an absolute indication for tracheostomy. Patients with "difficult airways" include those with conditions such as significant maxillofacial trauma, angioedema, obstructing upper airway tumors, or other anatomic characteristics that would render translaryngeal intubation technically difficult to perform in the event of inadvertent airway loss. As a group, patients with difficult airways represent a small fraction of all patients undergoing tracheostomy in most ICUs. More commonly, patients requiring prolonged mechanical ventilation undergo this procedure in an effort to facilitate ventilator weaning, diminish the incidence of infectious complications, promote oral hygiene and pulmonary toilet, enhance patient comfort, provide airway security, and, in selected patients, allow oral nutrition and speech.[3] In most circumstances, tracheostomy is performed in an elective fashion. Accordingly, before undergoing this procedure, patients should be clinically optimized (e.g., minimal ventilatory support ($FIO_2 < 50\%$, positive end-expiratory pressure < 7.5 cm H_2O), hemodynamically stable, and have correction

of metabolic and hemostatic derangements. Because many of the benefits of tracheostomy relative to prolonged translaryngeal intubation are either unproven or subjective, unambiguous criteria for selecting patients for tracheostomy are lacking.

TIMING OF TRACHEOSTOMY IN ACUTE RESPIRATORY FAILURE

In the formative era of critical care medicine, endotracheal tubes were composed of relatively inflexible material and used a low-volume, high-pressure cuff. Consequently, tracheostomy was performed "early"—within 48 hours of initiating mechanical ventilation—in an effort to minimize laryngeal injury resulting from translaryngeal intubation.[4] With advances in material sciences leading to the manufacture of less rigid endotracheal tubes, the trauma associated with prolonged translaryngeal intubation appeared to lessen.[4] Furthermore, a prospective study conducted by Stauffer and coworkers to examine risks associated with tracheostomy suggested a high rate of morbidity (e.g., stomal hemorrhage and infection rates exceeding 30%, rates of tracheal stenosis exceeding 50%) and mortality (e.g., 4%) accompanied this procedure.[5] Accordingly, enthusiasm for the routine performance of tracheostomy diminished. With refinement in tracheostomy techniques, perioperative complication rates associated with this procedure diminished. In addition, subsequent studies attempting to establish the relationship between prolonged translaryngeal intubation, prolonged tracheostomy, and laryngotracheal damage have been conflicting.[4] At present no data clearly establish that translaryngeal intubation should be limited to any specific duration or that tracheostomy should be performed at any specific point in a patient's course in an effort either to limit chronic laryngeal dysfunction or minimize tracheal injury.

While early studies focused on the risks and adverse consequences associated with tracheostomy, more recent clinical investigations have centered on the potential benefits associated with timing of tracheostomy, particularly with respect to the development of infectious complications, duration of mechanical ventilation, and other measures of resource expenditure (Table 72-1). There is no consensus as to what constitutes "early" and "late" tracheostomy. Rodriguez and coworkers assigned 106 patients who developed acute respiratory failure after major trauma to either undergoing tracheostomy within 7 days of ICU admission ("early" tracheostomy) or to undergoing tracheostomy at least 8 days after ICU admission ("late" tracheostomy). Compared with patients undergoing "late" tracheostomy, patients in the "early" tracheostomy group had a trend toward a lower incidence of pneumonia, as well as significant reductions in duration of mechanical ventilation, ICU length of stay, and hospital length of stay. The reported morbidity associated with performance of tracheostomy in this study was 4%.[6] Likewise, Lesnik and associates reported a retrospective analysis of 101 patients who developed acute respiratory failure after blunt trauma, comparing patients who underwent "early" tracheostomy creation (within 4 days of ICU admission) to "late" tracheostomy creation (more than 4 days after ICU admission). Compared with patients undergoing "late" tracheostomy creation, patients having tracheostomy established early had a significantly shorter duration of mechanical ventilation and lower incidence of pneumonia.[7] Finally, Brook and coworkers performed a prospective cohort study of patients requiring prolonged mechanical ventilation and reported that "early" tracheostomy (performed within 10 days of intubation) was associated with significant reductions in duration of mechanical ventilation, shorter ICU length of stay, and lower hospital costs.[8] In contrast, Blot and associates reported that neutropenic patients developing acute respiratory failure who underwent "early" tracheostomy (within 48 hours of intubation) had longer duration of mechanical ventilation and longer hospital length of stay than did patients who either underwent tracheostomy formation after 7 days or not at all.[9] Given the conflicting results, variability in study quality, heterogeneity in populations enrolled, and inconsistency in endpoints studied, it is difficult to draw on the conclusions of these and similar studies to ascertain the optimal timing of tracheostomy creation.[10,11]

TABLE 72–1. EFFECT OF TRACHEOSTOMY TIMING ON INFECTIOUS COMPLICATIONS AND MEASURES OF RESOURCE UTILIZATION

Authors	Design	Population	Tracheostomy Timing	Outcome
Rodriguez, et al.[6]	Prospective, nonrandomized	Multiple trauma (n = 106)	< 7 days vs. > 8 days after ICU admission	Trend towards decreased incidence of pneumonia Decreased duration of MV, ICU LOS, hospital LOS ($P < .05$).
Lesnik, et al.[7]	Retrospective	Multiple trauma (n = 111)	< 4 days vs. > 4 days after ICU admission	Trend towards decreased incidence of pneumonia Decreased duration of MV ($P < .001$)
Dunham, et al.[11]	Prospective, randomized	Multiple trauma (n = 74)	< 4 days vs. > 14 days after initiation of MV or no tracheostomy	No difference in incidence of laryngotracheal trauma or infectious complications
Blot, et al.[9]	Retrospective	Neutropenia (n = 53)	<2 days vs. > 7 days after initiation of MV or not at all	No difference in incidence of pneumonia or death Increased duration of MV and hospital LOS in early tracheostomy group ($P < .05$)
Brook, et al.[8]	Prospective, observational	Medical intensive care unit population (n = 90)	< 10 days vs. > 10 days after initiation of MV	Decreased duration of MV and ICU LOS in early tracheostomy group ($P < .05$)

MV, mechanical ventilation; LOS, length of stay.

There are several reasons why a tracheostomy may facilitate weaning from mechanical ventilation.[4] Resistance to airflow in an artificial airway is proportional to air turbulence, tube diameter, and tube length. Air turbulence is increased in the presence of extrinsic compression and inspissated secretions.[4] Because of its rigid design, shorter length, and removable inner cannula (to allow for evacuation of secretions), airflow resistance and associated work of breathing should theoretically be less with tracheostomies relative to endotracheal tubes. This, however, has not been demonstrated clinically. Furthermore, the presence of a tracheostomy may allow clinicians to be more aggressive about weaning patients from mechanical ventilation. Specifically, if a patient with a tracheostomy tube in place does not tolerate liberation from mechanical ventilation, he or she may be reconnected to the ventilator without difficulty. In contrast, if a patient who is translaryngeally intubated does not tolerate extubation, he or she must be sedated and re-intubated. This might represent a potential barrier to extubation in patients who are of a marginal pulmonary status. Finally, efforts to determine the relative advantages of tracheostomy and translaryngeal intubation with respect to aspiration are inconclusive.[12] However, if the presence of a tracheostomy does translate into earlier liberation from mechanical ventilation, one might expect the incidence of ventilator-associated pneumonia in this group to be lower.

A clinical study that adequately addresses the question as to optimal timing of tracheostomy in the setting of prolonged mechanical ventilation must have a homogeneous patient population, protocols in place for ventilator weaning and other facets of clinical management, and well-defined endpoints. Given the lack of evidence on which to base decision-making on this issue, the following guidelines have been formulated by a consensus conference of the American College of Chest Physicians[3]:

- For patients in whom the need for ventilatory support is anticipated to be less than 10 days, translaryngeal intubation is preferred.
- If the need for ventilatory support is anticipated to exceed 21 days, a tracheostomy is preferred.
- When the anticipated need for mechanical ventilation is unclear, daily assessment is required to determine when conversion to tracheostomy is indicated.

Once the decision to proceed with tracheostomy has been made, patients should undergo this procedure as quickly as practical to limit the duration of the translaryngeal airway.[13]

METHODOLOGY—SURGICAL VERSUS PERCUTANEOUS DILATIONAL TRACHEOSTOMY

Traditionally, tracheostomies have been performed in the operating room using standard surgical principles.[14] In 1985, Ciaglia and colleagues described percutaneous dilational tracheostomy (PDT) in which tracheostomy is accomplished via a modified Seldinger technique, typically with the aid of bronchoscopy.[15] Percutaneous dilational tracheostomy has subsequently gained wide acceptance and has become the predominant method of tracheostomy creation in many centers.[16-18] The technical aspects of percutaneous dilational tracheostomy are covered elsewhere in this text (see Chapter 219). In this section we discuss the potential benefits, indications, and limitations of this approach.

There are several potential advantages of PDT relative to surgically created tracheostomies (SCT). PDT may be performed at the bedside and thus avoids the inconvenience and risk of transporting a critically ill patient, as well as the expense of utilizing operating room resources. In a prospective randomized study comparing PDT and SCT, Freeman and associates found that PDT was associated with a reduction of approximately $1500 in patient charges per procedure.[19] Other investigators have reported comparable findings.[20,21] In addition, whereas studies comparing PDT and SCT vary with respect to quality and endpoints measured (Table 72-2),[21-29] a meta-analysis of prospective trials comparing PDT with SCT suggests that PDT may be associated with fewer complications, specifically postprocedure bleeding and peristomal infection (Fig. 72-1).[23] This may reflect that there is minimal deadspace between the tracheostomy tube and adjacent pretracheal tissues after PDT, which may have a tamponading effect on minor bleeding and serve as a barrier to infection.[23] Finally, PDT is relatively simple to learn. Individuals who have not received formal surgical training may become facile with this procedure and perform it safely and effectively.[12,17]

TABLE 72–2. SELECTED STUDIES COMPARING PERCUTANEOUS DILATIONAL TRACHEOSTOMY (PDT) AND SURGICALLY CREATED TRACHEOSTOMIES (SCT)

Authors	Design	Size (SCT/PDT)	Outcome
Crofts, et al.[22]	Prospective, randomized	28/25	No difference in complication rates comparing SCT and PDT
Freeman, et al.[19]	Prospective, randomized	40/40	PDT performed more quickly and associated with decreased patient charges
Friedman, et al.[24]	Prospective, randomized	26/27	PDT performed more quickly and associated with fewer postprocedural complications
Griggs, et al.[25]	Prospective, nonrandomized	153/74	SCT associated with higher perioperative complication rate
Gysin, et al.[26]	Prospective, randomized	35/35	Complication rate similar comparing techniques
Hazard, et al.[27]	Prospective, randomized	24/22	SCT associated with higher perioperative and postoperative complication rate
Heikkinen, et al.[21]	Prospective, randomized	30/26	PDT associated with lower costs but comparable complication rate
Holdgaard, et al.[28]	Prospective, randomized	30/30	PDT performed more quickly and associated with lower perioperative and postoperative complication rate
Porter, et al.[29]	Prospective, randomized	12/12	PDT performed more quickly; similar complication rate comparing techniques

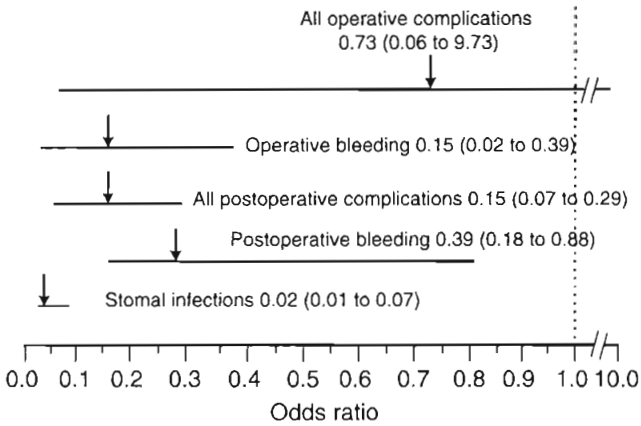


FIGURE 72–1. Rate of complications comparing surgically created tracheotomies (SCT) and percutaneous dilational tracheotomies (PDT). Odds ratios with 95% confidence intervals (represented by *arrows* and *horizontal bars*, respectively) for operative and postoperative complications comparing these two techniques. An odds ratio of 1.0 *(dashed line)* indicates no difference in complication rates comparing these procedures, an odds ratio less than 1 suggests a lower complication rate with PDT, and an odds ratio of greater than 1 suggests a lower complication rate with SCT. There was no difference comparing these two techniques with respect to overall operative complication rates (OR with 95% CI 0.73 [0.06 to 9.37]). However, relative to SCT, PDT was associated with less perioperative bleeding (0.15 [0.02 to 0.39]), a lower overall postoperative complication rate (0.15 [0.07 to 0.29]), as well as a lower postoperative incidence of bleeding (0.39 [0.18 to 0.88]), and stomal infection (0.02 [0.01 to 0.07]). This may reflect that there is minimal deadspace between the tracheostomy tube and adjacent pretracheal tissues after PDT, which may have a tamponading effect on minor bleeding and serve as a barrier to infection. (Used with permission from Freeman BD, Isabella K, Lin N, Buchman TG: A meta-analysis of prospective trials comparing percutaneous and surgical tracheostomy in critically ill patients. Chest 2000;118:1412-1418.)

Patient selection is essential to achieving satisfactory results with PDT. Candidates for PDT should be on low levels of ventilatory support (i.e., $FiO_2 < 50\%$, PEEP < 7.5 cm H_2O), have an intact coagulation system (international normalized ratio and platelet counts correctable to less than 1.3 and greater than 100,000/mm^3, respectively), and have suitable neck anatomy such that external landmarks (cricoid cartilage, trachea, and sternal notch) are easily palpable with the neck fully extended. PDT is contraindicated in patients who are sufficiently obese so as to make identification of these landmarks difficult as well as in patients with unstable cervical spines precluding neck extension. Likewise, PDT is contraindicated in patients with "difficult airways," such as patients with maxillofacial trauma, glottic edema, poorly visualized vocal cords, or any condition that would make it difficult to reestablish translaryngeal intubation in the event of airway loss. Finally, PDT is an elective procedure and should not be used to establish an emergent airway.

Although there are many potential advantages of PDT, this procedure has been associated with a significant number of highly morbid complications, many of which, such as pretracheal insertion, tracheal laceration, esophageal perforation, pneumothorax, and loss of airway, are unusual in surgically created tracheostomies.[30-35] Accordingly, whereas PDT may be performed competently by those not trained in surgical techniques, persons who are expert at surgical airway management should be immediately available in the event complications arise.[12]

SELECTION, MAINTENANCE, AND CARE OF TRACHEOSTOMY TUBES

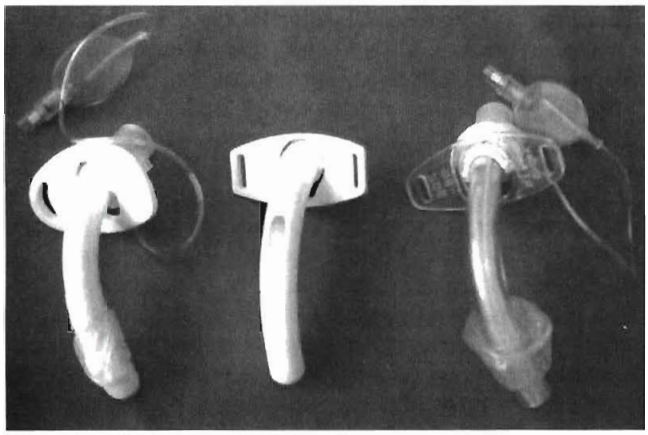
TRACHEOSTOMY TUBE SELECTION

While a detailed discussion of the various types and designs of tracheostomy tubes is beyond the scope of this text,[36,37] a working knowledge of tracheostomy tube features is essential to the competent care of patients who have undergone placement of these devices (Fig. 72-2). Briefly, most tracheostomy tubes are manufactured from polyvinyl chloride, silicone, a combination of these materials, or metal. They are available in either single-lumen (no removable inner cannula) or dual-lumen (removable inner cannula) configurations. The purpose of the removable inner cannula is to facilitate cleaning of inspissated secretions that may lead to tube occlusion. Because silicone is relatively secretion resistant, tubes manufactured from this material frequently do not have an inner cannula. Tracheostomy tubes are available with and without cuffs (the internal balloon surrounding the outer cannula). The purpose of the cuff is to maintain a seal between the tube and the trachea sufficient to prevent escape of air from around the tracheostomy tube during mechanical ventilation (e.g., cuff leak). Furthermore, the cuff minimizes but does not prevent aspiration. Tracheostomy tubes with foam cuffs conform to a patient's trachea and remain consistently inflated at low pressure. These tubes are indicated in patients who have sustained damage from excessive cuff pressure (e.g., tracheomalacia). Once a cuffed tracheostomy tube is no longer required, that is, the patient no longer requires mechanical ventilatory support and is not considered an aspiration risk, the cuffed tube is exchanged for a cuffless tube. Tracheostomy caps are generally provided with tracheostomy tubes for use in the decannulation process, as noted later. Fenestrated tubes are used to promote speech and are generally used in individuals who tolerate liberation from mechanical ventilation for varying periods. Fenestrated tubes have an opening or openings on their superior aspect such that when the inner cannula is removed, the cuff deflated, and the external orifice occluded (e.g., with a Passey-Muir type valve), air can pass the vocal cords allowing phonation.

EXCHANGING TRACHEOSTOMY TUBES

In general, tracheostomy tubes should be changed because of malfunction (e.g., pilot balloon rupture), inspissated secretions compromising luminal diameter, or when another tracheostomy tube design is desired.[38] We believe that "routine" changing of a tracheostomy tube (e.g., every 7 days) is neither indicated nor supported by available literature. Changing a tracheostomy tube is not a benign procedure, is frequently uncomfortable for the patient, and may be complicated by the inability to insert the replacement tube or by insertion of the replacement tube into a false passage in the pretracheal space. If indicated, it is desirable to postpone the initial tracheostomy tube exchange for at least 1 week after creation of the tracheostomy to allow the surgical track to sufficiently mature.

To accomplish tracheostomy tube exchange, the replacement tube should have the pilot balloon tested to ensure that there are no leaks. The tube should be lubricated with either sterile water or a small amount of water-soluble lubricant and inserted over a semi-rigid rubber catheter (e.g., a Robnel) or a



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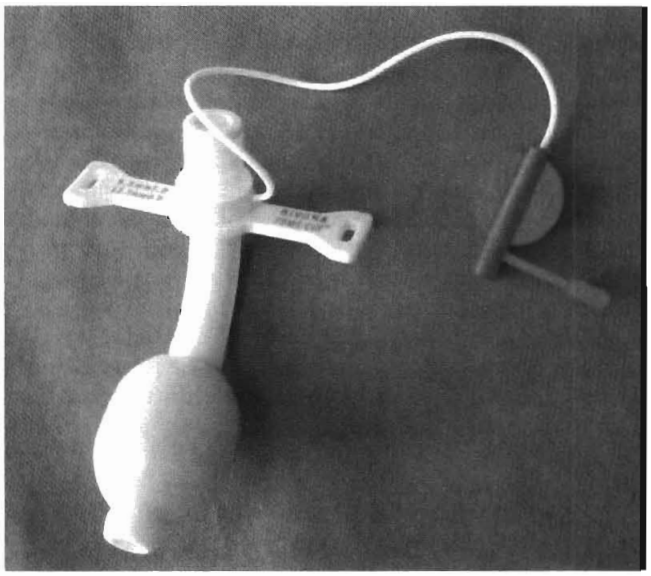

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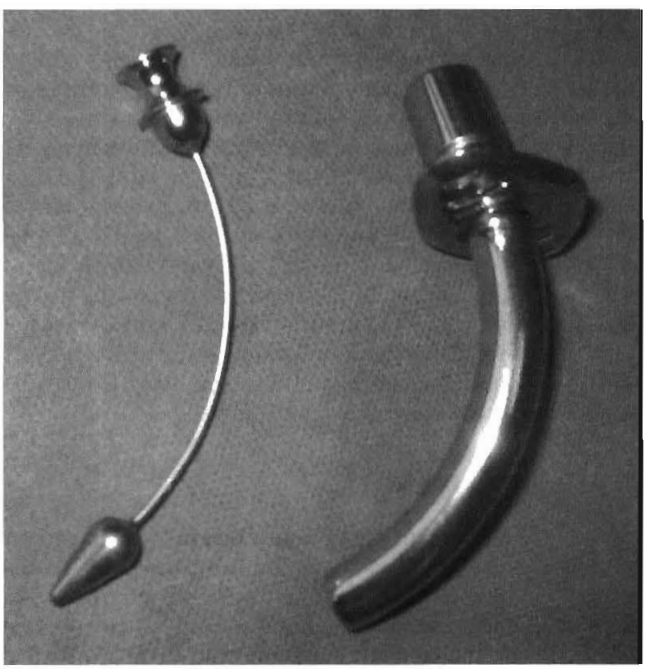

C

FIGURE 72–2. Standard tracheostomy tube designs. **A,** Pictured left to right are a standard cuffed tracheostomy tube, a cuffless fenestrated tube, and a cuffed tracheostomy tube with elongated "limbs" (portion of tube proximal and distal to curvature) to accommodate patients with variant neck anatomy. **B,** Tracheostomy tube with a foam cuff. These tubes are designed to provide a large-volume, low-pressure cuff and are particularly suited to patients with tracheomalacia or in patients who have sustained complications from tracheostomy tube or endotracheal tube cuffs. **C,** Cuffless metal tracheostomy tubes (shown with obturator on the left) are useful for decannulation or in patients who require a tracheostomy but without need for a cuff.

suctioning catheter to lessen the likelihood that the tracheostomy tube is inserted into a false passage. Gentle dilatation of the tracheostomy tract may be useful when exchanging a tracheostomy that has been placed by percutaneous technique.

MONITORING CUFF INFLATION PRESSURE

Tracheostomy tube cuffs require monitoring to maintain an inflation pressure of 20 to 25 mm Hg. Assuming that a tracheostomy tube is of appropriate size, an insufficiently inflated cuff may both result in a sizable amount of air leaking around the cuff ("cuff leak"), rendering mechanical ventilation difficult as well as providing poor protection against aspiration. Alternatively, excessive cuff pressures (exceeding 25 mm Hg) may result in compression of mucosal capillaries, giving rise to mucosal ischemia and attendant complications such as tracheomalacia and tracheal stenosis. The most reliable method of monitoring cuff inflation pressure is through direct measurement. Maneuvers such as pilot balloon palpation to estimate cuff pressure or inflation of the cuff until end-inspiratory leaks are extinguished during positive-pressure ventilation are not recommended because of their inaccuracy.[38] Tracheal cuff inflation pressures should be measured and recorded on a regular basis for purposes of quality assurance.

ORAL NUTRITION

The presence of a tracheostomy both provides opportunity for oral nutrition in the mechanically ventilated patient with its attendant psychological benefits and complicates alimentation

because of the interference of the tracheostomy tube with mechanisms of normal swallowing and airway control.[38] The presence of a tracheostomy inhibits physiologic upward movement of the larynx during deglutition, hinders glottic closure, and produces dysphagia due to mechanical compression of the esophagus. Furthermore, an inflated tracheostomy balloon does not protect from aspiration. Patients with tracheostomies who are candidates for oral nutrition should mentate normally, have adequate oxygenation with low inspired oxygen concentrations (e.g., 30% FiO_2), and possess sufficient ventilatory reserve such that they can physiologically tolerate an episode of aspiration during the introduction of oral feeding. Ideally, a speech therapist should assess aspiration risk before institution of an oral diet. Initial efforts at feeding should be carefully supervised.

DECANNULATION

Patients who remain stable for 24 to 48 hours after discontinuation of mechanical ventilation may be evaluated for decannulation. The patient's ability to protect the airway should be assessed for 24 hours by deflating the tracheostomy tube balloon and observing for signs of aspiration. If aspiration is present, laryngoscopic examination should be performed. Airway strictures and adequacy of the native airway can be assessed by deflating the tracheostomy tube balloon and occluding the tracheostomy tube. Patients who are able to breathe around a capped and deflated No. 8 tracheostomy tube most likely have adequate respiratory reserve and a sufficiently preserved native airway to tolerate decannulation. Patients who have difficulty breathing around a capped No. 8 tube should be reassessed with a capped No. 7 tracheostomy tube. Successful breathing with a capped and deflated No. 7 tube in place suggests that a patient will tolerate decannulation. Patients who fail breathing trials with capped tracheostomy tubes should undergo laryngoscopic evaluation to exclude the presence of tracheal stenosis. Many patients recovering from long-term mechanical ventilatory support may have normal airways but fail breathing around a capped No. 7 or No. 8 tracheostomy tube because of limited ventilatory reserve (e.g., neuromuscular disease or underlying chronic obstructive pulmonary disease). These patients may benefit from "downsizing" of the tracheostomy stoma using progressively smaller cuffless tracheostomy tubes with intermittent capping using stomal obturators. Tracheostomy tubes with foam cuffs should not be used for decannulation trials because these cuffs spontaneously reinflate, making the assessment of airway stenosis difficult.

COMPLICATIONS

A variety of complications resulting from tracheostomy placement have been described. A brief discussion of the more common complications occurring in the critical care setting and their management follows.

CUFF LEAKS

Cuff leak is a commonly encountered problem in patients with tracheostomies and may be manifest by either an audible leak around the tracheostomy tube or loss of returned volume in mechanically ventilated breaths. A mechanical problem with the tracheostomy tube should first be excluded by determining that when the cuff is inflated it does not leak air. A malfunctioning tracheostomy tube requires exchange (see earlier). Once tracheostomy tube malfunction is excluded, the most common cause of cuff leak is tracheomalacia with resulting dilation adjacent to the tracheostomy tube cuff. This is particularly common in patients who have been maintained on mechanical ventilation for extended periods. It should *not* be treated by hyperinflating the tracheostomy tube cuff in an effort to achieve total occlusion, in that this will result in further dilation of the trachea and may lead to mucosal ischemia. If the cuff leak is well tolerated, such that the ability to ventilate the patient is not compromised, we recommend maintaining the tracheostomy tube in place at the appropriate inflation pressure (e.g., 20 to 25 mm Hg). Conversely, if the cuff leak is sufficient so as to impair gas exchange, consideration should be given to exchanging the tracheostomy tube for either a larger size or for a tracheostomy tube design that incorporates a large-volume, low-pressure cuff (e.g., a foam-cuffed tracheostomy tube).

TUBE OCCLUSION

A second frequently encountered problem in patients with tracheostomies is tracheostomy occlusion. This is typically manifest by either high airway pressures or inability to pass a suctioning catheter. Tracheostomy tube occlusion is frequently the result of inspissated secretions. Many commonly used tube designs have a removable inner cannula to facilitate cleaning of the inner portion of the tracheostomy tube. A second common cause of tracheostomy tube occlusion is tube malpositioning, such that the end of the tracheostomy tube abuts the tracheal wall or the tube has migrated such that its tip resides in the pretracheal tissues. If tracheostomy malpositioning is suspected, the operating surgeon should assist in assessing it for either reinsertion or use of another tube design.

TUBE DISLODGMENT

Although dislodgment of the tracheostomy tube may occur at any time after tracheostomy placement, this complication is most problematic in the immediate postoperative period, before the tracheostomy tract has matured.[39] Factors predisposing to tracheostomy tube dislodgment include an inadequately secured tube, excessive coughing, and patient agitation. Tracheostomy tube dislodgment should be suspected when a patient is able to speak immediately after tracheostomy placement, the airway becomes obstructed, or respiratory distress develops. Because it is generally technically difficult to reinsert the tracheostomy tube in this situation, the authors recommend that the airway be reestablished by means of translaryngeal intubation. The tracheostomy should then be reinserted in the operating room with appropriate anesthetic assistance, lighting, and instrumentation. If tracheostomy tube dislodgment occurs once the tracheostomy track is sufficiently mature (i.e., the tracheostomy track is at least 1 week old), it is generally technically feasible to reinsert the tracheostomy tube at the patient's bedside as noted above (see Exchanging Tracheostomy Tubes, earlier).

TRACHEOESOPHAGEAL FISTULA

The development of tracheoesophageal fistulas after tracheostomy is rare, occurring in fewer than 1% of patients,

and is typically the result of pressure necrosis of the tracheal and esophageal mucosa from the tracheostomy cuff. A number of potential risk factors have been reported (e.g., high airway pressures, excessive cuff inflation pressures, the use of nasogastric tubes, excessive tracheostomy tube movement). Clinical manifestations are nonspecific and include excessive tracheal secretions, coughing, and gastric distention. The presence of a tracheoesophageal fistula can be demonstrated on fiberoptic examination after removal or retraction of the tracheostomy tube. Because the use of fiberoptic examination alone is insensitive, it should be combined with an enterally contrasted esophageal evaluation if clinical suspicion exists (e.g., water-soluble contrast swallow or computed tomography). Tracheoesophageal fistula requires surgical repair. Temporizing measures include positioning of an endotracheal tube cuff below the level of the fistula to limit aspiration, removal of nasogastric tubes, and placement of feeding gastrostomy tubes.[40]

TRACHEOINNOMINATE ARTERY FISTULA

Tracheoinnominate artery fistula likewise is a rare complication after tracheostomy formation and theoretically results from pressure necrosis or injury to the trachea adjacent to the course of the innominate artery.[39] A number of risk factors have been postulated, including excessive tube movement, aberrant innominate artery anatomy, use of an excessively long or curved tracheostomy tube that erodes through the tracheal wall, inferior positioning of the tracheostomy tube, tracheal infection, and corticosteroid therapy.[39] Tracheoinnominate artery fistula may become apparent as quickly as a few days or as late as several months after tracheostomy placement. The classic presentation is of a "sentinel hemorrhage" in which a large volume of blood emanates from the tracheostomy tube. Fiberoptic examination to evaluate for the presence of tracheoinnominate artery fistula should be performed in the operating room in the event that airway manipulation results in massive hemorrhage. Temporizing measures in patients who develop massive bleeding include hyperinflation of the tracheostomy cuff, insertion of an endotracheal tube through the tracheostomy stoma in an effort to tamponade bleeding, or translaryngeal intubation and digital compression of the bleeding site through the tracheostomy stoma. Definitive repair entails median sternotomy ligation of the innominate artery and generous drainage of the mediastinum.

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Chapter 73
HYPERBARIC OXYGEN IN CRITICAL CARE

Stephen R. Thom

KEY POINTS

1. **Advances in research have led to identification of several therapeutic mechanisms of action** for hyperbaric oxygen therapy that stem from two fundamental effects: hyperoxygenation of perfused tissues and reduction of gas bubble volume.
2. **Safe treatment of critically ill patients** can be accomplished in either one-man, "monoplace" or larger, multiple-person hyperbaric chambers.
3. **Efficacy of hyperbaric oxygen therapy** has been documented by randomized clinical trials for a heterogeneous group of disorders.

Hyperbaric oxygen (HBO_2) treatment involves intermittent breathing of pure oxygen at greater than ambient pressure. There has been a progressive increase in interest with this treatment modality since the 1960s, when investigational treatment of clostridial myonecrosis (gas gangrene) suggested that HBO_2 may have applications in addition to treatment of gas bubble diseases, such as air embolism and decompression sickness.[1] Over the past 20 years HBO_2 has undergone a refinement, with clarification of mechanisms of action and clinical applications. Along with an expansion of the knowledge base, formalized education now exists for emergency, critical care/anesthesia, and surgically trained physicians, who may obtain special competency board certification through the American Board of Medical Specialists. This chapter will summarize existing literature on uses for hyperbaric oxygen therapy and some special issues related to care of critically ill patients.

APPLICATIONS

HBO_2 treatment is carried out in either a monoplace (single person) or multiplace (typically 2 to 14 patients) chamber. Pressures applied while in the chamber are usually 2 to 3 atmospheres absolute (ATA), the sum of the atmospheric pressure plus additional hydrostatic pressure equivalent to one or two atmospheres. Treatments usually are for 2 to 8 hours, depending on the indication, and may be performed from one to three times daily. Monoplace chambers are usually compressed with pure oxygen. Multiplace chambers are pressurized with air, and patients breathe pure oxygen through a tight-fitting facemask, a hood, or endotracheal tube. During treatment, the PaO_2 typically exceeds 2000 mm Hg and levels of 200 to 400 mm Hg occur in tissues.[2]

HBO_2 should be viewed as a drug and the hyperbaric chamber as a dosing device. Elevating tissue oxygen tension is a primary effect. Although this may alleviate physiologic stress to hypoxic tissues, lasting benefits of HBO_2 must relate to abatement of underlying pathophysiologic processes. The accepted indications[3] comprise a heterogeneous group of disorders (Table 73-1), thus implying that there are several mechanisms of action (Table 73-2).[4-21]

ARTERIAL GAS EMBOLISM (AGE) AND DECOMPRESSION SICKNESS (DCS)

Among the earliest applications of hyperbaric therapy was to treat disorders related to gas bubbles in the body. Compressed air construction work required exposure to elevated ambient pressure within compartments (caissons) for many hours to excavate tunnels or bridge foundations in muddy soil that otherwise would flood. In the 19th century, workers were noted to frequently experience joint pains, limb paralysis, or pulmonary compromise when they returned to ambient pressure. This condition—DCS, caisson disease, or bends—was later attributed to nitrogen bubbles in the body, and recompression was found to relieve symptoms.[22] The mechanism, based purely on Boyle's law with reduction of gas bubble volume due to pressure, was later improved by adding supplemental oxygen to hasten inert gas diffusion out of the body. Similar observations were made at later times for scuba divers, who are also prone to develop AGE due to pulmonary overpressurization on decompression.

Iatrogenic AGE has been reported in association with cardiovascular, obstetric/gynecologic, neurosurgical, and

TABLE 73-1. ACCEPTED INDICATIONS FOR HYPERBARIC OXYGEN THERAPY

- Air or gas embolism
- Carbon monoxide poisoning
- Clostridial myositis and myonecrosis
- Crush injury, compartment syndrome, acute traumatic ischemia
- Decompression sickness
- Enhancement of healing in selected wounds
- Exceptional blood loss anemia
- Necrotizing fasciitis
- Chronic refractory osteomyelitis
- Radiation necrosis
- Skin flap or graft compromise
- Thermal burns

From Hampson NB (ed): Hyperbaric Oxygen Therapy: Committee Report. Kensington, MD, Undersea and Hyperbaric Medical Society, 1999.

TABLE 73–2. MECHANISMS OF ACTION OF HYPERBARIC OXYGEN

Related to Hyperoxygenation of Tissues

- Angiogenesis in ischemic tissues[4-6] (mechanisms likely include O_2 behaving as intracellular signal transducer leading to augmentation of one or more growth factors[7-9])
- Bacteriostatic/bactericidal actions[10-12]
- Carboxyhemoglobin dissociation hastened[13]
- *Clostridium perfringens* α toxin synthesis inhibited[14,15]
- Phagocytic bacterial killing improved[16]
- Temporary inhibition of neutrophil β_2 integrin adhesion[17-19]
- Vasoconstriction[20,21]

Related to Pressurization

- Reduction of gas bubble volume (Boyle's law)

orthopedic procedures and generally whenever disruption of a vascular wall occurs. Nonsurgical processes reported to cause AGE include overexpansion during mechanical ventilation, hemodialysis, and after accidental opening of central venous catheters.

Treatment of gas bubble disorders includes standard support of airway, breathing, and circulation plus application of HBO_2. Recommendation is for referral as soon as possible, but even when treatments may be delayed for hours to days a trial of therapy is recommended. Gas bubbles have been reported to persist for several days, and many reports note success when HBO_2 is begun after long delays.[23-27] Controlled animal trials support efficacy of HBO_2, but randomized clinical trials have not been done.[28]

Mechanisms of action of HBO_2 in AGE and DCS treatment include the well-recognized reduction of gas volume to acutely reduce vascular compromise (Boyle's law), hyperoxygenation to hasten inert gas diffusion, and a hypothetical effect associated with leukocyte adherence to endothelium. Neutrophils have been implicated as exacerbating tissue injury in bubble-related disorders, presumably because of endothelial irritation that leads to perivascular adherence.[29,30] Animals depleted of leukocytes before experimental cerebral air embolism suffer less severe reduction of cerebral blood flow and better neurologic outcome.[31] A recent report demonstrated that efficacy of HBO_2 in a decompression sickness model was associated with inhibition of neutrophil β_2-integrin adhesion.[32] This action has been described in a number of animal models including skeletal muscle ischemia-reperfusion, cerebral ischemia-reperfusion, pulmonary smoke inhalation injury, and brain injury after carbon monoxide (CO) poisoning.[18,33-35] The mechanism appears to be related to impairment of cytoskeletal control of the adhesion molecules expressed on the cell surface, a process related to function of the membrane-bound guanylate cyclase.[17] The same mechanism has been described in human neutrophils, and exposure to HBO_2 has been shown to temporarily inhibit human β_2-integrin adhesion function.[19]

CARBON MONOXIDE POISONING

Carbon monoxide is the leading cause of injury and death by poisoning in the world.[36] The affinity of CO for hemoglobin, to form carboxyhemoglobin (COHb), is more than 200-fold greater than that of O_2. CO-mediated hypoxic stress is a primary insult, but COHb values correlate poorly with clinical outcome.[37-43] Therefore, alternative mechanisms to explain the toxicity of CO have been sought. Oxidative injury to brain after CO poisoning has been shown to occur in several animal models.[44,45] Excessive release of excitatory amino acids, such as glutamate, has been implicated as a component of CO-mediated brain injury.[46-48]

Survivors of acute CO poisoning are at risk for developing delayed neurologic sequelae (DNS) that include cognitive deficits, memory loss, dementia, parkinsonism, paralysis, chorea, cortical blindness, psychosis, personality changes, and peripheral neuropathy. DNS typically occur from 2 to 40 days after poisoning, and their incidence is from 25% to 50% after severe poisoning.

Administration of supplemental oxygen is the cornerstone of treatment of CO poisoning. Oxygen inhalation will hasten dissociation of CO from hemoglobin, as well as provide enhanced tissue oxygenation. HBO_2 causes carboxyhemoglobin dissociation to occur at a rate greater than that achievable by breathing pure oxygen at sea level.[12] Additionally, HBO_2, but not ambient pressure oxygen treatment, has several actions that have been demonstrated in animal models to be beneficial in ameliorating pathophysiologic events associated with central nervous system (CNS) injuries mediated by CO. These include an improvement in mitochondrial oxidative processes,[49] inhibition of lipid peroxidation,[50] and impairment of leukocyte adhesion to injured microvasculature.[18] Animals poisoned with CO and treated with HBO_2 have been found to have more rapid improvement in cardiovascular status,[51] lower mortality,[52] and lower incidence of neurologic sequelae.[53]

Five prospective, randomized trials have assessed clinical efficacy of HBO_2 for acute CO poisoning.[41-43,54,55] Several failed to find benefit,[41,55] but methodologic weaknesses as discussed by several authors[45,56] have diminished their clinical impact. The current consensus is that HBO_2 treatment significantly reduces the incidence of DNS and in retrospective comparisons appears to also diminish acute mortality.[56] As yet, however, there is no agreement among hyperbaric practitioners as to the length of delay from poisoning beyond which there is no chance for benefit from HBO_2.[57]

BLOOD LOSS ANEMIA

In rare instances when transfusion is not possible due to crossmatching incompatibilities or religious beliefs, intermittent use of HBO_2 has been applied to temporarily relieve physiologic stress from severe, acute anemia. Anecdotal reports describe using 2.5 to 3.0 ATA O_2 to raise PaO_2 in plasma to meet metabolic needs.[58-60] Treatments are often administered for only brief times, when physiologic decompensation occurs, because O_2 toxicity can be a problem (see later). Short-term treatments, applied many times over several days, have been used to support life until red cells become available or until adequate red cell mass is generated endogenously.

CLOSTRIDIAL MYONECROSIS (GAS GANGRENE)

Successful treatment of gas gangrene is highly dependent on prompt recognition and aggressive intervention. Mortality rates from 11% to 52% have been reported. There are four retrospective comparisons and 13 case series in the literature,

and many were cited in a previous review.[2,61-65] Because of difficulties with comparison among patient groups, impartial assessment based on mortality or "tissue salvage" rates is difficult. Most authors comment on clinical benefit to treatment, and I share this opinion. Temporal improvement of vital signs in patients with gangrene can be among the most dramatic observations in day-to-day practice.

CRUSH INJURY

There is limited experience with HBO_2 for acute traumatic peripheral ischemia and suturing of severed limbs. A single randomized controlled trial (involving 36 patients) on this type of injury has been performed, which found HBO_2 to improve healing and reduce infection and wound dehiscence.[66] In a case series of 23 patients, HBO_2 was deemed to improve limb preservation and it was also observed that the change in transcutaneous tissue oxygen level from ambient to hyperbaric conditions may predict outcome.[67] The rationale for considering HBO_2 is to temporarily improve oxygenation to hypoperfused tissues and because arterial hyperoxia will cause vasoconstriction that can diminish edema formation.[20,21] This latter mechanism has been demonstrated most convincingly in the context of experimental compartment syndrome.[68]

PROGRESSIVE NECROTIZING INFECTIONS

The use of HBO_2 for treatment of necrotizing fasciitis and Fournier's gangrene, which are mixed aerobic-anaerobic infections, has been reported in six nonrandomized comparisons and three case series.[69-77] As with gas gangrene, variations in time of diagnosis and clinical status on admission compromise assessment of the existing literature. Riseman and coworkers reviewed their experience of 29 patients and found HBO_2 in addition to surgery and antibiotics reduced mortality versus surgery and antibiotics alone.[69] Most recently, Brown and associates reported a multicenter experience where 30 patients received HBO_2 and 24 received only surgery and antibiotics.[70] Although only a nonsignificant trend toward increased survival was seen in the HBO_2 group (30% with HBO_2 and 42% without), the authors state their support for continued use of HBO_2 because of apparent selection bias between groups. Animal trials have been difficult to assess, because synergistic bacterial processes are difficult to establish. One report has found HBO_2 to potentiate antibiotics in streptococcal myositis,[78] and several animal models of polymicrobial bacteremia and sepsis have reported increased survival with HBO_2.[79-81] Mechanisms of action may include suppressed growth of anaerobic microorganisms and improved bactericidal action of leukocytes (that function poorly in hypoxic conditions).[10-12,16]

THERMAL BURNS

Some burn centers employ adjunctive HBO_2 to severe burns, but as controversy persists this is not a universal practice. Animal models have documented benefits with HBO_2 in reducing partial to full-thickness skin loss, hastened epithelialization, and lower mortality.[2] Randomized clinical trials, albeit with small patient numbers, have reported improved rates of healing with shorter hospitalization stays and therefore reduced costs.[82-84] Uncontrolled series have also reported efficacy, but some studies have failed to find benefit.[85-87] Rationale for treatment has been based on reducing tissue edema and increasing capillary angiogenesis. The latter mechanism has not been directly shown with thermal injuries but is a well-documented effect in chronic applications of HBO_2 for radiation injuries and microvascular deficient wounds as occur in many diabetics.[2,88-94]

CRITICAL CARE IN HYPERBARIC MEDICINE

Hyperbaric treatment centers typically have the ability to manage patients who require critical care support. This is accomplished with close cooperation among the treating physicians, nurses, and respiratory therapists and the presence of specialized equipment to manage and monitor the patients.

Plans for treatment begin while the patient is still in the ICU, before transport to the hyperbaric chamber is initiated. Issues to be addressed include informed consent, determination that all intravenous/arterial lines and nasogastric tubes/Foley catheters are secured, capping all unnecessary intravenous catheters, placing chest tubes to one-way Heimlich valves, and adequately sedating or paralyzing the patient as clinically indicated. During transport, emergency drugs for advanced life support resuscitation should be available.

The environment of the hyperbaric chamber imposes limitations on equipment, including space restrictions, fire codes, and the effect of pressure on equipment function. Electrical components of equipment are located outside the hyperbaric chamber. Cables penetrate the chamber bulkhead to make connection to the pneumatic portion of ventilators, internal cardiac pacer wires, electrocardiogram attachments, and arterial line transducers. The patient is attached to equipment at ambient pressure before treatment, and once the treatment pressure is achieved all settings are checked and transducers recalibrated. Among the items that must be checked is the cuff pressure of endotracheal tubes. The usual practice is to replace the air in these cuffs with an equivalent volume of sterile saline before treatment to avoid volume changes related to pressurization.

There are several intravenous infusion pumps that operate normally in the multiplace chamber environment. If glass bottles, pressure bags, or any other gas-filled equipment are used inside a hyperbaric chamber, they must be adequately vented and closely monitored during a treatment. IVAC Medsystem Infusion Pumps (IVAC Corporation, San Diego, CA) or the Abbott-Shaw Hyperbaric Pump are typically used with monoplace chamber operations. These pumps can remain on the outside of monoplace chambers and are capable of infusing despite the elevated pressure differential. The Abbott is a volumetric pump, so flow rate is a function of chamber pressure and must be closely monitored. The IVAC is a pulsatile pump and infusion volume is influenced by both the pump rate that is set and the drip chamber.

ADVERSE EFFECTS

HBO_2 therapy should never be considered unless proper supportive medical care can be delivered. Most chamber facilities today have equipment and treatment protocols analogous to an ICU. The inherent toxicity of O_2 and potential for

injury due to elevations of ambient pressure must be addressed whenever HBO_2 is used therapeutically.

BAROTRAUMA

Middle ear barotrauma is the most common adverse effect of HBO_2 treatment.[95] As the ambient pressure within the hyperbaric chamber is increased, a patient must be able to equalize the pressure within the middle ear by autoinsufflation. If a pressure gradient develops across the tympanic membrane, pain followed by hemorrhage or serous effusion will develop. Standard protocols include instruction of patients on autoinsufflation techniques and adding oral or topical decongestants when needed. When autoinsufflation fails, tympanostomy tubes must be placed. The incidence of tube placement has been reported to be approximately 4% in one series.[96] Others report an overall incidence of aural barotraumas to be between 1.2% and 7%.[97,98]

Pulmonary barotrauma during HBO_2 treatment is extremely rare but should be suspected when any significant chest or hemodynamic symptoms occur during, or shortly after, decompression. Because the offending gas in virtually all cases will be pure O_2, absorption within the body may occur. If symptoms do develop, however, decompression should be stopped and the patient evaluated. If pneumothorax is suspected, placement of a chest tube is appropriate. Preexisting pneumothorax should be treated with chest tube drainage before initiating therapy.

OXYGEN TOXICITY

Biochemical toxicity due to O_2 can be manifested by injuries to lungs, central nervous system (CNS), and eyes. Pulmonary insults can impair mechanics (elasticity), vital capacity, and gas exchange.[2] These changes are typically observed only when treatment duration and pressures exceed typical therapeutic protocols. There is one report of reversible small airways changes in 4 of 21 patients treated daily for 90 minutes at 2.4 ATA for 21 days.[99] Most studies have failed to identify any adverse pulmonary effect from standard protocols.[100-102]

CNS O_2 toxicity is manifested as a grand mal seizure. This occurs at an incidence of approximately 1 to 4 in 10,000 patient treatments.[103-105] The risk is higher in hypercapnic patients, and possibly those who are acidotic or with compromise due to sepsis, because an incidence of 7% (23 in 322 patients) was reported in case series of HBO_2 treatment of gas gangrene.[61-65] Seizures are relatively easy to manage in most cases: simply reduce the inspired O_2 tension while leaving the patient at the same ambient pressure (to avoid pulmonary overexpansion injury when a patient is in tonic convulsion phase). Pathologic changes in association with isolated O_2-mediated seizures have not been found in studies with guinea pigs, rabbits, and humans.[106]

Progressive myopia has been reported in patients who undergo prolonged daily therapy, but this typically reverses within 6 weeks after termination of treatments.[107] Development of nuclear cataracts has been reported with excessive treatments that exceed a total of 150 to 200 hours, and the change does not spontaneously reverse.[108] Although there is a theoretical risk for retrolental fibroplasia in neonates,[109] there are no reports of this having occurred. Currently, experimental and clinical evidence does not indicate that typical HBO_2 therapy protocols have detrimental effects on neonates or the unborn fetus.[110] This is likely due to the relatively short duration of hyperoxia.

OTHER RISKS

Confinement anxiety may occur and is typically managed with use of sedating agents. Any environment with an elevated concentration of O_2 presents a risk for fire. Scrupulous attention to avoiding an ignition source is standard in HBO_2 therapy programs. Over the past 20 years no fires resulting in injury have been reported in the United States; however, worldwide 52 deaths have been reported.[111] Virtually all these were preventable. In 10 incidents, fire resulted when banned substances such as cigarettes and lighters were taken into the chamber.

ANNOTATED REFERENCES

Bouachour G, Cronier P, Gouello, et al: Hyperbaric oxygen therapy in the management of crush injuries: A randomized double-blind placebo-controlled clinical trial. J Trauma 1996;41:333-339.

This blinded, randomized trial of 36 crush injury patients documented efficacy of hyperbaric oxygen therapy in improving wound healing and reducing repetitive surgery, particularly in those older than 40 years and with severe (grade III) injuries.

Faglia E, Favale F, Aldeghi A, et al: Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. Diabetes Care 1996;19:1338-1343.

This prospective, randomized trial involving 70 consecutive diabetic patients with diabetic ulcers documented efficacy of hyperbaric oxygen therapy in improving limb salvage and wound healing for those with Wagner grade IV ulcers.

Marx RE, Johnson RP, Kline SN: Prevention of osteoradionecrosis: A randomized prospective clinical trial of hyperbaric oxygen versus penicillin. J Am Dental Assoc 1985;111:49-54.

This prospective, randomized trial of 74 patients who required dental extractions after receiving in excess of 6800 cGy external beam radiotherapy demonstrated efficacy of prophylactic hyperbaric oxygen therapy in reducing the incidence and severity of postoperative osteoradionecrosis.

Riseman JA, Zamboni WA, Curtis A, et al: Hyperbaric oxygen therapy for necrotizing fasciitis reduces mortality and the need for debridements. Surgery 1990;108:847-850.

This retrospective analysis of 29 patients with necrotizing fasciitis having similar age and illness severity describes the apparent efficacy of adjunctive hyperbaric oxygen therapy plus surgery and antibiotics in reducing mortality and wound morbidity.

Weaver LK, Hopkins RO, Chan KJ, et al: Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med 2002;2347:1057-1067.

This prospective, randomized, placebo controlled trial of 152 patients with carbon monoxide poisoning describes the efficacy of hyperbaric oxygen therapy in reducing neurologic morbidity among those with a history of unconsciousness, or with cerebellar dysfunction, or those with a carboxyhemoglobin level greater than 25%.

Chapter 74

IMAGING OF THE CHEST IN ICU

Nisa Thoongsuwan • Jeffrey P. Kanne • Eric J. Stern

KEY POINTS

1. Although **portable chest radiographs** are limited by both technical and patient factors, knowledge of complications of various diseases and therapies as well as their respective radiographic appearances can lead to improved patient care.
2. **Knowledge of the normal position of life support devices** on the chest radiograph is important so that malposition can be corrected and potential complications averted.
3. Even though many chest radiographs in the ICU setting may have a similar appearance, particularly with respect to parenchymal opacification, **understanding the diverse pathology** encountered in critical care and the specific clinical settings in which they are found provides a context for interpretation and may improve the diagnostic yield.

Chest imaging plays a central role in management of critically ill patients. Both bedside chest radiography and computed tomography (CT) aid in diagnosis as well as in evaluating response to therapy. In this chapter we review chest imaging in the ICU setting, focusing on radiography and CT, and discuss radiographic techniques used at the bedside and appropriate positioning of various monitoring and life support devices. In addition, imaging findings of common pathologic processes encountered in critically ill patients are described. A discussion of imaging of neonatal and pediatric ICU patients is beyond the scope of this chapter.

PRINCIPLES OF IMAGING IN THE ICU

Portable chest radiography plays a major role in patient care, especially in critically ill patients. In some hospitals, up to 50% of all chest radiographs are obtained at the bedside.[1] The benefit of obtaining routine daily chest radiographs in the ICU remains controversial. Some studies support the concept of routine chest radiographs in ICU patients[2] whereas others dispute the usefulness of obtaining chest radiographs in the ICU without a clear indication, arguing that a very small minority of examinations have any significant impact on patient management.[3-7] We believe that radiographs showing no new significant findings, even given their limitations, can be reassuring that no new serious abnormalities are present.

Interpretation of bedside chest radiographs can be quite challenging because of the degree of variation in quality from both technical and patient factors. The ill health of the patient and multiple cumbersome life support devices limit proper patient positioning while difficulty controlling respiratory and body motion can blur the radiographic images, all potentially leading to low-quality radiographs. The importance of having dedicated and competent radiology technologists and an effective quality assurance program cannot be overemphasized.

In addition to film quality issues, common pathologic processes such as pleural effusion or pneumothorax have different appearances on supine or semi-upright bedside examinations as compared with standard upright posteroanterior chest radiographs.[8] Understanding and accepting the limitations of bedside chest radiography allows for appropriate utilization of other imaging modalities such as CT.

CONVENTIONAL RADIOGRAPHY

By its very nature, conventional portable chest radiography suffers from several disadvantages, some technical and others related to patient factors. Bedside chest radiographs are obtained in the anteroposterior projection, ideally with the patient upright. However, supine and semi-upright positioning is often the rule and not the exception owing to the severity of these patients' illnesses. The combination of the anteroposterior projection and a shorter film-tube distance lead to geometric magnification of structures more anterior in the chest, such as the heart. The maximum tube current and voltage are limited on portable units, so exposure times are relatively long and image contrast may be excessive.[9]

DIGITAL RADIOGRAPHY

In addressing the technical and patient-related problems encountered in portable chest radiography, development of digital image technology has shown promising improvement over conventional radiography. Digital (or computed) radiography uses a phosphor plate in lieu of a film-screen combination to capture and store the radiographic image and has the advantages of consistent film density, flexible image processing, and lower radiation dose to the patient. The diagnostic accuracy of digital chest radiography systems is similar to that obtained with conventional film-screen radiography.[10]

Digital image processing identifies the portion of the dynamic range containing the diagnostic information and

adjusts the final output for display at consistent and optimized contrast and density, obviating the need for repeated examinations because of errors in exposure. This also decreases the need to interpret radiographs of marginal diagnostic quality. These advantages, however, do not preclude the need for accurate positioning of the patient and alignment of the x-ray beam, and overall time required for obtaining the radiograph remains the same. Nevertheless, not only does computed radiography have the immediate advantages of improved image quality and flexibility but also it readily allows for placing images on a digital network.

COMPUTED TOMOGRAPHY

Computed tomography provides better anatomic detail and a higher degree of diagnostic accuracy than conventional chest radiography, but for critically ill patients, transportation and cumbersome monitoring devices limit access to CT. Appropriate use of CT in critically ill patients can aid in patient management.[11-13] A mobile CT scanner has been developed to image critically ill patients in the ICU and avoid the need for transportation, but these units have not been widely accepted because of their suboptimal image quality.[14]

PICTURE ARCHIVING AND COMMUNICATIONS SYSTEM (PACS)

Immediate access to bedside chest images is particularly useful in the ICU, where information is desired without delay. A picture archiving and communications system (PACS) permits transmission of medical images over a digital network for simultaneous display within minutes of their acquisition at multiple locations such as in the ICU, clinics, or operating rooms.[15] In addition, PACS allows for rapid retrieval of previous examinations for comparison and workstation tools enable accurate measuring and adjustment of digital image parameters such as window and level settings.

MONITORING AND SUPPORT DEVICES

ENDOTRACHEAL TUBES

Endotracheal tubes (ETTs) are placed in the setting of airway obstruction, failure to maintain adequate gas exchange, or inability of a patient to protect the airway from aspiration or obstruction.[16] On the chest radiograph, position of an ETT is determined by the location of the tube's tip in relation to the carina with respect to the position of the patient's chin.[17] With the chin in the neutral position, the tip of the ETT should be 3 to 7 cm above the carina (Fig. 74-1). When the carina is not visible, the tip of the ETT should project over the T3 or T4 vertebral body, because the carina is located between T5 and T7 on anteroposterior radiographs in about 92% of individuals.[18] Alternatively, carinal position can be ascertained by following the inferior margins of one or both of the main bronchi proximally.

When assessing ETT position, the position of the chin should also be assessed. Neck flexion and extension can result in 2 cm of downward and upward displacement, respectively, of the ETT.[19] Projection of the anterior portion of the mandible over the lower cervical spine indicates neck flexion whereas a nonobscured cervical spine denotes that the neck is in extension.

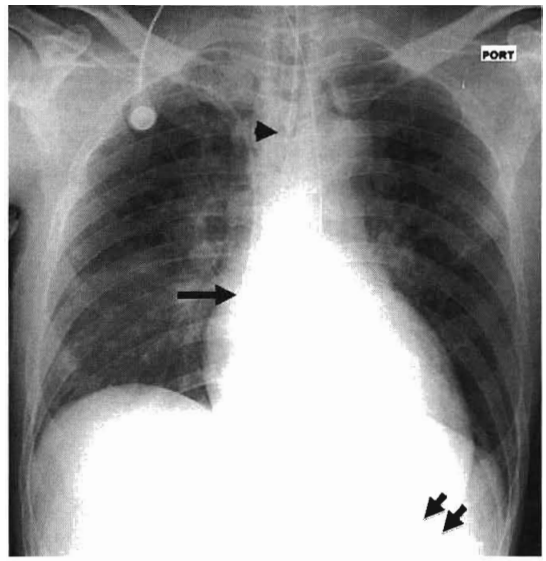


FIGURE 74–1. Typical normal line and tube positions. Note the expected positions of the ETT (superimposed over the T3 vertebral body *[arrowhead]*), a central venous catheter (in the origin of SVC *[arrow]*), and the nasogastric tube (in the stomach *[double arrows]*).

The most common complication of ETT placement is inadvertent intubation of the right main bronchus (Fig. 74-2) because of the smaller angle the right main bronchus has in relationship to the trachea as compared with the left main bronchus.[20] Additionally, esophageal placement of the ETT can occur, but this is usually detected on physical examination. However, when esophageal intubation is not appreciated clinically, the chest radiograph may identify the errant position of ETT. Radiographic findings of esophageal intubation include direct visualization of the ETT lateral to the tracheal wall, gaseous distention of the stomach, and displacement of the trachea by an overdistended balloon cuff.[21]

TRACHEOSTOMY TUBES

A tracheostomy tube is required in patients who need long-term assisted ventilation or tracheal suction or in whom

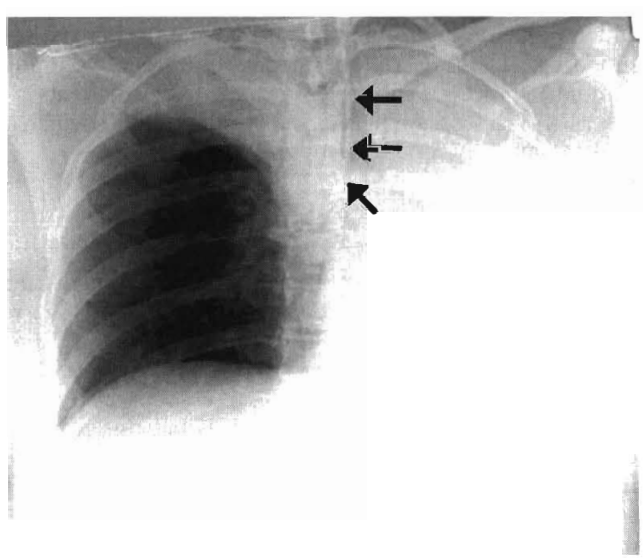


FIGURE 74–2. Anteroposterior chest radiograph shows the ETT *(arrows)* extending into the bronchus intermedius with resulting collapse of the left lung and right upper lobe from hypoventilation.

transoral or transnasal tracheal intubation is not possible. The tip of the tube should be several centimeters above the carina, and the tube's diameter should be approximately two-thirds that of the trachea.[22] Unlike with ETTs, chin position does not affect tracheostomy tube position. The presence of air in the subcutaneous tissue of the neck and upper mediastinum is usually an insignificant finding immediately after tracheostomy tube placement.[23] However, pneumothorax and mediastinal hematoma, the latter manifesting as a widened mediastinum, are complications of tracheostomy tube placement that can be identified on the chest radiograph.

CENTRAL VENOUS CATHETERS

Central venous catheters are used for monitoring central venous pressure, for venous access for fluid and medication administration, and for parenteral nutrition.[17] They are inserted from an internal jugular, subclavian, or femoral approach. The optimal location of the catheter tip is at the origin of the superior vena cava, distal to the central venous valves. On the anteroposterior chest radiograph, the origin of the superior vena cava usually lies to the right of midline at the level of the first intercostal space (see Fig. 74-1).[24] Catheters should ordinarily not be placed beyond the level of the azygos vein because the superior vena cava enters the pericardium at this location and unintentional vessel perforation may cause pericardial effusion or cardiac tamponade.[17]

Portable chest radiographs should be obtained immediately after central venous catheter placement to determine catheter position and identify any complications such as pneumothorax, vessel perforation (Fig. 74-3), cardiac perforation, retained or fragmented introducer or catheter, or a knotted catheter.

SWAN-GANZ CATHETERS

Swan-Ganz catheters are used for measuring the pulmonary capillary wedge pressure, which is an indirect assessment of both left atrial pressure and left ventricular end-diastolic volume. This catheter is typically used to distinguish cardiogenic from noncardiogenic pulmonary edema, particularly in patients who have underlying systemic or pulmonary disease in addition to left ventricular failure. The Swan-Ganz catheter has a small balloon near the tip and is introduced via a jugular, subclavian, or femoral venous approach. The ideal position for the catheter tip is within the left or right main pulmonary artery or in a proximal interlobar artery. If the tip extends beyond these larger arteries (Fig. 74-4), pulmonary infarction from occlusion of the pulmonary vessel or pseudoaneurysm can ensue.[17] The balloon should be inflated only when obtaining pressure measurements, so an inflated balloon should never be present on a portable chest radiograph. Complications are similar to those that occur with other central venous catheters but also include pulmonary vascular perforation and pulmonary hemorrhage when the catheter extends into the lung periphery.[25]

INTRA-AORTIC BALLOON PUMPS

An intra-aortic balloon pump (IABP) is used for assisting left ventricular function in patients with cardiac shock or serious left ventricular dysfunction, usually after myocardial infarction. The device consists of an inflatable balloon, about 16 cm in length, which is inflated during systole, thereby reducing afterload and augmenting coronary artery perfusion.[26] The IABP is advanced into the descending thoracic aorta through the common femoral artery. On the frontal chest radiograph, the tip of the balloon should be located within the descending thoracic aorta just distal to the origin of the left subclavian artery, typically at the level of aortic arch.[24] A more proximal location of the balloon can result in occlusion of the subclavian and vertebral arteries, whereas a more distal location can lead to occlusion of the mesenteric and renal arteries.[27] IABPs can migrate, so position should be reassessed on subsequent chest radiographs.

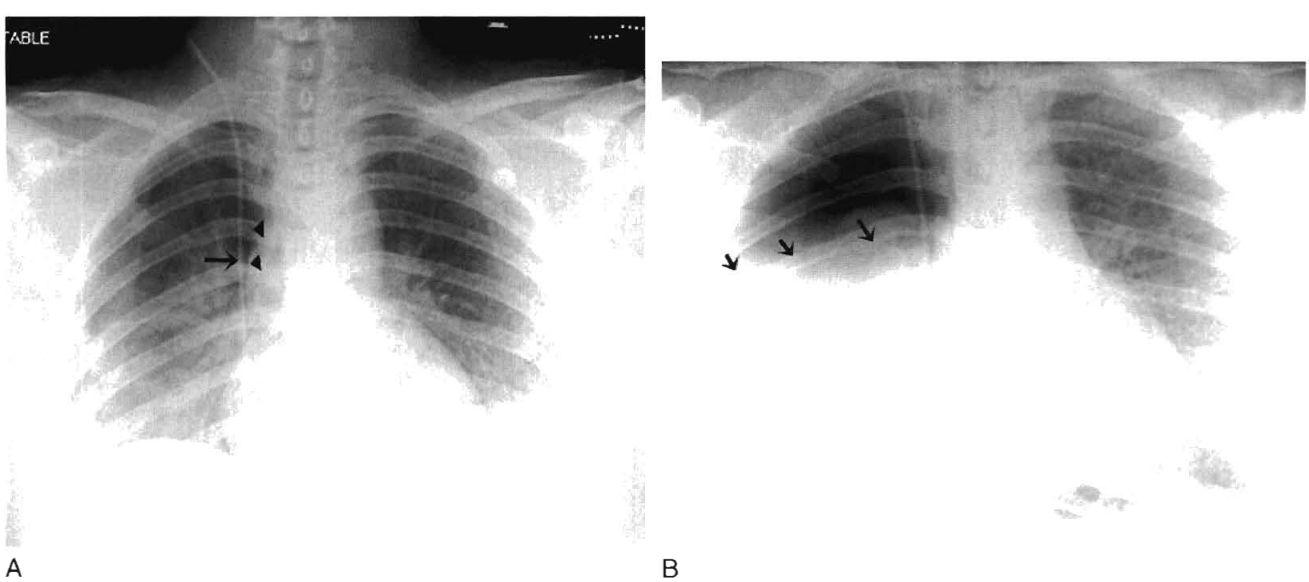


FIGURE 74–3. Complication of intravenous catheter placement. **A,** The right IJ catheter *(arrow)* is lateral to the right mediastinal margin *(arrowheads)*, indicating that the catheter is extravascular. **B,** Twelve hours later, a pleural fluid collection has developed from inadvertent infusion of saline into the right pleural space *(arrows)*. A CT scan *(not shown)* showed the catheter to be in the pleural space.

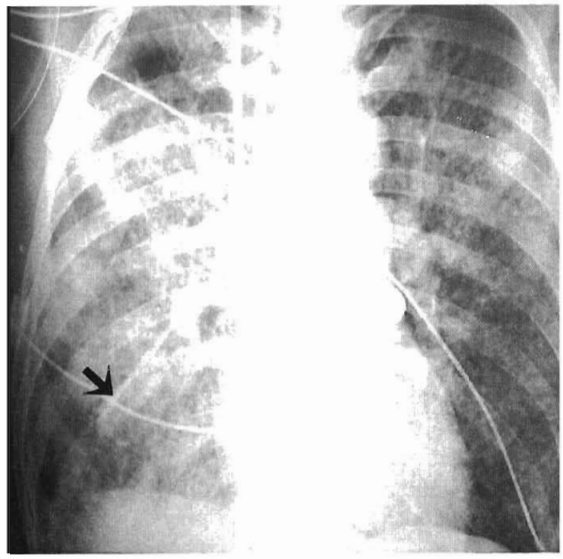


FIGURE 74–4. The tip of the Swan-Ganz catheter extends into the right lower lobe pulmonary artery. In this location, the risk of vessel injury increases.

PERIPHERALLY INSERTED CENTRAL CATHETERS

The peripherally inserted central catheter (PICC) is a relatively new device gaining widespread acceptance for long-term central venous access. PICCs allow for administration of medications, blood products, or intravenous alimentation. The catheter is small, with sizes ranging from 2 to 5 French, and is placed into the superior vena cava through a large upper extremity vein. Complication rates are low when compared with other central vascular catheters.

PICCs may be difficult to visualize on the bedside chest radiographs because of their small size and faint opacity. They, in particular, are more susceptible to displacement than other intravenous catheters owing to increased flexibility of the material.[28] As with all tubes, location should be reassessed on all subsequent radiographs.

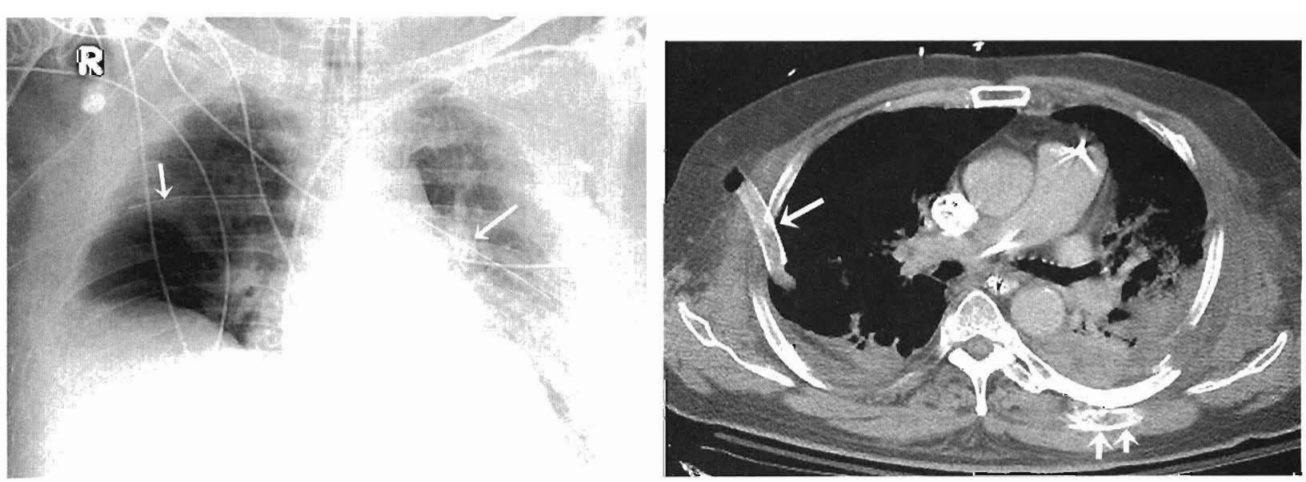
THORACOSTOMY TUBES

Thoracostomy tubes are placed in the pleural space to drain unwanted fluid or gas, both of which are frequently encountered in critically ill patients. The position of the thoracostomy tube can usually be assessed on a chest radiograph. The side port, marked by the disruption in the radiographically opaque line, should be located medial to the inner margin of the ribs. However, thoracostomy tubes, particularly those placed at the bedside, can be malpositioned, with the tips residing in the subcutaneous soft tissues, pulmonary fissures, or, rarely, within the lung parenchyma. Poor positioning of the tube is suspected when the tube does not drain as expected.

In some instances, the precise location of the thoracostomy tube cannot be determined from the bedside chest radiograph.[17] Subcutaneous placement can be very difficult to ascertain, and a fissural location can only be suspected when the tube follows the course of one of the pulmonary fissures.[29] CT, because of its cross-sectional nature, is superior to chest radiography for accurately identifying the course of the thoracostomy tube[30] and its relationship to abnormal gas or fluid collections (Fig. 74-5).

ENTERIC TUBES

Enteric tubes are placed into the stomach or proximal small bowel through a transoral or transnasal approach and come in a variety of sizes and configurations (see Fig. 74-1). They are used for gastric decompression or lavage, medication administration, and providing nutrition.[31] These tubes are frequently placed in ICU patients, especially those with endotracheal intubation. Although the best position of tubes used for feeding is controversial, placement distal to the pylorus may decrease the risk of aspiration.[31] Position of enteric tubes is



A B

FIGURE 74–5. Malpositioned thoracostomy tubes after bedside placement. **A,** Anteroposterior chest radiograph shows bilateral thoracostomy tubes *(arrows)* with tips and side ports projecting over the lungs. **B,** CT shows that the left thoracostomy tube *(double arrows)* is in the posterior chest wall The right thoracostomy tube *(single arrow)* is in satisfactory position.

easily assessed from the chest or abdominal radiograph. The most common complication from insertion of these tubes is coiling in the pharynx or esophagus. However, inadvertent insertion into the tracheobronchial tree (Fig. 74-6), occurring in 0.2% to 0.3% of patients,[32,33] and esophageal perforation have more serious consequences.

APPROACH TO ICU CHEST IMAGING

In many large hospitals, the ICU has evolved from a single unit for patients requiring mechanical ventilation to system- or illness-specific units to provide the most effective patient care. Understanding the diversity of pathologic processes in critical care and the specific settings in which they are found provides a context for interpretation of radiographic abnormalities and may improve diagnostic accuracy.

CARDIAC ICU

The most common lung opacity found in the cardiac ICU setting is cardiogenic pulmonary edema. Other causes of parenchymal opacity include atelectasis, pneumonia, and, less commonly, noncardiogenic pulmonary edema from any cause. In the setting of cardiogenic pulmonary edema, lung opacity is almost always associated with an enlarged heart, engorgement of central pulmonary veins, interstitial edema, effusions, and altered distribution of pulmonary blood flow (Fig. 74-7). The classic pattern of bilateral perihilar fluffy opacity, referred to as the butterfly or bat-wing appearance, is seen in less than 10% of patients with pulmonary edema.[34] Asymmetry of pulmonary edema can also occur because of variations in patient position and underlying cardiopulmonary disease such as emphysema or mitral valve insufficiency.[35] The lung opacity associated with cardiogenic pulmonary edema can fluctuate rapidly, a clue to its diagnosis.

NEUROLOGIC ICU

Patients cared for in the neurologic ICU include both surgical and nonsurgical patients with conditions affecting the nervous system such as intracranial hemorrhage, recent intracranial or spinal surgery, and seizure. The most common abnormalities encountered on the chest radiographs of these patients include hypervolemia, neurogenic pulmonary edema, and aspiration.

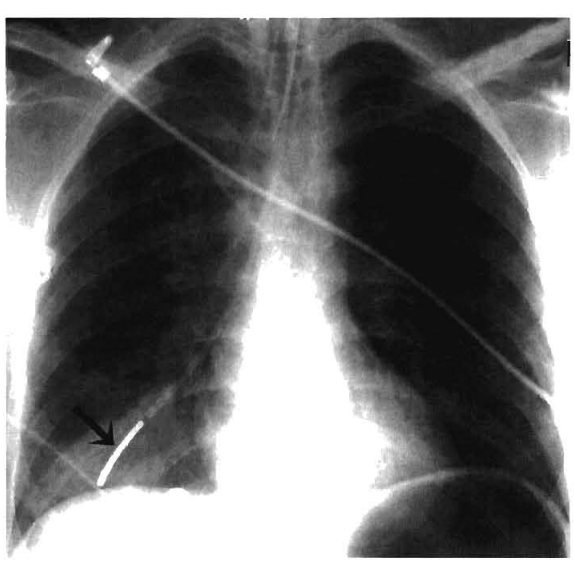


FIGURE 74–6. Distal-weighted enteric feeding tube *(arrow)* extending into the right lower lobe bronchus.

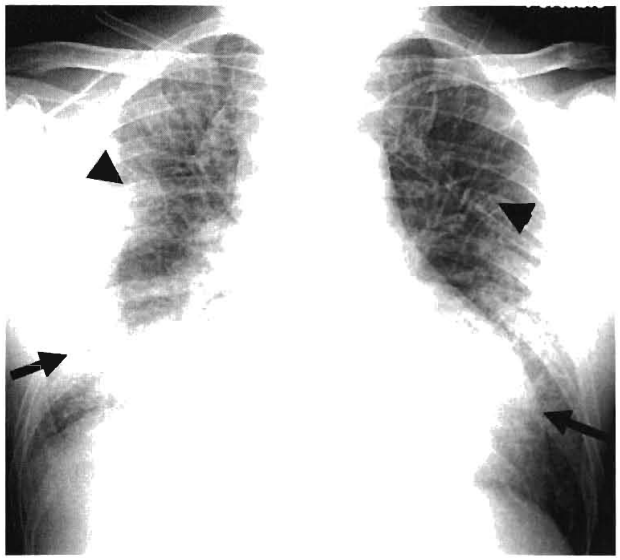


FIGURE 74–7. Cardiogenic pulmonary edema in a 54-year-old man with acute myocardial infarction. Chest radiograph shows cardiomegaly with bibasilar opacities and diffuse interlobar thickening in both lungs. Note Kerley's A *(arrowheads)* and Kerley's B lines *(arrows)*.

Neurogenic Pulmonary Edema

Neurogenic pulmonary edema occurs with many neurologic conditions that increase intracranial pressure, such as head trauma, intracranial hemorrhage, intracranial tumor, stroke, seizures, and infection.[36] Elevated microvascular pressure and increased vascular permeability in the lungs are thought to play a role in its development. Neurogenic pulmonary edema can develop immediately after the insult to the central nervous system, within minutes to hours, or several days later.[37]

On the chest radiograph, neurogenic pulmonary edema usually manifests as a homogeneous pulmonary opacity similar to that of cardiogenic pulmonary edema but without cardiomegaly or engorgement of the pulmonary vasculature and interstitium. The distribution of the opacity is usually diffuse,[38] but sometimes the opacity is focal.[39] Variability in the radiographic appearance of neurogenic pulmonary edema likely reflects gravity, patient position, and heterogeneity in pulmonary venous pressure.[40] Radiographic abnormalities may not develop until 24 hours after the onset of neurogenic pulmonary edema. Rapid clearing of the lungs several days after the insult to the central nervous system is removed is characteristic, in contrast to other forms of noncardiogenic pulmonary edema in which opacity can persist.[41]

In addition to neurogenic pulmonary edema, evidence of positive fluid balance is almost always found on radiographs of patients in the neurologic ICU, whether directly related to neurogenic pulmonary edema or as an indirect effect from treatment with large volumes of intravenous fluid. In other ICU settings, however, evidence of fluid volume overload may have different clinical implications.[42]

Aspiration

Patients with a decreased level of consciousness after stroke or head injury and those experiencing seizure are at high risk for

aspiration.[42] The clinical severity and radiographic appearance depend on both the amount of fluid aspirated as well as its composition.[43] Radiographically, aspiration can result in development of bilateral, multilobar pulmonary opacities predominating in the dependent portions of the lungs, including the posterior segments of the upper lobes and the superior and posterior basilar segments of the lower lobes (Fig. 74-8). Aspirated particulate matter can obstruct the airways and add to volume loss.[42,44]

SURGICAL ICU

Patients in the surgical ICU can develop complications directly relating to recent thoracic surgery. Thoracotomy with or without pneumonectomy or lobectomy can alter the expected appearance of the intrathoracic structures, and knowledge of the normal expected changes after surgery allows for better identification of changes that may indicate a complication.

Pneumonectomy

Radiographs obtained immediately after pneumonectomy normally show midline position of the mediastinum and gas filling the pneumonectomy space. After several days, fluid begins to accumulate within the pneumonectomy space as the gas is resorbed. The rate of the fluid accumulation varies, but in most cases one half to two thirds of the hemithorax fills within the first week. However, this process can take up to 6 months in some patients.[45,46]

After pneumonectomy, the ipsilateral hemidiaphragm elevates and the mediastinum begins to shift toward the operative side as the remaining lung hyperinflates. The degree of mediastinal displacement depends primarily on the compliance and the degree of hyperinflation of the remaining lung.[46] Appropriate mediastinal displacement is the most reliable indicator of a normal course after pneumonectomy. Failure of the mediastinum to shift to the operative side almost always indicates an abnormality in the pneumonectomy cavity.[45] Complications of pneumonectomy, as described later, are categorized as either acute or chronic, but most of those encountered in the ICU are acute.

Post-pneumonectomy Pulmonary Edema

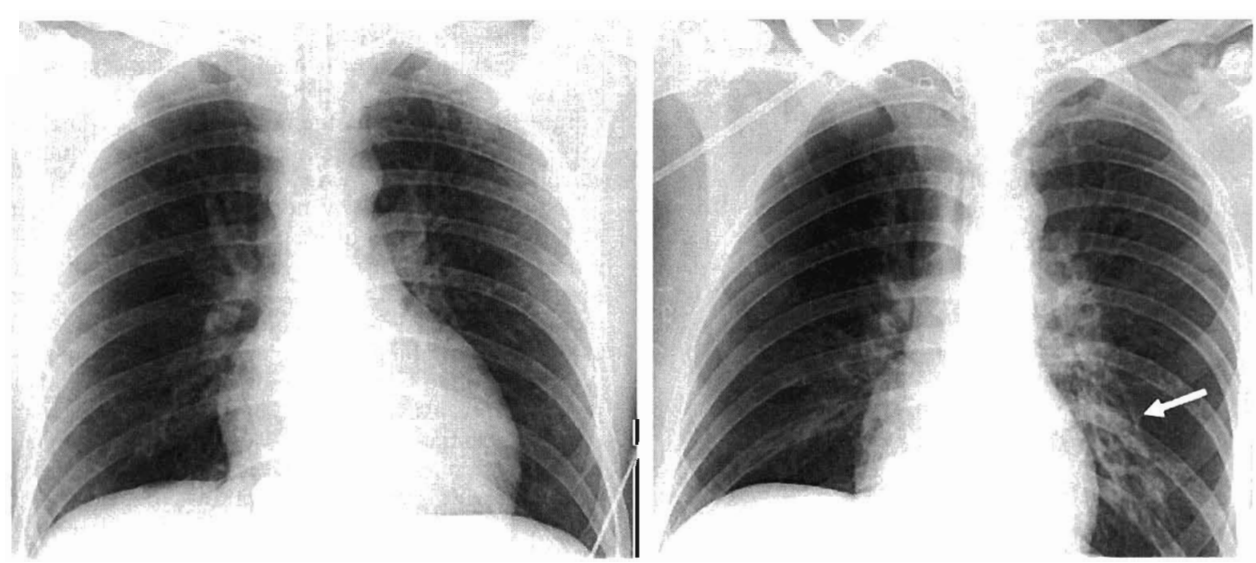
Post-pneumonectomy pulmonary edema describes a fall in P_{O_2} with an increase in water content in the lung.[47] It is an uncommon condition[48,49] but carries a high mortality rate.[49] An increase in pulmonary capillary permeability is believed to be the central factor for developing post-pneumonectomy pulmonary edema.[48] Radiographic features include mild interstitial edema and ill-defined vascular structures. In more severe cases, the pattern of radiograph is identical to that of noncardiogenic pulmonary edema.[35]

Bronchopleural Fistula

Although an uncommon complication after pneumonectomy, bronchopleural fistula, with an incidence of 2% to 5%,[50,51] has a high morality rate ranging from 30% to 70%.[50,52,53] Clinical characteristics of bronchopleural fistula include sudden onset of dyspnea and bloody expectoration during the first 10 days after surgery.[53] The time at which the fistula develops reflects its cause, because leakage in the first week after pneumonectomy usually indicates inadequate closure of the bronchial stump whereas leakage developing during the second or third week is usually the result of poor healing.[46] Radiographic findings of bronchopleural fistula include an unexpected disappearance of fluid or abrupt decrease in the gas-fluid level in the pneumonectomy cavity (more than 2 cm in height)[54] and contralateral shift of the mediastinum (Fig. 74-9).[46]

Hemothorax, Chylothorax, and Empyema

The nature of fluid within the pneumonectomy cavity usually cannot be determined on the chest radiograph. However, hemothorax, chlyothorax, and empyema, as complications of pneumonectomy, differ in when they develop. Rapid opacification of the pneumonectomy cavity likely indicates hemorrhage, whereas chylothorax occurs with a delay up to 10 days. Empyema usually occurs several weeks after surgery.[46] On the chest radiograph, hemothorax, chylothorax,



A B

FIGURE 74–8. A 49-year-old man presented with seizure and witnessed aspiration. **A,** Initial anteroposterior chest radiograph is normal. **B,** Twenty-four hours later, patchy left lower lobe opacity *(arrow)* has developed, consistent with aspiration pneumonia. Note the increased opacity behind the heart.

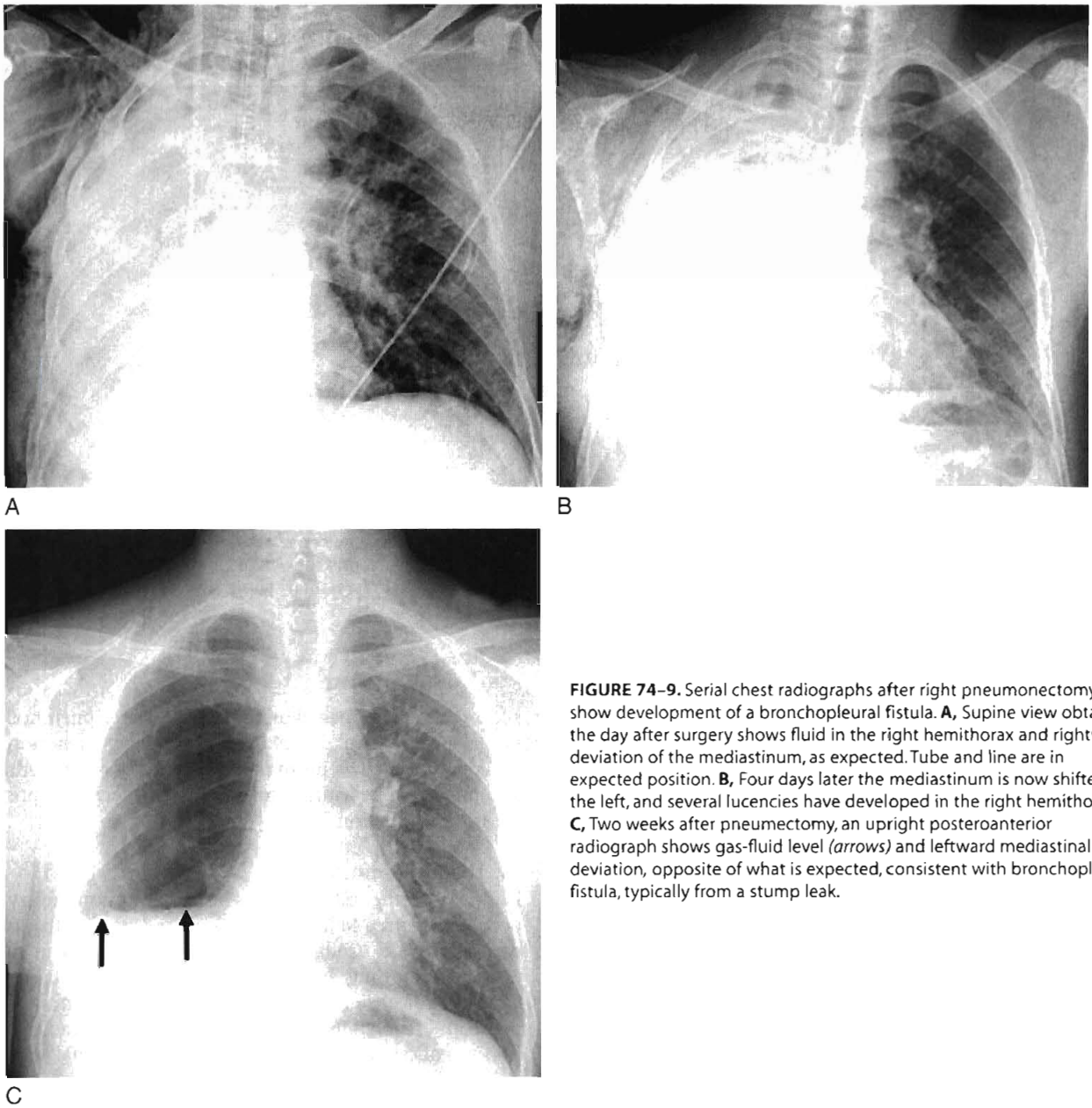


FIGURE 74–9. Serial chest radiographs after right pneumonectomy show development of a bronchopleural fistula. **A,** Supine view obtained the day after surgery shows fluid in the right hemithorax and rightward deviation of the mediastinum, as expected. Tube and line are in expected position. **B,** Four days later the mediastinum is now shifted to the left, and several lucencies have developed in the right hemithorax. **C,** Two weeks after pneumectomy, an upright posteroanterior radiograph shows gas-fluid level *(arrows)* and leftward mediastinal deviation, opposite of what is expected, consistent with bronchopleural fistula, typically from a stump leak.

and empyema opacify the hemithorax on the operative side with contralateral shift of the mediastinum in contrast to the ipsilateral shift seen with normal filling of the pneumonectomy space. In the case of empyema, gas may develop in the previously opacified pneumonectomy cavity.[46]

Lobectomy

After uncomplicated lobectomy, the chest radiograph can show rotation and hyperinflation of the remaining lobe(s),[55] change in the orientation of the remaining bronchovascular structures, as well as other subtle changes such as subsegmental atelectasis and development of pleural effusion. Reorientation of the remaining bronchovascular anatomy should not be confused with atelectasis. Complications of lobectomy occur with a lower frequency than with pneumonectomy but are similar. In addition, lung torsion, which has a high mortality rate, occurs rarely and manifests as rapid opacification of a lobe or lung associated with unusual configuration of the hilum.[56] Anastomotic suture lines are evident when the fissure incompletely divides the lung into lobes.[57]

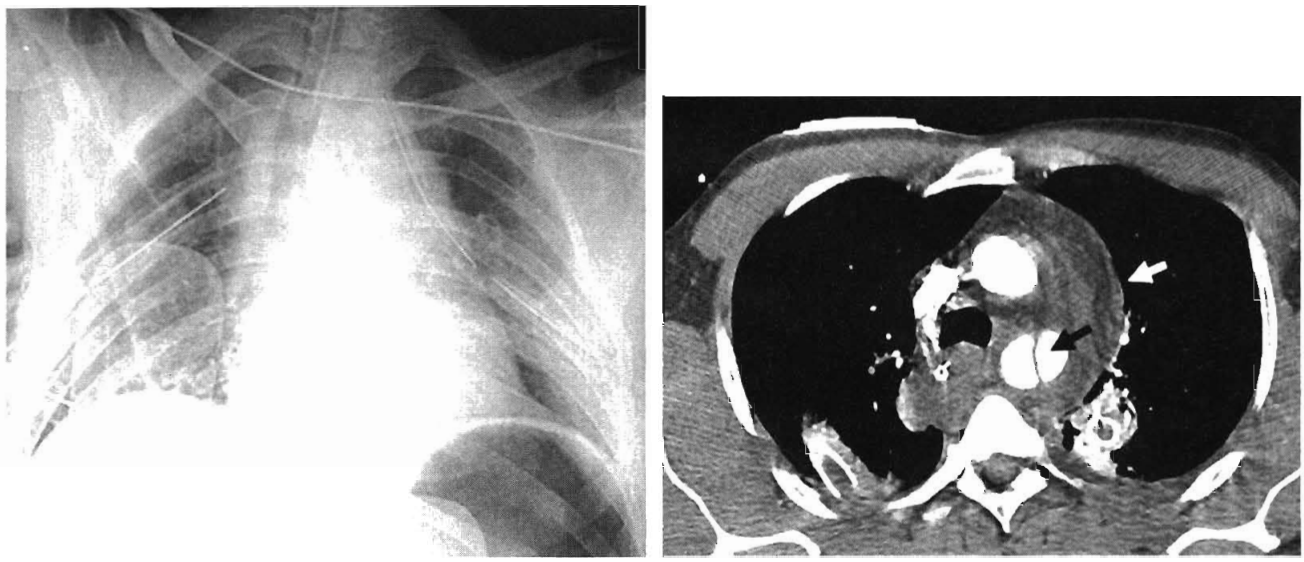
TRAUMA ICU

Patients in the trauma ICU usually have multiple injuries ranging from visceral lacerations to complex fractures of an extremity. Chest trauma, in particular, affects the morbidity and mortality of these patients owing to impairment of the cardiovascular and respiratory systems. Imaging of these patients focuses on identifying acute complications from the trauma as well as recognizing additional injuries that may have been obscured or overlooked on initial evaluation.

Mediastinal Injury

Acute Traumatic Aortic Injury

Tears of the thoracic aorta (Fig. 74-10) are caused by acute deceleration injury such as occurs with a high-speed motor vehicle crash or a fall or as a result of crush injury to the chest.



A B

FIGURE 74–10. A 35-year-old man was involved in a high-speed motor vehicle crash. **A,** Anteroposterior chest radiograph shows abnormal contour of the mediastinum, obscuration of the aortic knob, and rightward displacement of the trachea, consistent with mediastinal injury. Note tubes are in satisfactory position. **B,** Axial CT image shows intimal flap within the aortic lumen *(black arrow),* representing aortic dissection, surrounded by mediastinal hematoma *(white arrow).*

A tear of the thoracic aorta almost always occurs in a transverse orientation, typically at the aortic isthmus,[58] with the adventitia remaining intact in 60% of cases.[59] Tears of the ascending aorta or complete transection are nearly universally fatal.

Many radiographic abnormalities suggest aortic injury in the acute setting. These include a widened mediastinum, indistinct aortic contour, rightward deviation of the trachea, downward displacement of the left main bronchus, and thickening of the right paratracheal stripe.[59,60] Of these, mediastinal widening and abnormal contour of the aortic arch are shown to be the most reliable.[61-63] Chest radiographs have great value in excluding traumatic aortic injury with a negative predictive value around 98%.[59,61]

In patients whose chest radiographs are equivocal or highly suspicious for aortic injury, contrast medium–enhanced CT is indicated.[64] CT findings of acute aortic injury include irregularity of the aortic wall, pseudoaneurysm, abrupt change in aortic caliber, intimal flap, extravasation of contrast material, and periaortic hematoma.[64-66] Digital subtraction aortography should follow abnormal or equivocal CT scans.

Tracheobronchial Tree Rupture

Rupture of the tracheobronchial tree is an uncommon result of blunt trauma, with bronchial rupture occurring more often than rupture of the trachea.[67] With bronchial rupture, the injury is usually located in the main bronchus 1 to 2 cm distal to the carina. Disruption of the trachea typically involves the membranous portion just proximal to the carina.[67] Associated vascular injury occurs more frequently with tracheal tear than with the bronchial injury.[68,69]

About 70% of chest radiographs show pneumomediastinum or pneumothorax in the setting of tracheobronchial disruption.[70] The "fallen lung" sign (Fig. 74-11), indicating complete bronchial disruption, describes the severed and collapsed lung lying against the posterolateral aspect of the chest wall or the diaphragm.[71-73] Other findings that strongly suggest tracheobronchial injury include a large pneumothorax not responding to percutaneous drainage, pneumothorax and pneumomediastinum in the absence of pleural effusion, and pneumomediastinum in patients not receiving positive-pressure ventilation.[74-76]

Esophageal Rupture

Rupture of the esophagus is an uncommon injury that occurs more frequently by iatrogenic means than from blunt chest trauma.[77] Mediastinitis and septic shock can rapidly ensue, accounting for the relatively high mortality rate. Typical clinical signs and symptoms include vomiting, chest pain, and subcutaneous emphysema.[78] The radiographic findings of esophageal rupture include mediastinal widening, pneumomediastinum, pleural effusion, pneumothorax, and hydropneumothorax.[70,79] Contrast esophagography is the standard approach for diagnosis esophageal rupture. On CT, the area of greatest esophageal thickening often represents the perforation site.[70] CT also provides more detailed information than radiography on developing complications.

Thoracic Duct Rupture

The most common cause of thoracic duct disruption is iatrogenic injury, reported in about 0.2% of patients undergoing thoracic surgery.[80] Thoracic duct injury from blunt chest injury is very rare[81] and is thought to occur with hyperextension of the thoracic spine.[82] Chylothorax, which usually develops several days to weeks after the trauma, is the typical radiographic finding. However, chylothorax and pleural effusion are radiographically indistinguishable. The delay in development of chylothorax, a clue to the diagnosis, occurs because chyle accumulating in the mediastinum needs sufficient pressure to rupture into the pleural space.[83] CT findings are usually the same as with other pleural effusions, and the injury site is best identified with lymphangiography.

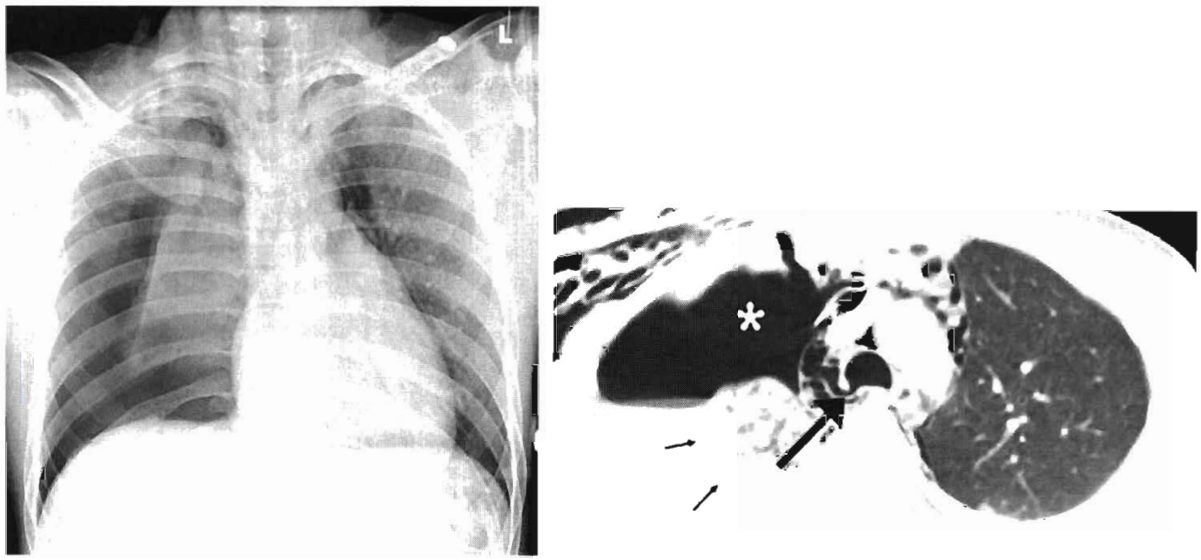


FIGURE 74–11. A 22-year-old man was involved in a high-speed motor vehicle crash. **A,** Anteroposterior chest radiograph shows right pneumothorax, pneumomediastinum, right lung collapse, and subcutaneous emphysema. **B,** Axial CT image shows tracheal laceration *(large arrow)*, right pneumothorax *(asterisk)*, and the collapsed right lung *(small arrows)* in the dependent portion of the chest (fallen lung sign).

Lung Parenchyma

Pulmonary Contusion

Pulmonary contusion is the most common pulmonary injury after blunt chest trauma.[84] It is characterized by leakage of blood into the pulmonary interstitium and alveolar spaces and clinically presents as dyspnea, tachycardia, and hypoxia after blunt injury to the chest. On chest radiographs, the contusion manifests as pulmonary opacity in a nonanatomic distribution,[85] in contrast to the usual segmental or lobar distribution of pneumonia or atelectasis. The contusion is usually found in the lung periphery deep to the site of chest wall impact (Fig. 74-12). Sometimes, however, contusion can occur opposite from the location of the chest wall injury due to a contrecoup effect.[86] Bilateral contusions usually occur from blast injuries.[86]

The timing of the developing opacity on the chest radiograph suggests the diagnosis in the setting of acute trauma, invariably presenting within 6 hours of injury.[87] Contusion usually resolves without sequelae within 3 to 10 days.[67] CT is more sensitive than conventional radiography for detecting pulmonary contusion[88,89] as well as associated chest wall injuries.[90]

Pulmonary Laceration

Pulmonary laceration is more severe than pulmonary contusion and is characterized by frank disruption of the lung parenchyma. Radiographic features of pulmonary laceration change over time and are usually masked by the surrounding contusion during the first few days. In the acute phase, the hematoma within the laceration appears as a well-circumscribed, homogeneous area of soft tissue attenuation. As the hematoma evolves, a round or elliptical gas collection, called a pneumatocele, becomes more obvious.[91] Most pneumatoceles appear within a few days, but some may develop over several weeks (Fig. 74-13). Diameters range from 2 to 5 cm but can be larger.[91] CT is more sensitive than conventional chest radiography in identifying pulmonary lacerations.[89]

Fat Embolism Syndrome

Fat embolism syndrome is a rare but serious complication characterized by pulmonary, cerebral, and cutaneous manifestation in the setting of recent severe fracture and usually occurs 12 to 72 hours after the injury.[92] Both mechanical obstruction from lipids and biochemical-mediated responses lead to the clinical manifestations of fat embolism syndrome.[93,94] In mild cases, the chest radiograph often shows no abnormality. In more severe cases, the initial chest radiograph may be normal but airspace and interstitial opacities resembling other causes of pulmonary edema (Fig. 74-14) can develop within 12 to 72 hours,[85] with

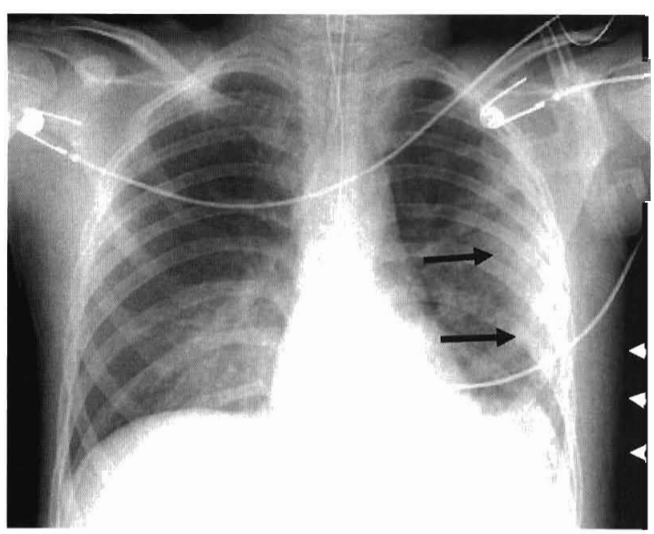
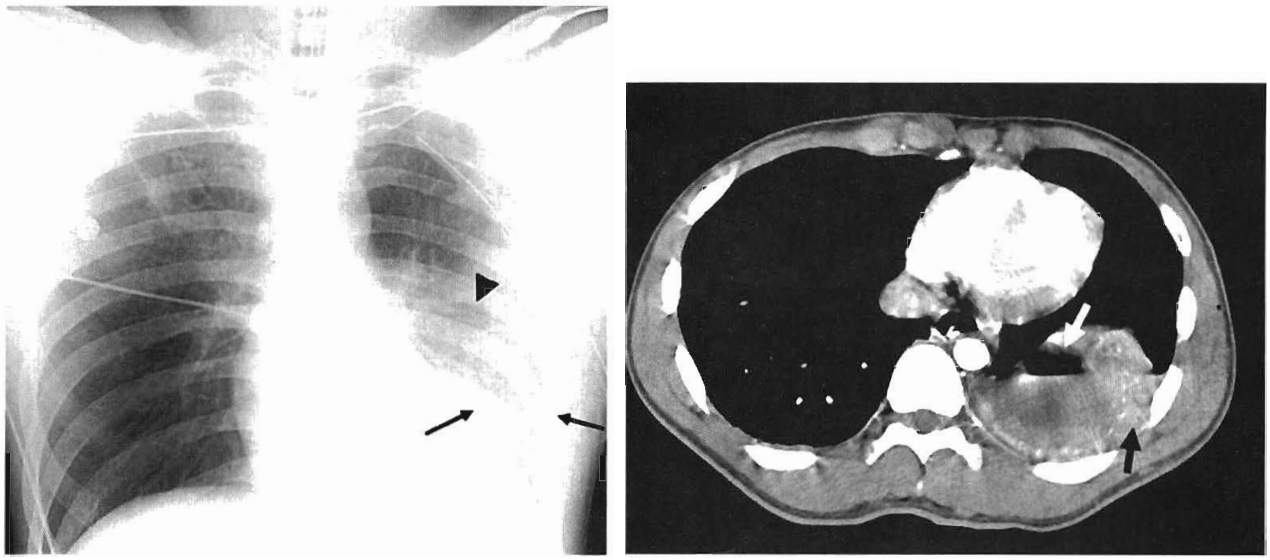


FIGURE 74–12. A 12-year-old boy presented with injuries sustained in a motor vehicle accident. Chest radiograph shows peripheral pulmonary contusion *(arrows)*. Swelling of the soft tissue of the left chest wall adjacent to the area of pulmonary contusion is noted *(arrowheads)*.



A B

FIGURE 74–13. A 30-year-old man was involved in motor vehicle crash. **A,** Chest radiograph shows small lucent area *(arrowhead)* within area of the left lower lobe opacity *(arrows)*. **B,** Axial CT image of the chest shows a "cavity" with an air-fluid level *(white arrow)* in the left lower lobe, representing a pulmonary laceration surrounded by pulmonary contusion and hemorrhage *(black arrow)*.

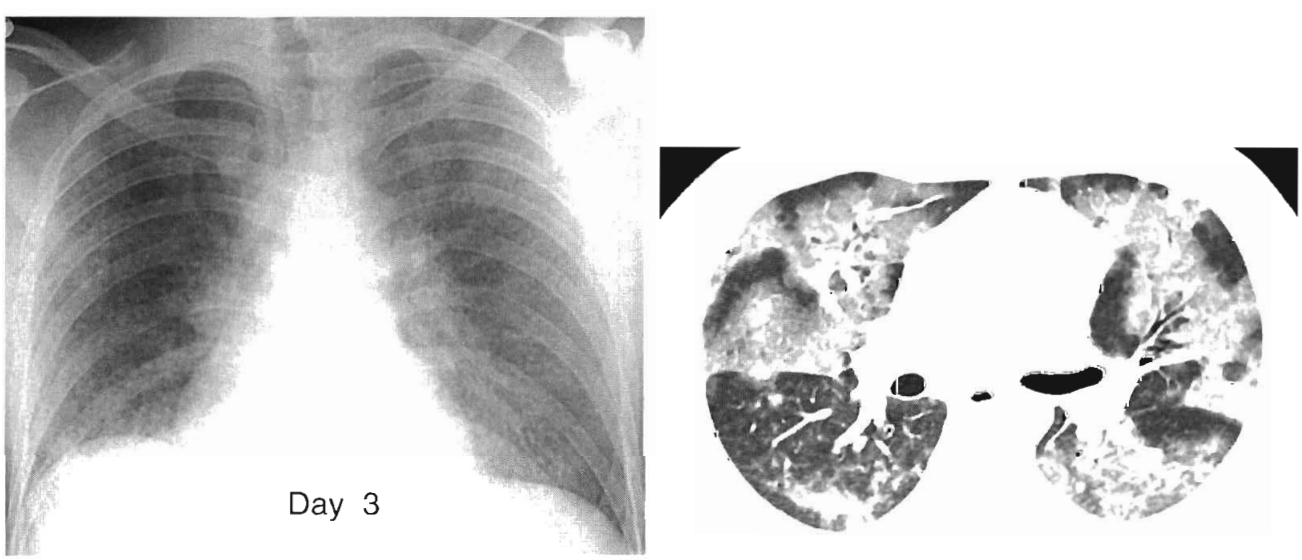
resolution typically occurring in 10 to 14 days in the absence of superimposed disease. The delay in onset of abnormal opacities on the chest radiograph and the history of fracture are clues that can distinguish fat embolism syndrome from pulmonary contusion or pneumonia.

Pleura

Pneumothorax

Pneumothorax is more common with blunt chest trauma (15% to 38%) than with penetrating injuries to the chest (18% to 19%).[95,96] The clinical significance of pneumothorax depends on the patient's underlying cardiopulmonary function and not on the physical size of the pneumothorax.[97] However, pneumothoraces in all trauma patients should be considered significant, regardless of the size, because they can rapidly become life threatening if positive-pressure mechanical ventilation is instituted.[98]

In the supine position free gas will localize in the nondependent caudal and anteromedial aspects of the pleural space. Evidence of pneumothorax on the supine chest radiograph is often indirect and includes a prominent costophrenic sulcus (deep sulcus sign), relative basilar hyperlucency, increased sharpness of the ipsilateral hemidiaphragm, increased sharpness of cardiac border, presence of gas in the minor fissure,



A B

FIGURE 74–14. A 33-year-old man presented with a left femur fracture and clinical fat embolism syndrome. The initial chest radiograph was normal. **A,** Seventy-two hours later, diffuse pulmonary opacity developed without cardiomegaly, coinciding with dyspnea, an altered level of consciousness, and diffuse petechiae. **B,** Axial CT image on the same day shows geographic appearance of ground-glass opacity in both lungs, consistent with noncardiogenic pulmonary edema.

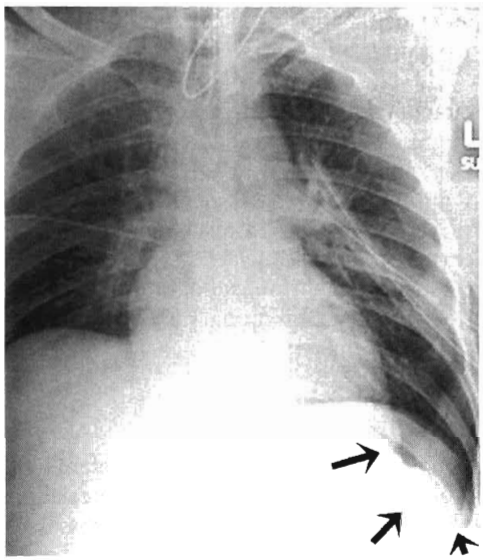


FIGURE 74–15. Bedside anteroposterior chest radiograph shows lucency without pulmonary vessels in the lower left lateral hemithorax expanding the costophrenic sulcus *(arrows)*, despite two left thoracostomy tubes, consistent with pneumothorax, reflecting the deep sulcus sign.

and caudal displacement of the ipsilateral hemidiaphragm (Fig. 74-15).[99-101] CT is more sensitive than chest radiography for detecting pneumothorax and is especially helpful in critically ill patients who cannot tolerate lateral decubitus positioning.

Hemothorax

In contrast to pneumothorax, hemothorax is more common with penetrating chest trauma (63.9% to 82.3%) than with blunt chest injuries (23.2% to 51%).[96,102] Clinical signs and symptoms include hypotension and decreased breath sounds with dullness to percussion over the affected hemithorax. The supine chest radiograph shows findings identical to those seen with pleural effusion and include increased opacity on the affected hemithorax, a crescentic opacity interposed between the inner margin of ribs and the lung, and an apical cap.[97]

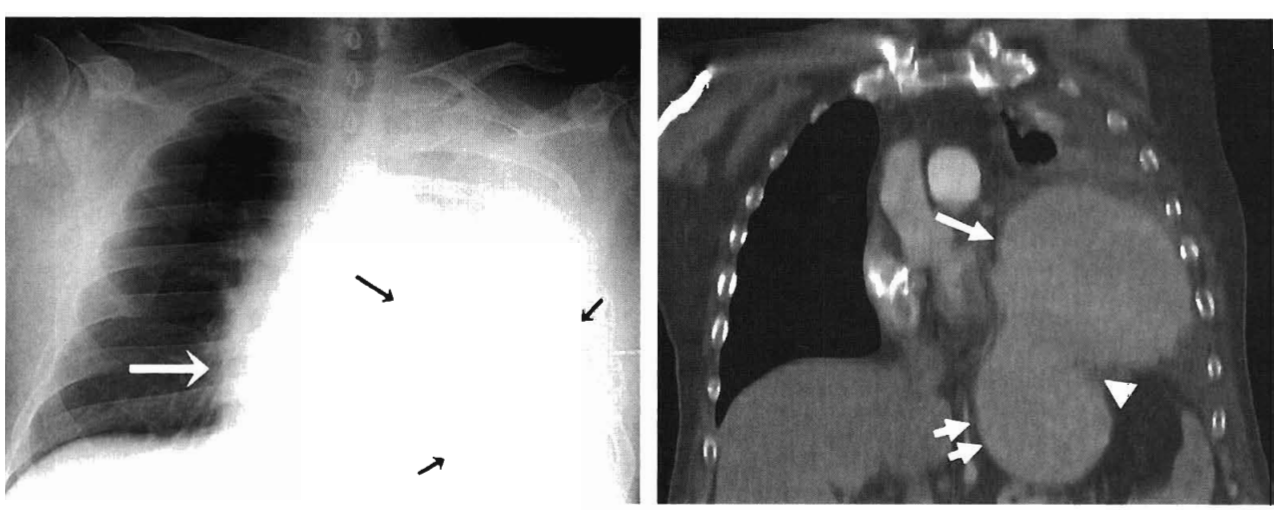
Diaphragmatic Rupture

Rupture of the diaphragm is a rare complication found in 0.8% to 1.6% of patients admitted with blunt trauma.[103] Radiographic findings of diaphragmatic rupture include a gas-filled viscus or the tip of a properly placed enteric tube above the diaphragm (the most strongly suggestive diagnosis sign),[104] irregularity of diaphragmatic contour, elevation of the affected hemidiaphragm without evidence of atelectasis, and contralateral shift of the mediastinum without pleural effusion or pneumothorax (Fig. 74-16).[97,104,105] However, the sensitivity of chest radiographs for detecting diaphragmatic rupture is quite low (46% for ruptures on the left and 17% for ruptures on the right).[104]

CT has proved to be more valuable in the detection of diaphragmatic injuries with a sensitivity of 71% (78% for injuries on the left and 50% for those on the right) and a specificity approaching 100%.[106,107] Findings of diaphragmatic rupture on CT include discontinuity of the diaphragm, visceral herniation, waist-like constriction of the bowel (the collar sign), and layering of the herniated viscus against the posterior ribs (the dependent viscera sign).[108-110] Delay in diagnosis is common, especially in patients receiving positive-pressure ventilation, because the injury is masked by the positive-pressure gradient between the thoracic and abdominal cavities.[111]

MEDICAL ICU

The medical ICU provides care for patients suffering from diseases requiring respiratory support, for patients with severe infections, and those who need close monitoring. This section will focus on patients with acute respiratory distress syndrome (ARDS), pulmonary infection, and pulmonary thromboembolic disease.



A B

FIGURE 74–16. A 48-year-old man involved in a motor vehicle crash sustained a diaphragmatic injury. **A,** Bedside chest radiograph shows diffuse opacity in the left hemithorax and rightward mediastinal displacement *(white arrow)*. A round lucency representing the gastric bubble is present within the opacified left hemithorax *(black arrows)*. **B,** Coronal CT re-formation shows partial herniation of the stomach (gastric fundus [*single arrow*] and gastric body [*double arrows*]) into the chest through a large defect in the diaphragm *(arrowhead)*.

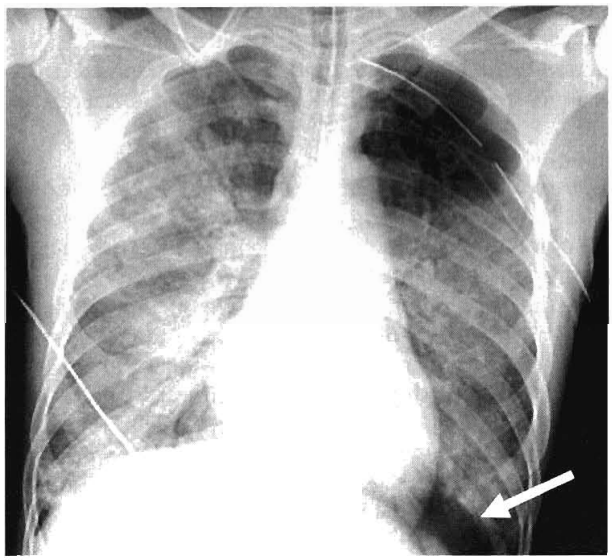


FIGURE 74–17. A 22-year-old man with clinical sepsis developed hypoxia 2 days after admission. An anteroposterior chest radiograph shows diffuse lung opacity with normal heart size, consistent with noncardiogenic pulmonary edema. Also note a pneumothorax in the left costophrenic angle *(arrow)*.

Acute Respiratory Distress Syndrome

ARDS represents a massive inflammatory reaction in the lungs resulting from a variety of causes and is characterized by severe hypoxemia. The incidence of ARDS is difficult to determine, partly owing to the variety of causes, but it is a common problem in hospital ICUs. Various published estimates have ranged from 1.5 to 71 cases per 100,000 people. Earlier estimates suggest that approximately 150,000 Americans are affected each year.[112] The radiographic manifestations depend on the stage of the disease. In the acute phase, diffuse ill-defined opacities may be present. Initially, these opacities predominate in the periphery of the lungs[113] and, as the disease progresses, the entire lung can become opacified (Fig. 74-17).[114] During the subacute phase (5 to 10 days later), proliferation of endothelial cells and fibroblasts leads to a pattern of progressive lung destruction on the chest radiograph.

Some patients recover from ARDS without any residual deficit in pulmonary function whereas others progress to the chronic phase several weeks after the initial lung injury with permanent respiratory sequelae. Fibrosis and focal emphysema are usually evident on radiographs at this stage.[115] In contrast to cardiogenic pulmonary edema, ARDS progresses gradually over several days.

Infection

Pneumonia

Nosocomial pneumonias are a serious problem in all critical care units and can have a high mortality, especially in elderly patients and those with other coexistent illnesses.[116,117]

Ventilator-associated pneumonia is defined as the development of new and persistent pulmonary opacities in a patient at least 48 hours after initiation of mechanical ventilation in association with two of the following clinical criteria: fever, leukocytosis, and purulent proximal airway secretions. However, sensitivity and specificity of these criteria are low and blood and airway secretion cultures may be useful in the setting of diffuse lung injury.[118]

The radiographic hallmark of community-acquired pneumonia is airspace consolidation with air bronchograms in a segmental, lobar, or diffuse distribution.[115] The majority of patients with nosocomial pneumonia, however, have a pattern of bronchopneumonia on the chest radiograph characterized by patchy peribronchial opacities, volume loss, and bronchial wall thickening (Fig. 74-18). In mild disease, usually only bronchial wall thickening is evident, whereas in more advanced stages, heterogeneous areas of consolidation develop in several lobes.[119,120] Because of primary involvement of the airways, volume loss in the affected segments or

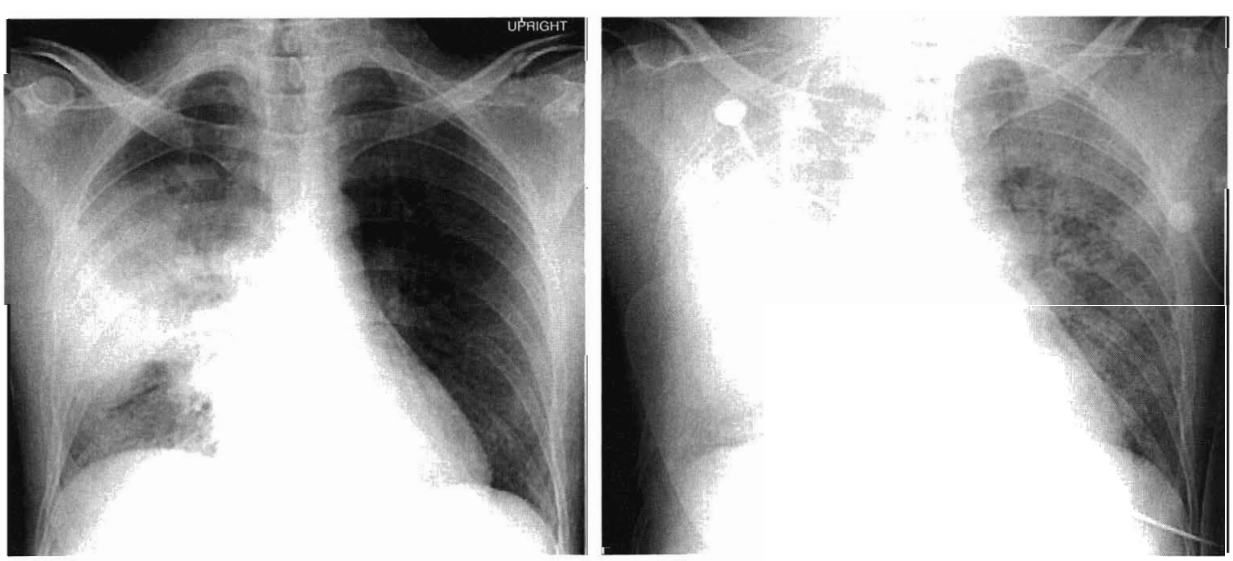
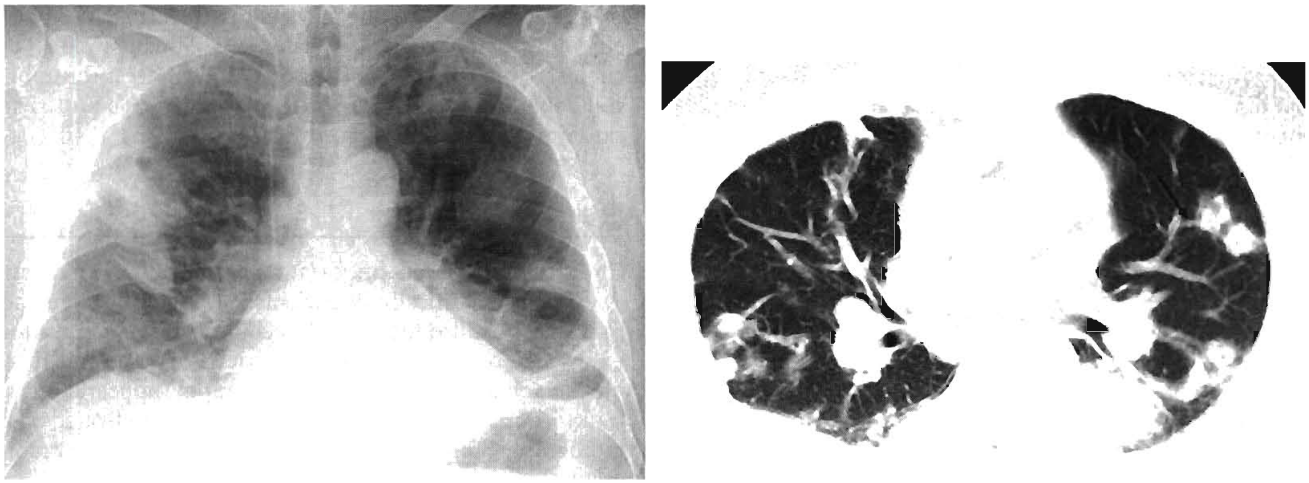
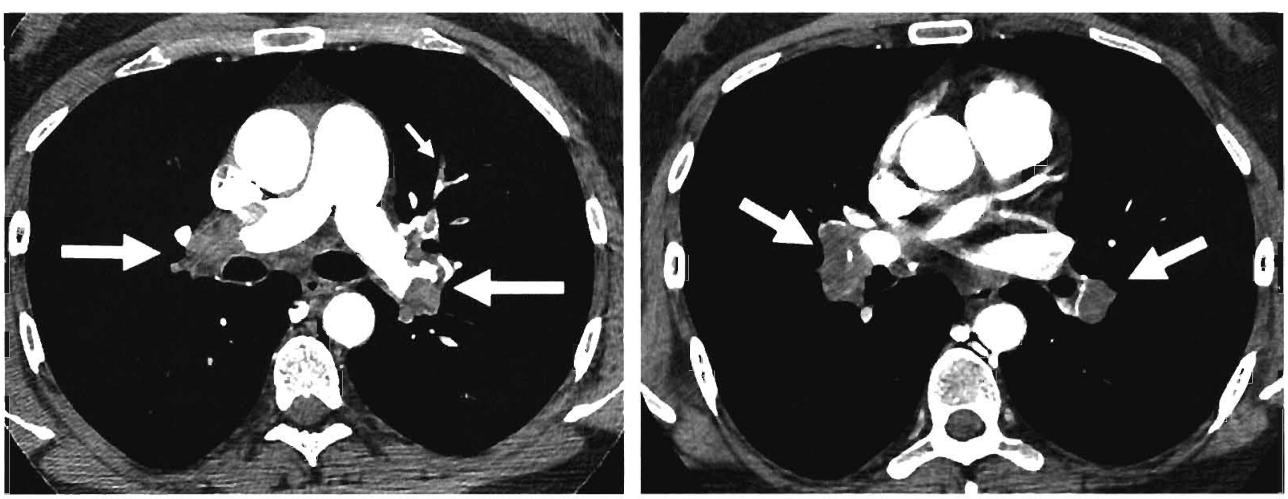


FIGURE 74–18. A 30-year-old man presented with *Klebsiella pneumoniae* infection. **A,** Initial chest radiograph shows right upper lobe opacity consistent with lobar pneumonia. **B,** Two days later, the right lung is nearly completely opacified, showing the rapid spread of infection. Tube and line are in expected location. Pacing pad is superimposing on the right chest.



A B

FIGURE 74–19. A 46-year-old intravenous drug abuser presented with septic emboli. **A,** Bedside chest radiograph shows multiple bilateral peripheral opacities, some of which are cavitating. **B,** Axial CT scan shows multiple peripheral well-defined pulmonary nodules with a pulmonary vessel terminating at one of the nodules *(arrow),* an example of the feeding vessel sign of septic embolism.



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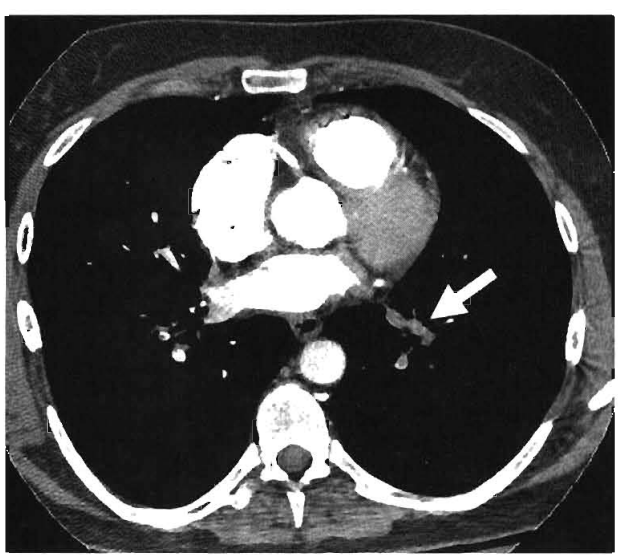

C

FIGURE 74–20. A 46-year-old woman presented with acute shortness of breath and hypoxia. Chest radiograph is normal. **A,** Axial CT scan of the chest shows evidence of low attenuation filling defect in the left and right main pulmonary arteries *(large arrows)* and left upper lobe segmental artery *(small arrow)* representing massive pulmonary embolism. The emboli extend to the left and right interlobar arteries *(arrows)* as well as left lower lobe segmental artery *(arrow)* as seen in **B** and **C,** respectively.

lobes may accompany bronchopneumonia.[120] Ventilatory-associated pneumonia is indistinguishable radiographically from other causes of nosocomial pneumonia. Radiographs may also show associated complications such as abscesses and pneumatoceles.

Septic Emboli

Septic emboli to the lungs come from a variety of sources, including infected right-sided heart valves, peripheral and pelvic thrombophlebitis, and infected intravenous catheters. The usual radiographic findings of septic emboli are bilateral ill-defined nodular opacities, with or without cavitation, in the lung periphery that develop at different times and show features of different stages of evolution.[121] On CT, multiple parenchymal nodules and wedge-shaped subpleural areas of consolidation are the usual findings. Location adjacent to the end of a pulmonary vessel (feeding vessel sign) often occurs (Fig. 74-19).[122]

Pulmonary Thromboembolic Disease

Acute pulmonary embolism is a potentially lethal condition that can be difficult to diagnose clinically because of the nonspecific clinical presentation. Prompt diagnosis and treatment reduce morbidity and mortality.[123,124] The annual incidence of pulmonary embolism is 70 to 133 per 100,000 individuals, with approximately 12% of patients with pulmonary embolism dying within 30 days.[125] Although many imaging modalities including ventilation-perfusion scintigraphy and conventional pulmonary angiography have been used to diagnose pulmonary embolism, CT pulmonary angiography (CTPA) has emerged as the initial imaging study of choice given its high sensitivity and specificity and the additional advantage of evaluating the entire thorax for other explanations for cardiopulmonary signs and symptoms.[126,127]

Many findings on conventional chest radiographs have been described in patients with pulmonary embolism, but they are inconsistently present and are nonspecific. Features diagnostic for acute pulmonary embolism on CTPA include a partial or complete filling defect in the pulmonary arteries (Fig. 74-20).[126,127] Associated parenchymal abnormalities such as regional oligemia, volume loss, and a wedge-shaped pleural-based opacity may also be present.

With the advent of multi-detector row CT, conventional pulmonary angiography has been relegated to an infrequently used problem-solving tool in pulmonary thromboembolic disease. Pulmonary angiography may be indicated in cases in which clinical suspicion for pulmonary embolism remains high despite normal pulmonary vasculature on CTPA and no evidence of deep venous thrombosis on sonographic evaluation of the veins of the lower extremities.[128] In addition, pulmonary angiography may be the appropriate diagnostic examination when visualization of the peripheral pulmonary arteries is limited by technical factors. However, even conventional angiography may fail to detect small peripheral emboli,[129-131] particularly isolated subsegmental clots. The clinical significance of these isolated peripheral thrombi is still debated and likely depends on the patient's underlying cardiopulmonary function.[128]

CONCLUSION

Chest imaging is an important component in diagnostic evaluation of critically ill patients. Although bedside chest radiography is limited by both technical and patient factors, knowledge of complications of various diseases and therapies as well as their respective radiographic appearances can lead to improvement in patient care. CT is indicated when radiographic findings are equivocal or when the chest radiograph does not explain the patient's clinical picture.

ANNOTATED REFERENCES

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Chapter 75

ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME

Lorraine B. Ware • Gordon R. Bernard

KEY POINTS

1. **ALI/ARDS is very common in critically ill patients and is underdiagnosed.** It is important to make the diagnosis so that appropriate therapy including a lung protective ventilatory strategy can be initiated.
2. The **most common causes of ALI/ARDS** are sepsis, pneumonia, aspiration of gastric contents, and multiple trauma.
3. Despite numerous randomized controlled clinical trials, there is **no specific treatment for ALI/ARDS** that has been proven to be beneficial other than a lung protective ventilatory strategy.
4. Ventilation in volume control mode with a tidal volume of 6 mL/kg predicted body weight and plateau pressure less than 30 cm H_2O has been shown to **improve mortality in ALI/ARDS** compared with a larger tidal volume (12 mL/kg).

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) are common problems in the ICU and can complicate a wide spectrum of critical illnesses. First described by Ashbaugh and colleagues in 1967,[1] ARDS was initially termed the *adult respiratory distress syndrome* to distinguish it from the respiratory distress syndrome of neonates. However, with the recognition that ALI/ARDS can occur in children, the term *acute* has replaced *adult* in the nomenclature, in recognition of the typical acute onset that defines the syndrome. Although specific treatments for ALI/ARDS have been slow to emerge, the recent development of new modes of mechanical ventilation that improve mortality emphasizes the importance of identifying and treating all patients with ALI/ARDS. Although this point would seem to be straightforward, in practice both disorders remain largely underdiagnosed,[2] which perpetuates inappropriate or inadequate treatment.

The exact incidence of ALI/ARDS has been difficult to estimate for a variety of reasons. Until recently, variable definitions were used.[3] The wide variety of causes and coexisting disease processes has also made identification of cases difficult both at the clinical and at the administrative coding level.[4] The National Institutes of Health (NIH) first estimated the incidence at 75 per 100,000 population in 1977.[5] A number of studies since then have reported lower incidences.[4] However, a recent study that utilized the enrollment logs from the National Heart, Lung and Blood Institute–sponsored ARDS Network of 20 hospitals estimated that the incidence could be as high as 64 cases per 100,000 population, not far off from the original NIH estimate. This dataset has the advantage of being prospectively collected from a large number of academic medical centers. Regardless of the exact incidence, it is clear that ALI/ARDS is a major public health problem that will be encountered frequently by all physicians who care for critically ill patients.

PATHOPHYSIOLOGY

The pathophysiology of ALI/ARDS is complex and remains incompletely understood. Microscopically, lungs from afflicted individuals in the early stages show diffuse alveolar damage with alveolar flooding by proteinaceous fluid, neutrophil influx into the alveolar space, loss of alveolar epithelial cells, deposition of hyaline membranes on the denuded basement membrane, and formation of microthrombi (Fig. 75-1).[6] The alveolar flooding occurs as a result of injury to the alveolar-capillary barrier and is a major determinant of the hypoxemia and altered lung mechanics that characterize early ALI/ARDS. The alveolar-capillary barrier is formed of two separate cell layers: the microvascular

FIGURE 75–1. Low-power photomicrograph of a histologic section from the lung of a patient with the acute respiratory distress syndrome. Note the presence of hyaline membranes (*arrows*), neutrophilic inflammation, and presence of microthrombi (*arrowhead*).

endothelium and the alveolar epithelium. Injury to the alveolar epithelium is a prominent feature histologically with loss of alveolar epithelial barrier integrity and necrosis and sloughing of alveolar epithelial type I cells. Although endothelial injury is less obvious at the microscopic level, ultrastructural studies reveal that it is widespread.[7,8] Endothelial injury allows leakage of plasma from the capillaries into the interstitium and airspaces. The alveolar flooding in ALI/ARDS is characteristically with a protein-rich edema fluid, owing to the increased permeability of the alveolar capillary barrier, in contrast to the low protein pulmonary edema that results from hydrostatic causes such as congestive heart failure or acute myocardial infarction.[9-12]

The mechanisms by which the microvascular endothelium and alveolar epithelium are injured are probably multiple and may vary depending on the inciting event. Neutrophils appear to play an important role.[13] Early ALI/ARDS is characterized by migration of neutrophils into the alveolar compartment.[7,8] Neutrophils can release a variety of injurious substances, including proteases such as neutrophil elastase, collagenase, and gelatinases A and B and reactive nitrogen and oxygen species. In addition, they can elaborate proinflammatory cytokines and chemokines that serve to amplify the inflammatory response in the lung. Resident alveolar macrophages are also involved in initiating and sustaining a proinflammatory cytokine cascade that leads to recruitment of neutrophils into the lung.

In addition to acute neutrophilic inflammation and elaboration of a proinflammatory cytokine cascade, a variety of other abnormalities contribute to the pathogenesis of ALI/ARDS. Surfactant dysfunction is characteristic with abnormalities in both the protein and lipid components[14-17] and likely results from disruption of normal surfactant activity by the influx of plasma proteins into the airspaces, intra-alveolar proteolysis, and injury to the alveolar epithelial type II cells. Surfactant dysfunction may have important implications both for lung mechanics and for host defense.[18] Activation of the coagulation cascade and impaired fibrinolysis are also apparent in patients with ALI/ARDS[19,20] both in the lung and systemically.[21,22] An alteration in the balance of endogenous oxidants and antioxidants with a fall in endogenous antioxidants[23] despite the increased oxidant production has also been observed.[24]

Recently, the contribution of ventilator-associated lung injury to the pathogenesis of ALI/ARDS has been recognized. There are several mechanisms by which mechanical ventilation can injure the lung. Ventilation at very high volumes and pressures can injure even the normal lung, leading to increased permeability pulmonary edema likely due to capillary stress failure.[25] In the injured lung, even tidal volumes that are well tolerated in the normal lung can lead to alveolar overdistention in relatively uninjured areas because the lung available for distribution of the administered tidal volume is greatly reduced and because of uneven distribution of inspired gas.[26,27] In addition to alveolar overdistention, cyclic opening and closing of atelectatic alveoli can cause lung injury even in the absence of alveolar overdistention. The combination of alveolar overdistention with cyclic opening and closing of alveoli is particularly harmful and can initiate a proinflammatory cytokine cascade.[28] A ventilatory strategy that was designed to minimize alveolar overdistention and maximize alveolar recruitment ameliorated this proinflammatory cytokine release.[29] This fundamental insight into the pathogenesis of clinical ALI/ARDS has led to multiple clinical trials of novel ventilatory strategies for patients with ALI/ARDS,[30-33] culminating in the landmark ARDS Network trial of 6 mL/kg versus 12 mL/kg tidal volume ventilation (see Treatment section below).

TABLE 75–1. RISK FACTORS ASSOCIATED WITH DEVELOPMENT OF ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME

Direct Lung Injury	Indirect Lung Injury
Pneumonia	Sepsis
Aspiration of gastric contents	Multiple trauma
Pulmonary contusion	Cardiopulmonary bypass
Fat, amniotic fluid, or air emboli	Drug overdose
Near-drowning	Acute pancreatitis
Inhalational injury	Transfusion of blood products
Reperfusion pulmonary edema	

The clinical syndrome of ALI/ARDS appears to be a characteristic and nonspecific response of the lung to a wide variety of insults (Table 75-1). The commonly associated clinical disorders can be separated into those that directly injure the lung and those that indirectly injure the lung. Although it is not always feasible to determine the exact cause of ALI/ARDS in a given patient, direct causes appear to account for approximately one half of all cases of ALI/ARDS.[34] It is not clear whether the distinction between direct and indirect lung injury is clinically useful.[35] Some investigators have demonstrated reduced respiratory system compliance in patients with ARDS due to direct pulmonary injury compared with indirect causes,[36] although total respiratory system compliance (including the chest wall) is similar.[37] Patients with direct lung injury may be more likely to have improved lung mechanics with the application of positive end-expiratory pressure (PEEP). However, in the largest cohort of patients studied to date there was no difference in mortality between those with direct (pulmonary) and indirect (extrapulmonary) causes of lung injury.[34] Regardless of the underlying cause of ALI/ARDS, most patients with ALI/ARDS appear to have a systemic illness with inflammation and organ dysfunction that is not confined to the lung.[38]

Sepsis is the most common cause of indirect lung injury, with an overall risk of progression to ALI or ARDS of 30% to 40%.[39-42] Severe trauma with shock and multiple transfusions also can cause indirect lung injury. Although the other causes of indirect lung injury are less common, many, such as blood transfusions, are frequent events in the ICU setting. The most common cause of direct lung injury is pneumonia, which may be of bacterial, viral, or fungal origin. The risk of developing ALI/ARDS increases substantially in the presence of multiple predisposing disorders.[39] Secondary factors may also increase the risk. Such factors include chronic lung disease[40] and chronic alcohol abuse.[43] To some extent, every patient in the ICU is at risk for developing ALI/ARDS, and vigilance is required to recognize the diagnosis and treat appropriately.

DIAGNOSIS

In 1994, the American European Consensus Conference published new clinical definitions for ALI/ARDS (Table 75-2).[3] Prior to this time, a variety of definitions were used clinically, including the Murray Lung Injury Score.[44]

TABLE 75–2. AMERICAN EUROPEAN CONSENSUS CONFERENCE DEFINITIONS OF ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

Acute Lung Injury	Acute Respiratory Distress Syndrome
Acute onset	Acute onset
Bilateral infiltrates on chest radiograph consistent with pulmonary edema	Bilateral infiltrates on chest radiograph consistent with pulmonary edema
Absence of clinical evidence of left-sided heart failure (PAWP ≤ 18 mm Hg if measured)	Absence of clinical evidence of left-sided heart failure (PAWP ≤ 18 mm Hg if measured)
PaO_2/FiO_2 ratio ≤ 300	PaO_2/FiO_2 ratio ≤ 200

PAWP, pulmonary artery wedge pressure; PaO_2, arterial partial pressure of oxygen; FiO_2, fraction of inspired oxygen.
From Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149:818-824.

To meet the Consensus diagnostic criteria for either ALI or ARDS, the acute onset of bilateral radiographic infiltrates is required. There should be no clinical evidence of left atrial hypertension, with a pulmonary artery wedge pressure (PAWP) less than or equal to 18 mm Hg if measured. Although not strictly part of these definitions, an underlying cause of lung injury should be sought. In the absence of an identifiable underlying cause (see Table 75-1), particular attention should be given to the possibility of other causes of pulmonary infiltrates and hypoxemia, such as hydrostatic pulmonary edema. If not already in place, flotation of a pulmonary artery catheter may be useful in differentiating high-pressure (hydrostatic) pulmonary edema from the increased permeability pulmonary edema of ALI/ARDS, based on the pulmonary artery wedge pressure. Even this measurement is not foolproof, however, because ALI/ARDS can be complicated by volume overload, severe hypoproteinemia (e.g., as in cirrhosis), or heart failure with concomitant increases in left atrial pressure.

The standardization of definitions for ALI/ARDS has been helpful from several perspectives. For clinical research, it has been valuable in allowing the comparison of different studies and the rapid identification of patients for enrollment in clinical trials. Clinically, the new definitions are easy to apply and facilitate the rapid identification and appropriate treatment of patients with ALI/ARDS. However, it should be noted the nature of ALI/ARDS is such that any definition will have significant shortcomings. First, the definitions must be based solely on clinical criteria because currently there is no laboratory test that allows clinical assessment of the presence or absence of ALI/ARDS. Second, there is no reference to pathogenesis or underlying cause. This is because the list of potential causes of ALI/ARDS is so long, diverse, and common in the critically ill. Third, the presence or absence of multiorgan dysfunction, an important determinant of outcome, is not specified. Finally, although the presence of bilateral infiltrates has major prognostic significance and is clearly a hallmark of ALI/ARDS, the radiographic findings are not specific.[45,46]

In the majority of patients, the initial diagnosis of ALI/ARDS is made clinically. Invasive techniques for diagnosis are of limited clinical utility, and the benefits rarely outweigh the risks. In the past, open lung biopsy was obtained more frequently for diagnosis. Interestingly, the degree of histologic abnormality on lung biopsy does not correlate with ultimate outcome as measured by pulmonary function.[47] Open or thoracoscopic lung biopsy may still be useful in some cases where the diagnosis is uncertain and the underlying cause is not apparent. Occasionally, unsuspected diagnoses requiring specific therapy can be made, such as miliary tuberculosis, pulmonary blastomycosis, or bronchiolitis obliterans organizing pneumonia. Bronchoscopy also has a limited role in diagnosis and may be most useful in the immunocompromised host. Bronchoalveolar lavage for cultures and cytologic examination can identify the cause of pneumonia and is particularly useful in the diagnosis of opportunistic infections. Lavage fluid usually has a predominance of neutrophils, and there may be evidence of diffuse alveolar hemorrhage. Cytologic examination can be used to confirm the presence of diffuse alveolar damage.[48]

In addition to familiarity with the Consensus definitions of ALI and ARDS, the critical care clinician should be aware that ALI and ARDS also have been called by a variety of other terms, some of which are seen mainly in older literature but some that remain in clinical use. Some of the more common of these terms include *adult hyaline membrane disease, postperfusion lung or pump lung, shock lung, ventilator-associated lung injury,* and *adult respiratory insufficiency syndrome.* The term *primary graft failure* or *transplant lung* has been used to describe ALI/ARDS from reperfusion pulmonary edema occurring immediately after lung transplantation. Regardless of the name applied, ALI/ARDS may have prognostic and therapeutic implications above and apart from the underlying cause (e.g., infections, aspiration, trauma). This fact should not take away the imperative to identify these underlying causes, if present, and treat them aggressively.

CLINICAL COURSE

EARLY ALI/ARDS

The Consensus definitions are designed to identify ALI/ARDS patients early in their course, in the acute or exudative phase. Clinically, the acute phase is manifested by the acute onset of radiographic infiltrates consistent with pulmonary edema, hypoxemia, and increased work of breathing. Radiographic infiltrates are bilateral (by definition) but may be patchy or diffuse and fluffy or dense (Fig. 75-2), and pleural effusions may occur.[49] Chest computed tomographic (CT) imaging, although rarely of use clinically, has been employed as an investigative tool to better define the nature of the infiltrates in patients with ALI/ARDS. The distribution of infiltrates by CT is surprisingly patchy; areas of alveolar filling and consolidation occur predominantly in dependent zones, whereas nondependent regions can appear relatively spared.[50,51] Even areas that appear spared in radiographic images may have substantial inflammation when sampled using bronchoalveolar lavage.[52]

The hypoxemia that characterizes early ALI/ARDS is usually relatively refractory to supplemental oxygen. The increased work of breathing in the acute phase of ALI/ARDS is due to decreased lung compliance as a result of alveolar and interstitial edema combined with increased airflow resistance.[53] The combination of hypoxemia and increased work of breathing usually necessitates endotracheal intubation

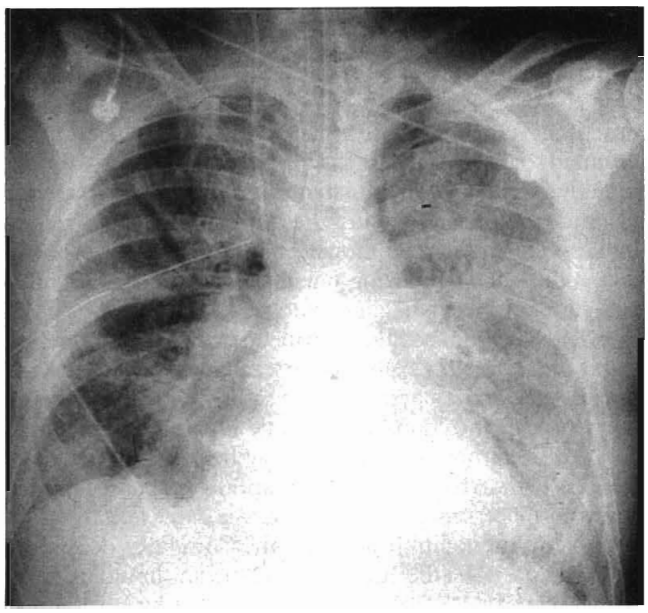

FIGURE 75–2. Portable anteroposterior chest radiograph from a patient with early acute respiratory distress syndrome. Note the diffuse bilateral infiltrates, normal heart size, endotracheal intubation, and the presence of a right-sided thoracostomy tube for drainage of pneumothorax.

and mechanical ventilation, although occasionally patients can be managed with noninvasive ventilation (see Treatment section).

LATE FIBROPROLIFERATIVE ALI/ARDS

In most patients, ALI/ARDS will substantially resolve after the acute phase. However, in others, a fibrosing alveolitis may become clinically apparent after 7 to 10 days, although evidence of deposition of extracellular matrix has been identified in alveolar lining fluid from patients as early as the first day after intubation.[54] Radiographically, linear opacities develop, consistent with the evolving fibrosis. Histologically, pulmonary edema and neutrophilic inflammation are less prominent. A severe fibroproliferative process fills the airspaces with granulation tissue that contains extracellular matrix rich in collagen and fibrin as well as new blood vessels and proliferating mesenchymal cells.[55,56]

Clinically, the late fibroproliferative phase of ALI/ARDS is characterized by continued need for mechanical ventilation, often with persistently high levels of PEEP and F_IO_2. The lung compliance may fall even further, and pulmonary dead-space is elevated. Pulmonary hypertension may develop owing to obliteration of the pulmonary capillary bed, and right ventricular failure may occur.[57] This phase of the illness can be prolonged, lasting weeks, and can be very frustrating for the clinician, patient, and family because small gains in pulmonary function are frequently offset by new problems such as hospital-acquired infections, organ failures, or barotrauma. Progressive deconditioning can make eventual weaning from mechanical ventilation difficult if the fibrosing alveolitis stage is prolonged.

RESOLUTION OF ALI/ARDS

Lung biopsy samples from ALI/ARDS survivors typically show normal or near-normal lung histology. For such histologically complete resolution of ALI/ARDS to occur, a variety of processes must be reversed. Alveolar edema is actively reabsorbed by the vectorial transport of sodium and chloride from the distal airway and alveolar spaces into the lung interstitium.[58] Water is passively absorbed along the osmotic gradient, probably through water channels, the aquaporins.[59] The majority of patients with early ALI/ARDS have impaired alveolar fluid transport; in those with intact alveolar fluid transport, faster rates of alveolar epithelial fluid transport are associated with better outcomes.[12] Soluble and insoluble protein must also be cleared from the airspaces. Soluble protein probably diffuses by a paracellular route into the interstitium, where it is cleared by lymphatics. Insoluble protein probably is cleared by macrophage phagocytosis or alveolar epithelial cell endocytosis and transcytosis.[60]

The denuded alveolar epithelium must be repaired. The alveolar epithelial type II cell serves as the progenitor cell for repopulating the alveolar epithelium. Type II cells proliferate, migrate, and differentiate to reconstitute a tight alveolar epithelial type I cell barrier. The inflammatory cell infiltrate must also resolve, but here the mechanisms are less clear. Resolution of neutrophilic inflammation may be predominantly via neutrophil apoptosis and phagocytosis by macrophages. However, one report suggests that neutrophil apoptosis is impaired in the lungs of patients with ALI/ARDS.[61] The resolution of fibrotic changes is also not well understood. Clearly, however, substantial remodeling is necessary to restore a normal or near-normal alveolar architecture. In patients with advanced fibrosis, this process likely takes place over many months, as pulmonary function abnormalities continue to improve, sometimes remarkably so, out to the first year in survivors of ALI/ARDS (see later).[62]

CLINICAL OUTCOMES

Reported mortality from ALI/ARDS appears to be gradually declining. Prior to the 1990s, mortality in clinical trials was 40% to 60%.[63] Several recent single center studies suggest that mortality rates measured in the same centers had declined over time.[64-67] In the recent ARDS Network study of 861 patients with ALI/ARDS, aggregate mortality to hospital discharge was 31% in the 6 mL/kg tidal volume arm and 40% in the 12 mL/kg tidal volume arm. However, mortality data from this study may significantly underestimate overall ALI/ARDS mortality because many severely ill patients were excluded, including those with advanced liver disease, bone marrow transplantation, severe chronic respiratory disease, burns greater than 30% body surface area, or any other underlying condition with a likelihood of death greater than 50% within 6 months. As has previously been observed in other studies, in this study, risk of in-hospital mortality was highest in those with sepsis (43%), intermediate in those with pneumonia (36%) or aspiration (37%), and lowest in those with multiple trauma (11%).[34] The low tidal volume strategy was effective at reducing mortality across all causes of ALI/ARDS.[34]

Several recent multicenter studies in France,[68] Sweden,[69] Australia,[70] and Argentina[71] attempted to define mortality and prognostic variables in observational population-based studies rather than from clinical trial participants. In these studies, mortality was variable, ranging from 32% for ALI to 58% to 60% for ARDS. The highest mortality observed in patients who met Consensus definitions of ARDS was reported from the French study (60%). Factors that were independently associated with mortality from ALI/ARDS

varied from study to study and included age, Acute Physiology Score, PaO_2/FIO_2 ratio, organ failures or septic shock, immunosuppression, and chronic liver disease.[68-71] Two other U.S. studies of patients with ALI/ARDS predominantly from medical ICUs reported high overall mortality rates (58%).[72,73] Mortality was associated with chronic liver disease and other underlying disease such as HIV infection or cancer. In summary, these studies suggest that while some improvements in ALI/ARDS mortality have been made, mortality remains quite high in population-based studies.

In addition to high mortality rates, ALI/ARDS survivors frequently have long-term functional disability. Interestingly, pulmonary function frequently returns to normal or near normal in survivors. In a recent report of 1 year follow-up in 109 survivors of ARDS,[62] lung volumes and spirometry had returned to normal by 6 months. However, carbon monoxide diffusing capacity was persistently low throughout the year. Six-minute walk distances were persistently low at 12 months, largely owing to muscle wasting and weakness rather than pulmonary function abnormalities.[62] Treatment with any systemic corticosteroid, the presence of illness acquired during the ICU stay, and the rate of resolution of the lung injury and multiorgan dysfunction during the ICU stay were the most important determinants of the 6-minute walk distance during the first year of follow-up. In other studies, patients who survive ALI/ARDS have been reported to have both reduced health-related quality of life and reduced pulmonary-disease–specific health-related quality of life.[74-76]

TREATMENT

STANDARD SUPPORTIVE THERAPY

The gradual decline in mortality attributable to ALI/ARDS over time likely reflects improvements in standard supportive therapy. Although it is beyond the scope of this chapter to discuss all aspects of supportive therapy in detail, a few aspects are considered.

Treatment of Predisposing Factors

First and foremost, a search for the underlying cause of ALI/ARDS should be undertaken. Appropriate treatment for any precipitating infection such as pneumonia or sepsis is critical to enhance the chance of survival. In the immunocompromised host, invasive diagnostic evaluation including bronchoscopy may be warranted to look for evidence of opportunistic infections. In a patient with sepsis and ALI/ARDS of unknown source, an intra-abdominal process should be considered. Timely surgical management of intra-abdominal sepsis is associated with better outcomes.[77] In some patients, the cause of lung injury will not be specifically treatable (e.g., aspiration of gastric contents) or will not be readily identifiable.

Fluid and Hemodynamic Management

The appropriate goals for management of volume status and hemodynamics in patients with ALI/ARDS are controversial. A theoretical case can be made for aggressive diuresis, in an effort to reduce the formation of pulmonary edema. Indeed, in experimental lung injury, lower left atrial pressures are associated with less formation of pulmonary edema.[57,78] There is some clinical evidence to support this approach.[79-82] However, reductions in intravascular volume can have adverse effects on cardiac output and tissue perfusion, factors that could contribute to multisystem organ failure. This is a legitimate concern, because mortality in ALI/ARDS is usually from nonpulmonary causes including other organ failures. In the study by Martin and coworkers, human serum albumin was used to support vascular volume while diuresis was simultaneously affected by furosemide to reduce lung edema.[82] In this pilot randomized clinical trial (n = 37), such treatment did produce transient improvements in oxygenation without compromising the circulation. However, additional studies will be needed to determine effects on ultimate outcome. Some investigators have proposed that clinical outcomes in ALI/ARDS can be improved by delivery of supranormal levels of oxygen using vigorous volume resuscitation and positive inotropes. However, no benefit to supranormal levels of oxygen delivery has been demonstrated in patients with ALI/ARDS.[83,84] One study suggested increased mortality with this approach.[85] Nevertheless, there continues to be a great deal of uncertainty about the appropriate goals for fluid and hemodynamic therapy in ALI/ARDS. While we await the results of ongoing randomized trials, a reasonable strategy is to aim to achieve the lowest intravascular volume that maintains adequate tissue perfusion as measured by urine output or other organ perfusion and metabolic acid-base status. If organ perfusion cannot be maintained in the setting of adequate intravascular volume, then administration of vasopressors and/or inotropes should be used to restore end-organ perfusion.[57] Available evidence does not support the use of one particular vasopressor or combination of vasopressors.

Nutrition

Standard supportive care for the patient with ALI/ARDS includes the provision of adequate nutrition. Although the provision of nutrition has never been studied in randomized controlled trials comparing feeding to withholding of feeding, the available evidence favors the provision of adequate nutrition in critically ill patients. The enteral route is preferred to the parenteral route and is associated with less infectious complications.[86] Enteral feeding may also have other beneficial effects. Experimentally, lack of enteral feeding promoted translocation of bacteria from the intestine.[87] In normal volunteers, administration of parenteral nutrition with bowel rest increased circulating levels of tumor necrosis factor-alpha, glucagon, and epinephrine and increased febrile responses, compared with volunteers who received enteral nutrition.[88]

The goals of nutritional support in any critically ill patient include the provision of adequate nutrients for the patient's level of metabolism and the treatment and prevention of any deficiencies in micronutrients or macronutrients.[89] Whether a particular dietary composition could be beneficial in patients with ALI/ARDS is unclear. Immunomodulation via dietary manipulation has been attempted by a number of investigators in critically ill patients using various combinations of omega-3 fatty acids, ribonucleotides, arginine, and glutamine. A meta-analysis of these trials suggested a beneficial effect on infection rate but not overall mortality.[90] In ALI/ARDS, only one randomized controlled trial of an immunomodulatory nutritional supplement has been published.[91] In that trial, a diet rich in fish oil, gamma-linoleic acid, and antioxidants was associated with a shorter duration of mechanical ventilation and fewer organ failures but no difference in mortality. This trial has yet to be duplicated in a larger patient population. Using a

different approach, a high-fat, low-carbohydrate diet reduced the duration of mechanical ventilation in patients with acute respiratory failure.[92] Although the mechanism of this beneficial effect was postulated to be due to reduction of the respiratory quotient and a resultant fall in carbon dioxide production, the most common cause of a high respiratory quotient in critically ill patients is not dietary composition but simply overfeeding.[89] Overall, there is still no compelling evidence to support the use of anything other than standard (enteral) nutritional support, with avoidance of overfeeding, in patients with ALI/ARDS. How early to attempt institution of feeding remains an unanswered question.

MECHANICAL VENTILATION

Lung Protective Ventilation

Although historically a tidal volume of 12 to 15 mL/kg was recommended in patients with ALI/ARDS, it is now clear that a low tidal volume, protective ventilatory strategy reduces mortality. In 2000, the NIH ARDS Network published the findings of their first randomized, controlled, multicenter clinical trial in 861 patients.[93] The trial was designed to compare a low tidal volume ventilatory strategy (6 mL/kg predicted body weight, plateau pressure less than 30 cm H_2O) with a higher tidal volume (12 mL/kg predicted body weight, plateau pressure less than 50 cm H_2O). The rationale for the clinical trial was the growing body of clinical and experimental evidence suggesting that ventilation with high tidal volumes and high plateau pressures might be harmful to the injured lung (see Pathophysiology earlier). In this trial, the in-hospital mortality rate was 40% in the 12 mL/kg group and 31% in the 6 mL/kg group, a 22% reduction. Ventilator-free days and organ-failure-free days were also significantly improved in the low tidal volume group. These findings were truly remarkable, because no prior large randomized clinical trial of any specific therapy for ALI/ARDS has ever demonstrated a mortality benefit.

The protocol for the ARDS Network low tidal volume ventilatory strategy is summarized in Table 75-3. Predicted body weight is calculated based on measured height, using the equations provided. This is a key point that is often overlooked by clinicians; use of actual rather than predicted body weight can result in the use of erroneously high and potentially

TABLE 75–3. SUMMARY OF THE NIH ARDS NETWORK LOWER TIDAL VOLUME STRATEGY

Calculate Predicted Body Weight (PBW):

- Males: PBW (kg) = 50 + 2.3[(height in inches) − 60] or 50 + 0.91[(height in cm) − 152.4]
- Females: PBW (kg) = 45.5 + 2.3[(height in inches) − 60] or 45.5 + 0.91[(height in cm) − 152.4]

Ventilator Mode:

- Volume assist/control until weaning

Tidal Volume (V_T):

- Initial V_T: adjust V_T in steps of 1 mL/kg PBW q1-2h until V_T = 6 mL/kg.
- Measure inspiratory plateau pressure (Pplat, 0.5 sec inspiratory pause) every 4 hours *and* after each change in PEEP or V_T.
- If Pplat > 30 cm H_2O, decrease V_T to 5 or to 4 mL/kg.
- If Pplat < 25 cm H_2O and V_T < 6 mL/kg PBW, increase V_T by 1 mL/kg PBW.

Respiratory Rate (RR):

- With initial change in V_T, adjust RR to maintain minute ventilation.
- Make subsequent adjustments to RR to maintain pH 7.30-7.45, but do not exceed RR = 35/min and do not increase set rate if $PaCO_2$ < 25 mm Hg.

I:E Ratio:

- Acceptable range = 1:1 to 1:3 (no inverse ratio)

F_IO_2, PEEP, and Arterial Oxygenation:

- Maintain PaO_2 = 55 to 80 mm Hg or SpO_2 = 88% to 95% using the following PEEP/F_IO_2 combinations:

F_IO_2	0.3-0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	1
PEEP	5	8	8	10	10	10	12	14	14	16	18	18-25

Acidosis Management:

- If pH < 7.30, increase RR until pH ≥ 7.30 or RR = 35 breaths/min.
- If pH remains < 7.30 with RR = 35, consider bicarbonate infusion.
- If pH < 7.15, V_T may be increased (Pplat may exceed 30 cm H_2O).

Alkalosis Management:

- If pH >7.45 and patient is not triggering ventilator, decrease set RR but not below 6 breaths/min.

Weaning:

- Initiate weaning by Pressure Support when all of the following criteria are present:
  - F_IO_2 < 0.40 and PEEP < 8 cm H_2O.
  - Not receiving neuromuscular blocking agents.
  - Inspiratory efforts apparent (ventilator rate may be decreased to 50% of baseline level for up to 5 minutes to detect inspiratory effort).
  - Systolic arterial pressure > 90 mm Hg without vasopressor support.

injurious tidal volumes. The tidal volume should initially be set at 6 mL/kg predicted body weight. Interestingly, a tidal volume of 6 mL/kg predicted body weight is similar to normal tidal volumes in spontaneously breathing adults at rest. So, although this size tidal volume is often referred to as low tidal volume, it is really *normal* tidal volume ventilation. *However*, if end-inspiratory plateau pressure (measured during a 0.5-second pause) is still greater than 30 cm H_2O, then tidal volume must be reduced in a stepwise fashion by 1 mL/kg to a minimum of 4 mL/kg. Ventilation with this size tidal volume is generally well tolerated. Some patients may have breath stacking or significant dyssynchrony with the ventilator. Increasing the inspiratory flow rate and, if necessary, the level of sedation is usually sufficient to manage these problems. As with any mode of ventilation in ALI/ARDS, occasionally patients will require neuromuscular blockade, but this should be used only as a last resort in patients with refractory hypoxemia because the use of paralytics may increase the risk of critical illness polyneuropathy and myopathy. Respiratory acidosis may develop but is usually not symptomatic. Raising the respiratory rate is usually sufficient to compensate for the decreased tidal volume; a rate as high as 35 breaths/min was used in the clinical trial.

In the ARDS Network protocol, the level of PEEP and F_IO_2 is titrated according to a set of predetermined values (see Table 75-3). The optimal level of PEEP in ALI/ARDS has been controversial and has never been established. Various strategies for the application of PEEP have been used, including prophylactic PEEP (Table 75-4). The levels of PEEP in the ARDS Network protocol were arrived at by consensus of the ARDS Network investigators. As discussed earlier, recurrent opening and closing of atelectatic alveoli at end expiration may trigger a cytokine cascade and propagate lung injury. This concern has led some to propose that higher levels of PEEP be used to maintain alveolar recruitment. In a small trial, one investigator reported that a ventilator strategy that incorporated low tidal volume and titration of the PEEP level to above the lower inflection point on each individual patient's pressure-volume curve improved mortality in ARDS.[30] However, measurement of the pressure-volume curve in any given patient is not practical clinically. To address the question of clinical utility of higher PEEP levels in ALI/ARDS, the ARDS Network has completed a large multicenter trial comparing the ARDS Network protocol (see Table 75-3) with a similar protocol that used higher PEEP levels for each level of F_IO_2.[94] There was no difference in clinical outcomes between the two groups.

Other Modes of Mechanical Ventilation

A variety of other modes of mechanical ventilation have been used anecdotally or in small clinical trials. Some of these strategies are summarized in Table 75-4. Currently there are no data from large randomized multicenter clinical trials to support the use of any alternative ventilatory strategy. However, the clinician caring for patients with ALI/ARDS may occasionally be faced with severe refractory hypoxemia that is unresponsive even to F_IO_2 of 1.0 and a PEEP level of 24 cm H_2O or more. In these situations, deeper sedation and neuromuscular blockade may be helpful. If hypoxemia persists, then alternative strategies might be considered as rescue therapies. Prone positioning and inhaled nitric oxide both can produce transient improvements in oxygenation. However, neither therapy has been shown to improve outcome from ALI/ARDS in large randomized clinical trials (see Table 75-4). More invasive strategies such as ECMO or ECCOR are not widely used outside of the pediatric setting, and there are no data to support their use. High-frequency ventilation and liquid or partial liquid ventilation remain experimental therapies in adults at this time.

Noninvasive Ventilation

Noninvasive positive-pressure ventilation delivered by nasal or full facemask has been highly successful in avoidance of intubation in patients with acute exacerbation of chronic

TABLE 75–4. SUMMARY OF ALTERNATIVE VENTILATOR STRATEGIES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

Ventilatory Strategy	Year	How Studied	No. of Patients	Comments	Study
High levels of PEEP	1975	Observational	28	Very high levels of PEEP may improve oxygenation but are associated with a high incidence of pneumothorax.	Kirby, et al.[127]
ECMO	1979	Phase III	90	In this relatively large, multicenter trial there was no benefit with the use of ECMO.	Zapol, et al.[128]
Prophylactic PEEP (8 cm H_2O)	1984	Phase III	92	Prophylactic PEEP did not decrease the incidence of ARDS in patients at risk in this study.	Pepe, et al.[129]
ECCOR	1994	Phase III	40	This newer form of extracorporeal therapy did not improve mortality in ALI/ARDS.	Morris, et al.[130]
Prone positioning	2001	Phase III	304	Although prone positioning improved oxygenation, there was no mortality benefit in this large multicenter trial.	Gattinoni, et al.[131]
Inhaled nitric oxide	1998 1999	Phase II Phase III	177 203	Although some patients will have improvement in oxygenation with inhaled nitric oxide, there was no mortality benefit in either of these large studies.	Dellinger, et al.[132]; Payen, et al.[133]
Low tidal volume	1999	Phase III	861	Mortality was reduced by 22% with a 6 mL/kg predicted body weight tidal volume. This is the first large randomized multicenter controlled trial to show a mortality benefit from a specific therapy in ALI/ARDS.	ARDS Network[93]
Low tidal volume with high PEEP	2002	Phase III	549	There was no mortality benefit to increased levels of PEEP compared with the standard ARDS Network low tidal volume strategy.	ARDS Network[94]

PEEP, positive end-expiratory pressure, ECMO, extracorporeal membrane oxygenation, ECCOR, extracorporeal CO_2 removal.

obstructive pulmonary disease (COPD).[95] The role for noninvasive ventilation in ALI/ARDS is less clear. A growing number of small studies suggest that bilevel noninvasive ventilation with pressure support ventilation and PEEP may reduce the need for intubation and improve outcomes in selected patients with ALI/ARDS.[96] However, data from large randomized controlled trials are still lacking. Furthermore, it seems likely that the majority of patients with ALI/ARDS will still require invasive mechanical ventilation. In one large multicenter study of 354 of 2770 patients with acute hypoxemic respiratory failure *who were not already intubated*, noninvasive ventilation failed in 30% of patients but failed in 51% of patients with ARDS.[97] One group of patients in whom noninvasive ventilation is particularly appealing is those patients who are immunosuppressed for various reasons and are at highest risk for nosocomial infections. Encouraging results have now been reported in a variety of patients with acute respiratory failure and immunosuppression.[98-100] Pending data from larger randomized clinical trials, a trial of noninvasive mechanical ventilation could be considered in a patient with ALI/ARDS who does not have a severe oxygenation defect, hemodynamic instability, or altered mental status as long as the patient can be closely observed and readily intubated if noninvasive ventilation fails.

Pharmacologic Therapy

There is no specific pharmacologic therapy for ALI/ARDS. A variety of treatment strategies have been investigated in large randomized trials with a predominant focus on anti-inflammatory strategies. Agents that appeared promising in experimental and early clinical studies, but failed in large randomized trials, include early glucocorticoids,[101,102] alprostadil,[103,104] surfactant,[105,106] ketoconazole,[107] *N*-acetylcysteine,[108] procysteine,[108] and lisofylline.[109] Some investigators have suggested that glucocorticoid therapy, although not helpful for the acute phase of ALI/ARDS, might hasten the resolution of late fibroproliferative ALI/ARDS. In one very small randomized study (plagued by crossovers such that only four patients remained in the placebo arm) there was a suggestion that glucocorticoid therapy might be beneficial in late ARDS.[110] However, given the serious concern about safety of high doses of glucocorticoids in critically ill patients, including the possibility of increasing the risk of nosocomial infections or critical illness polyneuropathy/myopathy, routine use of glucocorticoids cannot be recommended. An ARDS Network randomized, double-blind study of late corticosteroids in ALI/ARDS is ongoing and results are expected soon.

Despite the dismal findings in the numerous studies of pharmacologic therapy for ALI/ARDS to date, new therapeutic strategies are under investigation and may yet be beneficial. One area that has been largely ignored in the therapeutic realm is modulation of coagulation. There is mounting evidence that, like sepsis, ALI/ARDS is a procoagulant, antifibrinolytic state.[19,20] The recent report of a significant mortality reduction in severe sepsis with intravenous drotecogin alfa activated, a recombinant activated protein C, raises the hope that therapies that modulate coagulation or fibrinolysis may also have efficacy in ALI/ARDS.[111] Another area that is actively under investigation is strategies to hasten or facilitate the resolution of ALI/ARDS. Such therapies might be targeted at enhancing the rate of alveolar fluid clearance or at modulating alveolar repair.

COMPLICATIONS

Complications are common in any critically ill patient population. Supportive care for all critically ill patients must include vigilance in both preventing and diagnosing common complications such as pulmonary embolus, acute myocardial infarction, gastrointestinal bleeding, and nosocomial infection. Certain complications are more common in ALI/ARDS patients and deserve special mention.

Barotrauma

Barotrauma occurs when air dissects out of the airways or alveolar space into surrounding tissues, leading to pneumothorax, pneumomediastinum, pneumatocele, or subcutaneous emphysema (Fig. 75-3). The exact incidence of pulmonary barotrauma in ALI/ARDS is unclear but appears to be declining. Data from two recent large randomized trials of protective ventilatory strategies suggest an incidence of early pneumothorax of 12% to 13%.[31,93] Higher incidences have been reported in the past, a finding that may have been the result of the use of mechanical ventilation with high tidal volumes and very high inspiratory plateau pressures.[112] In 861 patients enrolled in the NIH ARDS Network trial, approximately 10% of patients developed some form of barotrauma regardless of whether they were in the 6- or 12-mL/kg tidal volume arm. Furthermore, PEEP level was the only factor that predicted the development of barotrauma in a multivariate analysis.[113]

Treatment of barotrauma depends on the location of the extravasated air. Pneumothorax can be life threatening,

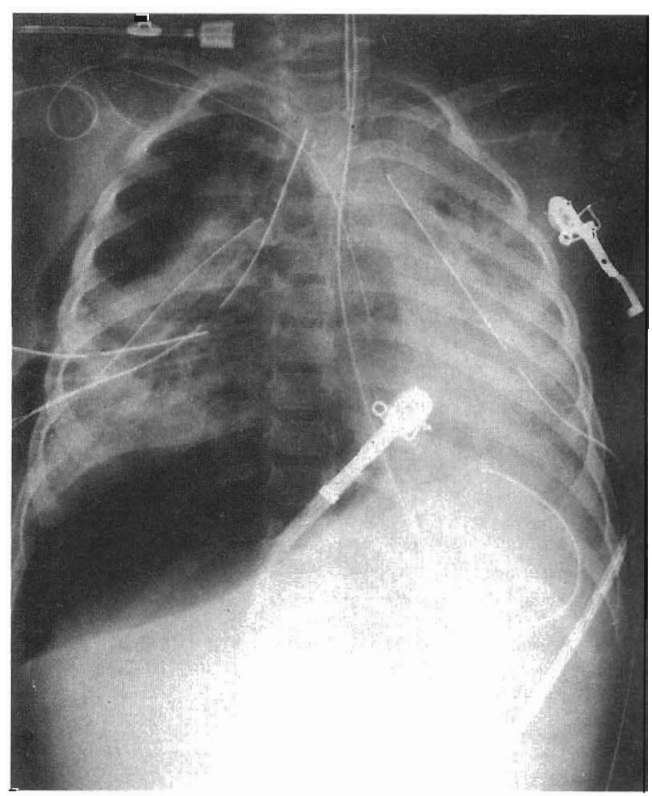

FIGURE 75–3. Portable anteroposterior chest radiograph from a patient with late fibroproliferative acute respiratory distress syndrome and large right sided tension pneumothorax. The patient had multiple episodes of tension pneumothorax due to pulmonary barotrauma and required multiple bilateral tube thoracostomies.

particularly if it is under tension, and immediate diagnosis and tube thoracostomy is essential. Pneumothorax should be considered in any mechanically ventilated patient with ALI/ARDS who develops sudden, unexplained worsening of hypoxemia, respiratory distress, or hemodynamic instability. A chest radiograph (preferably upright) is usually sufficient to make the diagnosis, but in many cases there may not be time to obtain one. Pneumomediastinum and subcutaneous emphysema can be painful but, other than analgesia, do not require specific therapy. Air embolus is a potentially fatal complication of positive-pressure mechanical ventilation that has been reported occasionally in patients with ALI/ARDS[114-116] and usually occurs in conjunction with other evidence of pulmonary barotrauma, many times simultaneously.

Nosocomial Pneumonia

The incidence of nosocomial pneumonia in patients with ALI/ARDS is difficult to quantify. Depending on the diagnostic definition and/or strategy employed, estimates range from 15% to 60% of patients.[117-119] There is yet no consensus regarding the appropriate way to diagnose nosocomial pneumonia in the mechanically ventilated patient. Because patients with ALI/ARDS frequently die of uncontrolled infection, recognition, although notably difficult, and treatment of nosocomial pneumonia is an important part of caring for the ALI/ARDS patient. Clinical criteria that are commonly used in the diagnosis include fever, elevated white blood cell count, purulent secretions, and pulmonary infiltrates. But these signs are often present in patients with ALI/ARDS, even in the absence of nosocomial pneumonia.[120] Autopsy studies of patients dying with ALI/ARDS show a high incidence of unsuspected pneumonia.[121-123] An in-depth discussion of diagnostic strategies is presented elsewhere in this text. Regardless of the methods used for diagnosis, early, appropriate empirical therapy is the mainstay of treatment for nosocomial pneumonia. The adequacy and timeliness of initial empirical therapy are important determinants of outcome. Knowledge of local resistance patterns is crucial, and a high index of suspicion is required.

Multiorgan System Dysfunction

Although ALI and ARDS are often thought of as primary pulmonary disorders, evidence is accumulating to suggest that they are systemic disorders with many similarities to sepsis or SIRS. Multiorgan system dysfunction is a common complication in ALI/ARDS. Organ dysfunction may result from the underlying cause of ALI/ARDS, such as sepsis, or occur independently. The exact incidence of multiorgan system dysfunction in ALI/ARDS is difficult to quantify. In the ARDS Network trial of low tidal volume ventilation, the mean number of nonpulmonary organ system failures was 1.8.[93] Given the simultaneous occurrence of multiple organ failures, it is often difficult to determine the exact cause of death in ALI/ARDS patients, and survival ultimately depends on the successful support of the failing organs.

Neuromuscular Weakness

Patients with ALI/ARDS are at high risk for developing prolonged muscle weakness that persists after resolution of pulmonary infiltrates and can complicate weaning from mechanical ventilation and rehabilitation. These clinical syndromes are commonly called critical illness polyneuropathy but actually have components of neuropathy and myopathy that can coexist or occur separately.[124] Although little prospective data are available, one study suggests that neuromuscular abnormalities are persistent in many survivors of critical illness, even when studied up to 5 years after ICU discharge.[125] Prolonged muscle weakness is most common in critically ill patients who are treated with glucocorticoids. In one study, use of corticosteroids was shown to be the best independent predictor of ICU-acquired paresis (odds ratio 14.9, 95% CI 3.2 to 69.8).[126] In other studies neuromuscular blockade has also been implicated, and for this reason the use of neuromuscular blockade should be reserved for those patients who are unable to be adequately oxygenated or who have problematic dyssynchrony with the mechanical ventilator despite deep sedation. In the absence of a compelling clinical indication such as underlying connective tissue disease, the use of glucocorticoids also should not be routine, unless new clinical evidence in support of their clinical utility in late ALI/ARDS becomes available.

ANNOTATED REFERENCES

Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149:818-824.

This paper presents the findings of the American-European Consensus Conference on ARDS, including the new definitions for acute lung injury and the acute respiratory distress syndrome that are now widely used both clinically and in research studies.

Herridge MS, Cheung AM, Tansey CM, et al: One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 2003;348:683-693.

In this multicenter study the authors evaluated 109 survivors of ARDS at 3, 6, and 12 months after discharge from the hospital. Notably, functional disability was very common even at 12 months and was largely caused by muscle wasting and weakness. By contrast, pulmonary function was normalized other than persistent decrements in the diffusing capacity for carbon monoxide.

Rubenfeld GD: Epidemiology of acute lung injury. Crit Care Med 2003;31:S276-S284.

This is a scholarly review of all the pertinent issues that hamper an accurate estimate of the incidence of ALI/ARDS.

The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342:1301-1308.

This was a multicenter trial of 6 mL/kg compared with 12 mL/kg tidal volume in 861 mechanically ventilated patients with ALI or ARDS. The major finding was a reduction in hospital mortality in the 6 mL/kg group from 40% to 31%.

Ware LB, Matthay MA: Medical progress: The acute respiratory distress syndrome. N Engl J Med 2000;342:1334-1349.

This review article presents a comprehensive overview of the pathogenesis, clinical features, and treatment of ALI and ARDS.

Chapter 76
ASPIRATION PNEUMONITIS AND PNEUMONIA

Paul E. Marik

KEY POINTS

1. ***Aspiration pneumonitis*** is defined as acute lung injury following the aspiration of regurgitated gastric contents and results in a chemical burn of the tracheobronchial tree and pulmonary parenchyma with an intense parenchymal inflammatory reaction.
2. **The severity of lung injury after aspiration of gastric contents** increases significantly with the volume of the aspirate and indirectly with its pH, with a pH less than 2.5 and a volume of 20 mL being required to cause aspiration pneumonitis.
3. **The treatment of aspiration pneumonitis** is essentially supportive; corticosteroids and antibiotics have no proven benefit.
4. **Aspiration pneumonia develops after the aspiration of colonized oropharyngeal contents in patients with dysphagia.**
5. **The most common causes of dysphagia** leading to aspiration pneumonia include cerebrovascular and degenerative central nervous system disease.
6. **The treatment of aspiration pneumonia** includes antibiotics directed against the most likely pathogens (including aerobic gram-negative organisms), an evaluation by a speech and language pathologist, aggressive oral hygiene, and treatment with an angiotensin-converting enzyme (ACE) inhibitor.

Aspiration is defined as the misdirection of oropharyngeal or gastric contents into the larynx and lower respiratory tract.[1] An assortment of pulmonary syndromes may occur after aspiration depending on the quantity and nature of the aspirated material, the frequency of aspiration, as well as the nature of the host's defense mechanisms and the host's response to the aspirated material.[2] The most important syndromes include *aspiration pneumonitis* or Mendelson's syndrome, which is a chemical pneumonitis caused by the aspiration of gastric contents, and *aspiration pneumonia*, an infectious process caused by the aspiration of oropharyngeal secretions colonized by pathogenic bacteria. Although there is some overlap between these two syndromes, they are distinct clinical entities.

ASPIRATION PNEUMONITIS

Aspiration pneumonitis is best defined as acute lung injury after the aspiration of regurgitated gastric contents. This syndrome occurs in patients with a marked disturbance of consciousness, such as drug overdose, seizures, massive cerebrovascular accident, following head trauma, and anesthesia. Drug overdose is the most common cause of aspiration pneumonitis, occurring in approximately 10% of patients hospitalized after a drug overdosage.[3,4] Adnet and Baud demonstrated that the risk of aspiration increases with the degree of unconsciousness (as measured by the Glasgow Coma Scale).[5] Historically, the syndrome most commonly associated with aspiration pneumonitis is Mendelson's syndrome, reported in 1946 in obstetric patients who aspirated while receiving general anesthesia.[6] Mendelson's original report consisted of 44,016 nonfasted obstetric patients whom he studied between 1932 and 1945, of whom more than half received "operative intervention" with ether by mask without endotracheal intubation. He described aspiration in 66 patients (1:667). Although several of the patients were critically ill from their aspirations, "recovery was usually complete" within 24 to 36 hours and only two patients died (1:22; $P = .0008$).

Although aspiration is a widely feared complication of general anesthesia, clinically apparent aspiration in modern anesthesia practice is exceptionally rare, and in healthy patients the overall morbidity and mortality are low. The risk of aspiration with modern anesthesia is about 1 in 3,000 anesthetics, with a mortality of approximately 1:125,000, accounting for between 10% to 30% of all anesthetic deaths.[7-10] The risk of aspiration is greatly increased in patients intubated emergently in the field, emergency department, or ICU. In these patients every effort should be made to reduce the risk of aspiration; this includes removing dentures and clearing the airway and in certain circumstances placing a nasogastric tube to empty the stomach before intubation.[10] If there is an immediate risk of airway compromise, endotracheal intubation should be performed before placement of a nasogastric tube. However, if the patient is likely to have a full stomach (e.g., upper gastrointestinal hemorrhage, small bowel obstruction, ileus), it may be prudent to place a nasogastric tube before endotracheal intubation. When intubating emergently, suction equipment must be immediately available and rapid-sequence induction using cricoid pressure should be performed. Those factors that are reported to increase the risk of aspiration during endotracheal intubation are listed in Table 76-1.

Mendelson emphasized the importance of acid when he showed that unneutralized gastric contents introduced into the lungs of rabbits caused severe pneumonitis indistinguishable from that caused by an equal amount of 0.1 N hydrochloric acid.[6] However, if the pH of the vomitus was neutralized before aspiration, the pulmonary injury was minimal.[11]

TABLE 76–1. RISK FACTORS FOR ASPIRATION DURING ENDOTRACHEAL INTUBATION

Emergent situations
Upper gastrointestinal hemorrhage
Difficult intubation/multiple intubation attempts
Advanced age (>70 yr)
Seizures
Conditions predisposing to gastroesophageal reflux:
Bowel obstruction
Ileus
Hiatal hernia
Peptic ulcer disease
Gastritis

Experimental studies have demonstrated that the severity of lung injury increases significantly with the volume of the aspirate and indirectly with its pH, with a pH of less than 2.5 being required to cause aspiration pneumonitis.[11-13] However, the stomach contains a variety of other substances in addition to acid. Several experimental studies have revealed that aspiration of small, particulate food matter from the stomach may cause severe pulmonary damage, even if the pH of the aspirate is above 2.5.[14,15]

Aspiration of gastric contents results in a chemical burn of the tracheobronchial tree and pulmonary parenchyma with an intense parenchymal inflammatory reaction. Experimental studies have shown a biphasic pattern of lung injury after acid aspiration.[16] The first phase peaks at 1 to 2 hours after aspiration and presumably results from the direct caustic effect of the low pH on the alveolar-capillary wall lining cells. The second phase, which peaks at 4 to 6 hours, is associated with infiltration of neutrophils into the alveoli and lung interstitium with a histologic picture of acute inflammation. The mechanisms causing the lung injury after gastric aspiration have been shown to involve a diverse spectrum of inflammatory mediators, inflammatory cells, adhesion molecules and enzymes, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-8, cyclooxygenase and lipoxygenase products, and reactive oxygen species.[17-21] However, neutrophils appear to play a key role in the development of lung injury after gastric aspiration. Experimental studies have demonstrated that neutropenia, inhibition of neutrophil function, and inactivation of IL-8 (a potent neutrophil chemoattractant) attenuates the acute lung injury induced by acid aspiration.[18,22,23] Intercellular adhesion molecule-1 (ICAM-1) may play a central role in the trafficking of neutrophils into the lung after acid aspiration. Bronchial epithelium expresses ICAM-1 constitutively, and this expression is increased with acid exposure.[24,25] In animal models anti–ICAM-1 antibodies reduce neutrophil infiltration after acid exposure.[21] Pentoxifylline inhibits surface expression of ICAM-1 on alveolar epithelial cells and has been demonstrated to decrease acid-induced lung injury.[26]

Gastric acid prevents the growth of bacteria, and thus the contents of the stomach are normally sterile. Bacterial infection, therefore, does not play a significant role in the early stages of acute lung injury after aspiration of gastric contents. Bacterial superinfection may occur at a later stage; however, the incidence of this complication has not been studied. Colonization of the gastric contents by potentially pathogenic organisms may occur when the gastric pH is increased by the use of antacids, H_2 blockers, or proton pump inhibitors.[27-29] In addition, gastric colonization by gram-negative bacteria occurs in patients receiving gastric enteral feedings, as well as in patients with gastroparesis and small bowel obstruction.[30-32] In these circumstances the pulmonary inflammatory response is likely to result from both bacterial infection and the inflammatory response of the gastric particulate matter.

Aspiration of gastric contents can present dramatically with a full-blown picture that includes gastric contents in the oropharynx, wheezing, coughing, shortness of breath, cyanosis, pulmonary edema, hypotension, and hypoxemia, which may progress rapidly to severe acute respiratory distress syndrome (ARDS) and death.[33] Many patients may not develop signs or symptoms associated with aspiration, whereas others may develop a cough or wheeze. In some patients aspiration may be clinically silent, manifesting only as arterial desaturation with radiologic evidence of aspiration. Warner and colleagues studied 67 patients who aspirated while undergoing anesthesia.[8] Forty-two (64%) of these patients were totally asymptomatic, 13 required mechanical ventilatory support for more than 6 hours, and 4 died.

MANAGEMENT

The upper airway should be suctioned after a witnessed aspiration. Endotracheal intubation should be considered in patients who are unable to protect their airway. While common practice, the prophylactic use of antibiotics in patients with suspected or witnessed aspiration is not recommended. Similarly, the use of antibiotics shortly after an aspiration episode in a patient who develops a fever, leukocytosis, and a pulmonary infiltrate is discouraged because it may select for more resistant organisms in a patient with an uncomplicated chemical pneumonitis. However, empirical antimicrobial therapy is appropriate in patients who aspirate gastric contents in the setting of small bowel obstruction or in other circumstances associated with colonization of gastric contents. Antimicrobial therapy should be considered in patients with an aspiration pneumonitis that fails to resolve within 48 hours. Empirical therapy with broad-spectrum agents is recommended. Antimicrobials with anaerobic activity are not routinely required. Lower respiratory tract sampling (protected specimen brush/bronchoalveolar lavage) and quantitative culture in intubated patients may allow targeted antimicrobial therapy and the discontinuation of antibiotics in culture-negative patients.[34-36]

Corticosteroids have been used in the management of aspiration pneumonitis since 1955.[37] However, limited data exist on which to evaluate the role of these agents, with only a single prospective, placebo-controlled study having been performed. In this study, Sukumaran and colleagues reported that radiographic changes improved more quickly in the steroid group; however, these patients had a longer ICU stay and there was no significant difference in the incidence of complications or outcome.[38,39] In a case-controlled study, Wolfe and colleagues reported that the occurrence of gram-negative pneumonia after aspiration was more frequent in the patients treated with corticosteroids.[40] Similarly, animal models have failed to demonstrate a beneficial effect of corticosteroids on pulmonary function, lung injury, alveolar-capillary permeability, or outcome after acid aspiration.[41,42] Furthermore, considering the failure of two multicenter, randomized, controlled trials to demonstrate a benefit from high-dose corticosteroids in ARDS, corticosteroids cannot be recommended.[43,44]

ASPIRATION PNEUMONIA

Aspiration pneumonia develops after the aspiration of colonized oropharyngeal contents. Aspiration of pathogens from a previously colonized oropharynx is the primary pathway by which bacteria gain entrance to the lungs. Indeed, *Haemophilus influenzae* and *Streptococcus pneumoniae* first colonize the naso/oropharynx before being aspirated and causing community-acquired pneumonia (CAP).[45] Furthermore, nosocomial pneumonia and ventilator-associated pneumonia occur after the aspiration of colonized oropharyngeal material.[46] However, when the term *aspiration pneumonia* is used, it refers to the development of a radiographic infiltrate in the setting of patients with risk factors for increased oropharyngeal aspiration (dysphagia). The clinical setting in which pneumonia develops largely distinguishes aspiration pneumonia from other forms of pneumonia. However, there is much overlap. This is illustrated by the fact that otherwise healthy elderly patients with CAP have been demonstrated to have a significantly higher incidence of silent aspiration when compared with age-matched controls.[47]

Several studies list "aspiration pneumonia" as the cause of CAP in 5% to 15% of cases.[48-50] It has been estimated that in the United States approximately 500,000 people each year are affected by dysphagia resulting from neurologic disorders.[51] Aspiration pneumonia is the major cause of death in these patients.[52,53] Epidemiologic studies have demonstrated that the incidence of pneumonia increases with aging, with the risk being almost six times higher in those over age 75 years, compared with those younger than age 60 years.[54-57] The attack rate for pneumonia is highest among those in nursing homes.[56] Marrie found that 33 of 1,000 nursing home residents per year required hospitalization for treatment of pneumonia, compared with 1.14 of 1,000 elderly adults living in the community.[58] The high rate of pneumonia in inhabitants of nursing homes and other long-term care facilities that house the aged is largely related to an increased incidence of dysphagia in this group of patients.

Approximately one half of all healthy adults aspirate small amounts of oropharyngeal secretions during sleep.[59,60] Presumably the low virulent bacterial burden of normal pharyngeal secretions together with forceful coughing, active ciliary transport, and normal humoral and cellular immune mechanisms result in clearance of the inoculum, without sequelae. However, if the mechanical, humoral, or cellular mechanisms are impaired or if the aspirated inoculum is large enough, pneumonia may follow. Any condition that increases the volume and/or bacterial burden of oropharyngeal secretion in the setting of impaired host defense mechanism may lead to aspiration pneumonia. Indeed, in stroke patients undergoing swallow evaluation there is a strong correlation between the volume of the aspirate and the development of pneumonia.[61] Factors that increase oropharyngeal colonization with potentially pathogenic organisms and that increase the bacterial load may augment the risk of aspiration pneumonia. Terpenning and colleagues demonstrated that an edentulous patient had a lower risk of aspiration pneumonia than a dentate patient.[62] Furthermore, a number of studies have demonstrated that a program of aggressive oral care in elderly patients living in nursing homes reduces the incidence of aspiration pneumonia.[63-65]

RISK FACTOR FOR DYSPHAGIA

Dysphagia occurs commonly after a stroke. In patients with an acute stroke the incidence of dysphagia ranges from 40% to 70%, with approximately 500,000 patients per year in the United States developing neurologic dysphagia.[51,52,66-71] Forty to 50 percent of stroke patients with dysphagia aspirate. Dysphagic patients who aspirate are at an increased risk of developing pneumonia.[71,72] Specifically, the development of pneumonia is seven times greater in stroke patients who aspirate, as compared with those who do not.[52,71] Although dysphagia improves in most patients following a stroke, in many the swallowing difficulties follow a fluctuating course, with 10% to 30% continuing to have dysphagia with aspiration.[67,68] Nakajoh and colleagues evaluated the cough reflex and swallowing in 143 stroke patients whom they followed for 1 year.[70] Forty-three patients had a normal cough reflex and swallow; none of these patients developed pneumonia. However, 24 of the 100 patients with abnormal cough reflex and swallow function developed pneumonia. Elderly patients are at risk of silent cerebral infarction. Nakagawa and coworkers demonstrated that elderly patients with silent cerebral infarction have a fivefold higher risk of developing pneumonia than elderly patients with normal head computed tomographic (CT) scans.[73]

Almost all patients with degenerative diseases of the central nervous system develop dysphagia.[74-80] In patients with Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Parkinson's disease, dysphagia usually occurs early in the course of the disease and the severity of dysphagia does not necessarily relate to the overall severity of the neurologic disease. Considering the high incidence of cerebrovascular and degenerative neurologic diseases in nursing home residents it is not surprising that the reported incidence of dysphagia in this population is between 50% to 75% and explains the extremely high attack rate of pneumonia in these patients.[58,81-83]

While the presence of dysphagia and the volume of the aspirate are key factors that predispose elderly patients to aspiration pneumonia, a number of other factors play an important role.[61] Colonization of the oropharynx is an important step in the pathogenesis of aspiration pneumonia. The elderly have increased oropharyngeal colonization with pathogens such as *Staphylococcus aureus* and aerobic gram-negative bacilli (e.g., *Klebsiella pneumoniae* and *Escherichia coli*).[84-86] Although this increased colonization may be transient, lasting less than 3 weeks, it underlies the increased risk in the elderly of pneumonia with these pathogens. The defects in host defenses that predispose to enhanced colonization with these organisms are uncertain; however, dysphagia with a decrease in salivary clearance and poor oral hygiene may be major risk factors.[84]

In patients with aspiration pneumonia, unlike the case of aspiration pneumonitis, the episode of aspiration is generally not witnessed. The diagnosis is therefore inferred when a patient with known risk factors for aspiration has an infiltrate in a characteristic bronchopulmonary segment. In patients who aspirate in the recumbent position the most common sites of involvement are the posterior segments of the upper lobes and the apical segments of the lower lobes. In patients who aspirate in the upright or semi-recumbent position the basal segments of the lower lobes are favored. The usual picture is that of an acute pneumonic process, which runs a course similar to that of a typical CAP. If untreated, however,

these patients appear to have a higher incidence of cavitation and lung abscess formation.[87]

BACTERIOLOGY

Despite extensive investigations, the diagnosis of the bacterial cause of CAP is made in 50% or less of patients overall; this is particularly so in the elderly, who may not be able to produce adequate sputum specimens for evaluation.[88,89] Oropharyngeal colonization with gram-negative pathogens and *S. aureus* with subsequent aspiration accounts for the greater prevalence of these pathogens in elderly patients with CAP. It is unclear, however, if patients with dysphagia are at an increased risk of developing pneumococcal pneumonia, because no study has specifically reported the microbiology of CAP in patients with oropharyngeal dysphagia and aspiration. However, Kikuchi and colleagues reported a high incidence of silent aspiration in otherwise healthy elderly ambulatory patients with no specific risk factors for gram-negative or *S. aureus* oropharyngeal colonization who developed CAP.[47] Unfortunately, in this study the microbial causes of CAP were not reported.

A number of studies performed in the early 1970s investigated the bacteriology of community-acquired "aspiration pneumonia."[87,90-92] Bacteriologic specimens were obtained by percutaneous transtracheal sampling and/or thoracocentesis. In all these studies anaerobic organisms were the predominant pathogens, isolated alone or together with aerobes. Based on these studies, antibiotics with anaerobic activity have became "the standard of care" for patients with aspiration pneumonia.[2,93] However, it is important to recognize that in all these studies the microbiologic specimens were obtained after a significant delay and frequently after complications such as abscesses, necrotizing pneumonia, or empyema had developed. Furthermore, many of the patients were chronic alcoholics, had been symptomatic for up to 90 days, and complained of having a putrid sputum. These patients are clearly distinct from the typical patients seen today with acute aspiration pneumonia. Furthermore, it is possible that the organisms recovered by transtracheal aspiration represent oropharyngeal flora that contaminated the trachea during the procedure (due to aspiration) or bacteria that colonized the trachea, rather than representing true pulmonary pathogens. This postulate is supported by Moser and colleagues, who demonstrated discrepancies between bacteria recovered by transtracheal aspiration and by transthoracic needle aspiration in dogs with experimental pneumonia.[94]

Recently, two studies have been reported in which invasive lower respiratory tract sampling (protected specimen brush) together with quantitative and anaerobic culture techniques were performed in the patients with acute aspiration syndromes.[95,96] Mier and colleagues studied 52 patients admitted to an ICU with "aspiration pneumonia."[95] Bacterial pathogens were isolated in significant concentrations ($\geq 10^3$ colony-forming units/mL) in only 19 patients, the spectrum of organism being determined by whether the aspiration was community or hospital acquired, with *S. pneumoniae, S. aureus, H. influenzae,* and Enterobacteriaceae predominant in patients with community-acquired aspiration and gram-negative organisms, including *Pseudomonas aeruginosa* in patients with hospital-acquired aspiration. No anaerobic organism was isolated in any of the patients. In a similar study, we performed blind protected specimen brush sampling in 25 patients with gastric aspiration.[96] Bacterial pathogens were isolated in 12 patients. Risk factors for gastric colonization were present in 8 of the 12 patients (small bowel obstruction/ileus, tube feeding, H_2 blockers). The spectrum of pathogens was similar to that reported by Meir and colleagues.[95] Furthermore, we did not isolate any pathogenic anaerobic organisms.

MANAGEMENT

Antimicrobial therapy is unequivocally indicated in patients with aspiration pneumonia. The choice of antibiotics should depend on the setting in which the aspiration occurs (home, nursing home, or hospital) as well as on the patient's premorbid condition. However, antimicrobial agents with gram-negative activity such as fluoroquinolones, third-generation cephalosporins, piperacillin, or a carbapenem are usually required. Penicillin and clindamycin, the "standard" antimicrobial agents for aspiration pneumonia, provide inadequate activity in the majority of patients with aspiration pneumonia.[95] Antimicrobials with specific anaerobic activity are not routinely warranted and may be indicated only in patients with severe periodontal disease, patients expectorating putrid sputum, and patients with a necrotizing pneumonia or lung abscess on chest radiograph.[95,96]

All elderly patients with CAP and all patients with aspiration pneumonia require consultation by a speech and language pathologist to assess for the presence of dysphagia. Assessment of the cough and gag reflex is unreliable in screening for patients at risk of aspiration; a comprehensive swallowing evaluation performed by a specialized speech-language pathologist is, therefore, required. The speech-language pathologist can reliably identify those patients who aspirate by performing a bedside swallowing evaluation supplemented by either a videofluoroscopic swallow study or a fiberoptic endoscopic evaluation.[97-99] This evaluation identifies those patients who require further behavioral, dietary, and medical management to reduce the risk of aspiration.

The neurotransmitter substance P is believed to play a major role in both the cough and swallow sensory pathways. Angiotensin-converting enzyme (ACE) inhibitors prevent the breakdown of substance P and may theoretically be useful in the management of patients with aspiration pneumonia. Arai and associates measured serum substance P levels in hypertensive patients with cerebrovascular disease and symptomless dysphagia and control patients with no dysphagia.[100] The patients with symptomless dysphagia had significantly lower serum levels of substance P than the control subjects. In this study, dysphagia as assessed by technetium-tin colloid scanning improved in 62% of patients treated with an ACE inhibitor, this improvement being associated with a normalization of the serum substance P levels. Sekizawa and colleagues studied the incidence of pneumonia in 127 stroke patients treated with ACE inhibitors compared with 313 patients treated with other antihypertensive agents.[101] During a 2-year follow-up period, pneumonia was diagnosed in 7% of patients receiving an ACE inhibitor compared with 18% in patients taking other hypertensive agents (RR of 2.65; 95% CI 1.3 to 5.3, $P = .007$). Similarly, Arai and associates compared the risk of pneumonia in 576 elderly hypertensive patients who were treated with an ACE inhibitor or a calcium channel blocker.[102] The rate of pneumonia was 3.3% in the ACE group compared with 8.9% in the patients who were treated with a calcium channel blocker ($P = .025$).

In a follow-up study, Arai and colleagues demonstrated a significantly lower rate of pneumonia in elderly hypertensive patients randomized to an ACE inhibitor compared with an angiotensin-II receptor antagonist.[103] These studies provide compelling evidence that patients with oropharyngeal dysphagia should be considered for treatment with an ACE inhibitor (even if normotensive).

Sedative medication has been demonstrated to increase the risk of pneumonia in residents of long-term care facilities and should therefore be avoided.[104] The prescription of a phenothiazine and haloperidol should be very carefully considered, because they reduce oropharyngeal swallow coordination, causing dysphagia.[105,106] Medications that dry up secretions, including antihistamines and drugs with anticholinergic activity, make it more difficult for patients to swallow and should therefore also be avoided.[105,107]

Occupants of residential homes have been shown to have poor oral hygiene and rarely receive treatment from dentists and oral hygienists.[108,109] An aggressive protocol of oral care will reduce colonization with potentially pathogenic organisms and decrease the bacterial load. These measures have been demonstrated to reduce the risk of pneumonia.[63-65] In addition, aggressive oral care has been shown to increase salivary substance P.[110] The elevated substance P levels in the saliva may reflect enhanced activity of the afferent pathway of the swallow mechanism.

TUBE FEEDING

Nutritional supplementation, as determined by the clinical dietitian, may be required. Tube feeding is not essential in all patients who aspirate. Every attempt to encourage safe oral intake is recommended. The practice of tube feeding in the end stages of degenerative illnesses in the elderly should be carefully reconsidered. Finucane and colleagues found no data to suggest that tube feeding of patients with advanced dementia prevented aspiration pneumonia, prolonged survival, reduced the risk of pressure sores or infections, improved function, or provided palliation.[111]

Short-term tube feeding, however, may be indicated in elderly patients with severe dysphagia and aspiration in whom improvement of swallowing is likely to occur. Nakajoh and colleagues demonstrated that the incidence of pneumonia was significantly higher in stroke patients with dysphagia who were fed orally compared with those who received tube feeding (54.3 vs. 13.2%, $P < .001$), despite the fact that the orally fed patients had a higher functional status (higher Barthel index).[112]

Colonized oral secretions are a serious threat to dysphagic patients, and feeding tubes offer no clear protection. There are no data to suggest that patients fed with gastrostomy tubes have a lower incidence of pneumonia than patients fed with nasogastric tubes.[113,114] Similarly, the incidence of aspiration pneumonia has been shown to be similar in stroke patients with postpyloric as compared with intragastric feeding tubes.[115-117] Over the long term, aspiration pneumonia is the most common cause of death in gastrostomy tube–fed patients.[118,119] Patients who are likely to recover their ability to swallow within a few weeks are not candidates for gastrostomy tubes.

CONCLUSION

In the management of patients with aspiration syndromes, it is vitally important to distinguish aspiration pneumonitis from aspiration pneumonia. Although some overlap exists, these are distinct clinical syndromes. Antibiotics are not indicated (at least initially) in the majority of patients with aspiration pneumonitis, with corticosteroids having no proven benefit. Aspiration pneumonia should be considered in all elderly patients with CAP and in any patient with dysphagia and an infiltrate in a dependent bronchopulmonary segment. Broad-spectrum antibiotics are indicated in most patients with aspiration pneumonia.

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Chapter 77
SEVERE ASTHMA EXACERBATION

Thomas Corbridge • Susan J. Corbridge

KEY POINTS

1. **Any asthmatic** can develop a severe exacerbation, even one with mild disease.
2. **The general appearance of the patient** provides a guide to severity, response to therapy, and need for intubation. Measurement of peak flow helps to confirm the diagnosis, assess severity, and determine treatment response.
3. **Inhaled beta agonists, systemic corticosteroids, and low-flow oxygen** are first-line therapies in asthmatics with severe exacerbation. Alternate therapies include ipratropium bromide, magnesium sulfate, leukotriene modifiers, heliox, and noninvasive ventilation.
4. **Hypotension after intubation** may occur from an inadequate expiratory time resulting in dynamic lung hyperinflation and decreased preload to the right side of the heart. A trial of apnea or hypopnea is diagnostic and therapeutic in this setting.
5. **During mechanical ventilation**, prolong the expiratory phase by setting low minute ventilation and adequate inspiratory flow. Assess the degree of hyperinflation by checking the plateau pressure and, if necessary, accept moderate hypercapnia to limit dangerous hyperinflation.
6. **Avoid prolonged use of paralytics** to decrease risk of myopathy.
7. Education, environmental control measures, and anti-inflammatory medications help prevent future exacerbations.

DEFINITIONS

Each year in the United States acute asthma accounts for 2 million emergency department (ED) visits, 500,000 hospitalizations, 25,000 episodes of respiratory failure requiring intubation, and 5,000 deaths.[1,2] The total annual cost is 5 billion dollars. Acute attacks frequently reflect inadequate outpatient management—particularly in the subgroup of patients who depend on crisis-oriented ED management. These patients commonly reside in urban environments, have low incomes, and demonstrate inadequate understanding of asthma and use of controller agents.[3,4] Indeed only between 28% and 42% of patients are taking inhaled corticosteroids before ED treatment for acute asthma.[5,6] Programs aimed at education and initiation of inhaled corticosteroids in the ED are crucial in this subgroup. These programs work[7]; so does referral to an asthma specialist.[8]

In most simple terms, asthma exacerbation is an acute deterioration in signs and symptoms of asthma, but there is considerable heterogeneity in the severity, tempo, and degree of inflammation and bronchospasm.[9] Severe asthma exacerbation (SAE) is defined by several, but not necessarily all, of the following features: dyspnea at rest, upright positioning, inability to speak in phrases or sentences, respiratory rate greater than 30 breaths/min, use of accessory muscles of respiration, pulse greater than 120 beats/min, pulsus paradoxus greater than 25 mm Hg, peak expiratory flow rate (PEFR) less than 50% predicted or personal best, hypoxemia, and eucapnia or hypercapnia.[10] Altered mental status, paradoxical respiration, bradycardia, a quiet chest, and absence of pulsus paradoxus from respiratory muscle fatigue are features of imminent respiratory arrest.

Insofar as it provides rationale for patient assessment and management, we begin this chapter with a review of pathophysiology. We then discuss clinical presentation, differential diagnosis, physical examination, and laboratory testing, followed by an update on pharmacologic therapy. Finally, we provide recommendations for ventilator management.

PATHOPHYSIOLOGY OF ACUTE AIRFLOW OBSTRUCTION

The speed with which SAE develops varies considerably.[11] Fewer than 15% of patients present with sudden-onset exacerbation in which severe airflow obstruction develops in less than 3 to 6 hours. These attacks represent a more pure form of smooth muscle–mediated bronchospasm with the potential to improve rapidly after use of bronchodilators.[12-15] Compared with attacks of slower progression, the airways have more neutrophils in the submucosa and fewer secretions.[16,17] Sudden attacks are triggered by allergen or irritant exposure, stress, inhalation of crack cocaine or heroin, or use of nonsteroidal anti-inflammatory agents or beta-adrenergic blockers in susceptible patients.[18-21] Respiratory tract infection is not a trigger; commonly, no cause is identified.[21]

Slower-onset attacks are triggered by a variety of infectious, allergic, and nonspecific irritant exposures. Airway wall inflammation, bronchospasm, and accumulations of intraluminal mucus are characteristic. Mucus plugs consisting of sloughed epithelial cells, eosinophils, fibrin, and other serum components that have leaked through the denuded

airway epithelium obstruct large and small airways.[22] The tempo of these attacks provides a clear opportunity to increase anti-inflammatory medications in the outpatient setting.[23] However, only 13% to 22% of patients initiate oral corticosteroids before arrival at the ED.[5,24]

No matter the tempo, patients with SAE have critical airflow obstruction limiting exhalation. In severe cases, expiratory flow may not cease for as long as 60 seconds. Because expiratory time is shorter (1 to 5 seconds) during spontaneous or assisted breathing, there is incomplete emptying of gas and dynamic lung hyperinflation (DHI). Fortunately, DHI is self-limiting because as lung volume increases so do lung elastic recoil pressure and airway diameter—factors that favor expiratory flow. However, DHI places the diaphragm in a mechanically disadvantageous position at a time when hypoperfusion and respiratory acidosis may further decrease diaphragm force generation.[25]

At end exhalation, incomplete gas emptying elevates alveolar volume and pressure, a state referred to as auto–positive end-expiratory pressure (PEEP).[26] Auto-PEEP is a threshold pressure that must be overcome to initiate inspiratory flow. This combines with narrowed airways and variable degrees of hyperinflation-induced parenchymal noncompliance to increase the inspiratory work of breathing. The resulting imbalance between respiratory muscle strength and work of breathing predisposes to ventilatory failure.

Multiple inert gas elimination technique (MIGET) analysis demonstrates small areas of high ventilation ($\dot{V}$) relative to perfusion ($\dot{Q}$) and slightly increased dead space in acute asthma, presumably because hyperinflation limits blood flow.[27,28] An increase in the dead space to tidal volume ratio (V_D/V_T) favors the development of hypercapnia:

$$P_{CO_2} = V_{CO_2} \times 0.863/V_A$$
$$= V_{CO_2} \times 0.863/[Ve \times (1\text{-}V_D/V_T)]$$

where V_{CO_2} is carbon dioxide production, V_A is alveolar ventilation, V_E is minute ventilation, and V_D/V_T is the dead space to tidal volume ratio.

In mild acute asthma, V_E increases more than V_D/V_T, causing respiratory alkalosis. As the severity of airflow obstruction increases (particularly when FEV_1 is < 1.0 L),[29] $PaCO_2$ increases owing to inadequate V_A (reflecting a decrease in V_E and an increase in V_D/V_T as the patient nears respiratory arrest).

Airway obstruction decreases ventilation relative to perfusion in other lung units causing hypoxemia. Because this is not shunt (a $\dot{V}/\dot{Q}$ of zero), oxygen supplementation readily corrects hypoxemia.[27] There is a rough correlation between severity of airflow obstruction and hypoxemia.[30] For example, most patients with PaO_2 less than 60 mm Hg have a PEFR less than 200 L/min or an FEV_1 less than 1.0 L.[29] However, the vast majority of patients present with PaO_2 greater than 60 mm Hg and an SaO_2 greater than 90% while breathing room air at sea level.[31] In one study of over 1000 children with acute asthma, only 4% had an initial SaO_2 less than 88%.[32] In this study, mean SaO_2 was 95% on room air: 93% for children admitted to hospital and 96% for those discharged home ($P < .001$). Twenty-three percent of patients were admitted, but in the subgroup of patients with SaO_2 less than 88%, the admission rate was 73% compared with 8% when SaO_2 was 100%.

In recovering patients, MIGET analysis demonstrates that spirometry often improves before PaO_2 and $\dot{V}/\dot{Q}$ inequality.[33] This may be because spirometry tracks large airway function, whereas gas exchange reflects the function of peripheral airways.[34]

Large swings in pleural pressure are responsible for the circulatory changes in SAE. Right heart preload decreases during expiration because of positive intrathoracic pressure, but during vigorous inspiration, intrathoracic pressure falls and blood flow increases. This fills the right ventricle early in inspiration and shifts the intraventricular septum leftward. Lung hyperinflation also increases pulmonary vascular resistance and right ventricular afterload.[35,36] The conformational change that occurs in the left ventricle causes diastolic dysfunction and incomplete left ventricular filling; furthermore, negative pleural pressures directly impair left ventricular emptying.[37,38] Rarely, diastolic dysfunction and increased left ventricular afterload cause pulmonary edema.[39] The net effect of these cyclical changes is to accentuate the normal drop in systolic blood pressure that occurs during inspiration, a phenomenon termed *pulsus paradoxus* (PP). The PP is a valuable indicator of asthma severity,[40] but the lack of a widened PP can also indicate fatigue and inability to generate large swings in pleural pressure.

CLINICAL ASSESSMENT

Analysis of several factors including the medical history, physical examination, measures of airflow obstruction, assessment of initial response to therapy, arterial blood gases, and occasionally the chest radiograph are necessary to assess severity, risk of deterioration, and differential diagnosis.[41] Imperative in the medical history are risk factors for asthma death (Table 77-1), of which prior intubation is the most important.[42-47]

"All that wheezes is not asthma" is a clinical saw worth considering during the initial evaluation. In older patients, an extensive smoking history suggests chronic obstructive pulmonary disease and the potential for compensated respiratory acidosis. Cardiac asthma refers to airway hyperreactivity and wheezing that may accompany congestive heart failure.[48] An enlarged cardiac silhouette, a left-sided third heart sound, and pulmonary edema suggest this diagnosis. Occasionally, distinguishing between heart failure and asthma is difficult because airflow obstruction can cause pulmonary edema (see earlier) and bronchodilators partially reverse cardiac asthma.[49] In the setting of coronary artery

TABLE 77–1. RISK FACTORS FOR FATAL OR NEAR-FATAL ASTHMA

Frequent emergency department visits
Frequent hospitalization
Intensive care unit admission
Prior intubation
Hypercapnia
Barotrauma
Psychiatric illness
Medical noncompliance
Illicit drug use
Low socioeconomic status
Inadequate access to medical care
Use of more than two canisters/month of inhaled beta agonist
Poor perception of airflow obstruction
Comorbidities such as coronary artery disease
Sensitivity to *Alternaria* species

disease, imbalance between oxygen supply and demand may cause myocardial ischemia.[50] Pulmonary embolism rarely causes wheeze; consider this diagnosis when dyspnea is out of proportion to signs and objective measures of expiratory flow.[51,52]

Vocal cord dysfunction (and other causes of upper airway obstruction) should be considered when there is stridor, normal oxygenation, or resolution of airflow obstruction after intubation.[53] In contrast to asthma, upper airway (extrathoracic) obstruction classically flattens the inspiratory portion of the flow-volume loop, leaving the expiratory loop intact. Fiberoptic laryngoscopy can confirm paradoxical vocal cord movement in a symptomatic individual. Response to breathing helium-oxygen mixtures (heliox) suggests upper airway obstruction, but heliox also may be of use in asthma and should not be used to distinguish upper from lower airway obstruction. In cases of suspected tracheal stenosis (e.g., from prior intubation), fiberoptic bronchoscopy or spiral computed tomography is indicated.

A foreign body should be considered in the very young and old, in individuals with altered mental status or neuromuscular disease, and when symptoms develop after eating or dental work. Localized wheeze and, rarely, asymmetrical hyperinflation on chest radiography are clues to foreign body aspiration.

Pneumonia complicating asthma is unusual, but it should be considered when there is fever, purulent sputum, localizing signs, and hypoxemia that does not correct with low-flow oxygen. Antibiotics are frequently prescribed for asthmatics with increased sputum. However, sputum that looks purulent in asthma may contain eosinophils, not neutrophils.

On physical examination, the general appearance of the patient (posture, speech, positioning, and alertness) provides a quick guide to severity, response to therapy, and need for intubation. Patients assuming the upright position have a higher heart rate, respiratory rate, and PP, and a significantly lower PaO_2 and PEFR than patients who are able to lie supine.[54] Diaphoresis is associated with an even lower PEFR. Accessory muscle use and a widened PP indicate severe asthma; however, their absence does not rule out a severe attack.[55]

Examination of the head and neck should focus on identifying barotrauma and upper airway obstruction. Prolonged inspiration, stridor, and suprasternal retractions suggest upper airway obstruction. The mouth and neck should be inspected for signs of previous surgery such as tracheostomy or thyroidectomy and angioedema. Tracheal deviation, asymmetrical breath sounds, "mediastinal crunch," and subcutaneous emphysema suggest pneumomediastinum or pneumothorax. Rarely, tracheal deviation is caused by atelectasis from mucus plugging, foreign body aspiration, or endobronchial tumor.

Chest auscultation reveals expiratory phase prolongation and wheeze. However, wheeze is not a reliable indicator of the severity of airflow obstruction.[56] A silent chest indicates that there is insufficient airflow for noise generation. Localized wheeze or crackles may represent mucus plugging and atelectasis but should prompt consideration of pneumonia, pneumothorax, and endobronchial obstruction.

Sinus tachycardia is common.[57] Supraventricular and ventricular arrhythmias are more common in the elderly[58] but rarely complicate management. Bradycardia is an ominous sign of impending respiratory arrest. PP greater than 20 mm Hg is common in SAE; PP less than 10 mm Hg suggests either a milder attack or respiratory muscle fatigue and imminent respiratory arrest.[10] SAE can cause examination and electrocardiographic findings of right-sided heart strain and, less commonly, pulmonary edema.[59] Dynamic hyperinflation, forceful exhalation, and tension pneumothorax distend neck veins.

Measuring PEFR or FEV_1 helps assess the severity of airflow obstruction. A PEFR or FEV_1 less than 50% predicted or the patient's personal best defines SAE. Objective measurements are important because physician estimates are often inaccurate (whereas patients are more accurate in guessing PEFR).[60] Emerman and Cydulka demonstrated a modest correlation between pretreatment estimates of pulmonary function and the actual value.[61] Physicians underestimated the degree of obstruction and changed management 20% of the time after PEFR measurements. In general, it is easier to measure PEFR than FEV_1, although this maneuver is still difficult for sick patients. In severely dyspneic patients we defer peak flow determination because it rarely alters initial management and may worsen bronchospasm,[62] even to the point of respiratory arrest.[63]

Measurement of the change in PEFR or FEV_1 predicts the need for hospitalization. Several studies have demonstrated that failure of initial therapy to improve expiratory flow after 30 minutes predicts a more severe course and need for ongoing treatment in the ED or hospitalization.[64-67] Values before 30 minutes of treatment are not predictive.[68]

When FEV_1 is less than 1 L or PEFR is less than 200 L/min, we recommend an arterial blood gas analysis to assess the degree of hypoxemia and acid-base status. In the early stages of SAE, mild hypoxemia and respiratory alkalosis are common. As the severity of airflow obstruction increases, $PaCO_2$ increases. Hypercapnia denotes severe disease; however, hypercapnic patients may improve with pharmacologic therapy and do not always require intubation.[69] Conversely, the absence of hypercapnia does not rule out impending respiratory arrest.[70]

Patients who waste serum bicarbonate in response to respiratory alkalosis develop a metabolic acidosis with a normal anion gap. Metabolic acidosis with an elevated anion gap reflects excess serum lactate likely due to increased work of breathing. Lactic acidosis is more common in men, in the setting of severe obstruction and during treatment with parenteral beta agonists.[71-73]

Repeat blood gas sampling is generally not necessary to determine clinical course. In most cases, serial attention to patient posture, use of accessory muscles, diaphoresis, estimates of air movement during auscultation, pulse oximetry, and PEFRs allows for valid determinations. Patients whose condition deteriorates on these grounds should be considered for intubation. In mechanically ventilated patients, serial blood gas analysis helps guide ventilator management.

Chest radiographs influence treatment in 1% to 5% of cases.[74-76] In one study,[77] atelectasis may have been the explanation for radiographic findings in 34% of cases. These data suggest that chest radiographs are indicated only when there are localizing signs, concerns regarding barotrauma or pneumonia, or if it is not clear that asthma is the correct diagnosis. In mechanically ventilated patients, chest radiographs confirm proper endotracheal tube position.

ADMISSION CRITERIA

Patients demonstrating a good response to initial therapy may be discharged home with close follow-up. These patients

should report no distress, have an essentially normal examination, and have an FEV_1 or PEFR of greater than or equal to 70% of predicted or personal best.[10] Observation for 60 minutes after the last dose of beta agonist helps ensure stability before discharge. Patients should receive written medication instructions, a written plan of action to be followed in the event of deterioration, and a follow-up appointment before discharge. In general, patients discharged home on oral corticosteroids do well, particularly if they had not been optimally treated before the ED visit.[78] An 8-day course of 40 mg/day of prednisone is as efficacious and safe as an 8-day tapering schedule.[79] Alternatively, a single intramuscular dose of 40 mg of triamcinolone diacetate has also been shown to be as effective as the 40 mg/day dose of prednisone for 5 days after ED treatment for asthma.[80]

Patients with mild cases with a good response to bronchodilators may be considered for inhaled corticosteroids alone. In children discharged from the ED, a short-term dose schedule of inhaled budesonide, starting at a high dose and then tapered over 1 week, was shown to be as effective as a tapering course of oral prednisolone.[81] Depending on the situation, inhaled steroids should be started, continued, or increased while the patient is in the ED.

Patients with SAE (PEFR < 50% predicted or personal best) who demonstrate a poor response to initial therapy (e.g., less than 10% increase in PEFR) or whose condition deteriorates during therapy should be admitted to an intensive care unit (ICU). ICU admission is also indicated for respiratory arrest, altered mental status, myocardial injury, and when there is need for frequent nebulizer treatments.

An incomplete response to treatment occurs when there is persistent dyspnea and a PEFR or FEV_1 between 50% and 70% predicted. Patients in this group require ongoing treatment either in the ED or on the general medical ward. Physicians should err on the side of admission when there is an undesirable home environment and when directly observed therapy is needed in noncompliant patients.

Contrary to the just described guidelines, in common practice half of patients with a final PEFR of less than 50% of predicted are discharged from the ED.[82] Interestingly, short-term relapse is uncommon in these patients and not associated with final PEFR, suggesting that strict adherence to PEFR cutoffs may be unnecessary.

PHARMACOLOGIC THERAPY

OXYGEN

Low-flow oxygen by nasal cannula is recommended to maintain arterial oxygen saturation greater than 90% (>95% in pregnancy and ischemic heart disease). This practice improves oxygen delivery to peripheral tissues (including respiratory muscles), reverses hypoxic pulmonary vasoconstriction, and may stimulate bronchodilation. Oxygen also protects against hypoxemia resulting from beta agonist–induced pulmonary vasodilation and increased blood flow to low $\dot{V}/\dot{Q}$ units.[28,83]

BETA AGONISTS

Beta agonists are central to treatment of bronchospasm and should be administered immediately, preferably by inhalation, regardless of prior use.[84] Approximately two thirds of asthmatics respond well enough to albuterol to be discharged from the ED. In the study by Rodrigo and Rodrigo, 67% of patients were discharged from the ED after 2.4 mg of albuterol, with half meeting the discharge criteria after receiving only 12 puffs of albuterol (Fig. 77-1).[85] Similarly, Strauss and coworkers found that two thirds of patients with acute asthma could be discharged after three 2.5-mg doses of albuterol by nebulization every 20 minutes.[86] Patients with a blunted cumulative dose-response relationship require hospitalization (or extended treatment in an ED holding area). These patients may have extensive inflammation, architectural disruption of the airways, and intraluminal mucus, limiting their response to beta agonists.

The most widely used and studied beta agonist is albuterol. Albuterol is more $beta_2$ selective and longer acting than metaproterenol, although metaproterenol and isoetharine are occasionally used for initial therapy because of their faster onset of action, despite the potential for increased side effects.[87-89] Levalbuterol, the R-isomer of racemic albuterol, is a newer therapeutic option for patients with asthma. Racemic albuterol consists of a 50:50 mixture of R- and S-albuterol, with the R-isomer conferring bronchodilator effects. Emerging preclinical data suggest that the S-isomer, previously thought to be inert, is not only proinflammatory

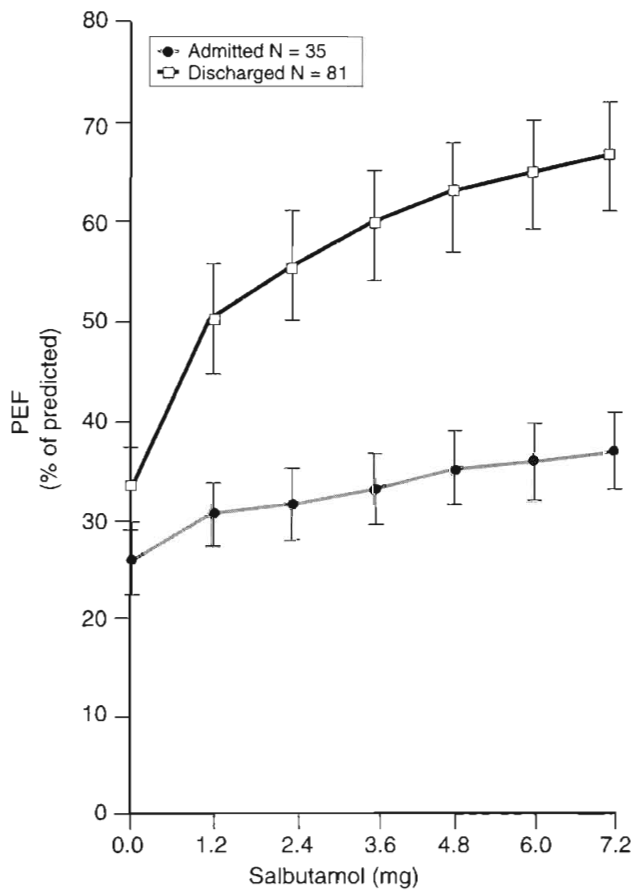

FIGURE 77–1. Dose-response relationship to albuterol 4 puffs (400 μg) every 10 minutes in 116 acute asthmatics. Sixty-seven percent of patients obtained discharge criteria after administration of 2.4 mg albuterol within 1 hour; half of responders met discharge criteria after 12 puffs. Patients with a blunted cumulative dose-response relationship were hospitalized. (Reproduced with permission from Rodrigo C, Rodrigo G: Therapeutic response patterns to high and cumulative doses of salbutamol in acute severe asthma. Chest 1998;113:593.)

but also preferentially retained in the lung.[90,91] These effects may help explain why levalbuterol, 1.25 mg, causes greater bronchodilation than the same amount of levalbuterol in a racemic mixture (2.5 mg) in stable asthmatics.[92] Fewer data are available in acute asthma. In an open-label study of 91 acutely ill patients with FEV_1 between 20% and 55% predicted, patients were stratified into cohorts receiving 0.63 to 5 mg of levalbuterol or 2.5 to 5 mg of albuterol (three treatments in 1 hour).[93] Patients receiving levalbuterol demonstrated faster onset of action and a greater degree of bronchodilation. Results of a large, multicenter trial are expected soon.

Long-acting beta agonists are not indicated in the initial treatment of SAE but may be considered for add-on therapy in hospitalized patients. In hospital, salmeterol added to albuterol results in greater improvements in FEV_1 after 48 hours without greater toxicity compared with placebo.[94] For maintenance, addition of a long-acting beta agonist to an inhaled corticosteroid results in fewer asthma exacerbations and exacerbations of lesser severity.[95]

Metered-dose inhalers (MDIs) or hand-held nebulizers deliver inhaled beta agonists equally well. Anywhere from 4 to 12 puffs by MDI with spacer achieves the same degree of bronchodilation as one 2.5-mg nebulized treatment of albuterol.[96-99] MDIs with spacers carry the advantage of lower cost and faster drug delivery times; hand-held nebulizers require fewer instructions, less supervision, and less coordination.

The recommended dose of albuterol is 2.5 mg by nebulization every 20 minutes during the first hour of treatment depending on clinical response and side effects.[10] Other dosing strategies have been studied. McFadden and colleagues compared two 5.0-mg treatments of albuterol by nebulization over 40 minutes to three 2.5-mg treatments with albuterol every 20 minutes in 160 ED patients.[5] Both treatment strategies were effective, but the 5-mg regimen increased peak flows more rapidly and to a greater extent than the standard 2.5-mg approach. Patients receiving 5-mg doses also reached discharge criteria quicker and left the ED with higher PEFRs. There was also a trend toward fewer hospitalizations in the high-dose group. Emerman and colleagues compared the effects of 2.5 to 7.5 mg albuterol every 20 minutes for a total of three doses in 160 acute asthmatics.[100] There was no difference in improvement in FEV_1 or admission rates between groups. In another study, a single high-dose treatment with albuterol (7.5 mg) was found to be no better (and more toxic) than three treatments with 2.5 mg every 20 minutes.[101] Dosing after the first hour of therapy depends on the clinical response and side effect profile. Fortunately, high-dose inhaled beta agonists are generally well tolerated. Tremor and tachycardia are common, but significant cardiovascular morbidity is not.[102,103]

Albuterol can be administered in a continuous or repetitive manner. Depending on the study, there is either no difference between continuous and repetitive dosing or there is a slight benefit to continuous administration (at the same total dose) in severely obstructed patients.[104-107]

There is no advantage to subcutaneous epinephrine or terbutaline over inhaled albuterol in the initial management of SAE, unless the patient is unable to comply with inhaled therapy because of an altered mental status or near-arrest situation.[108-110] However, if there is a poor response to several hours of inhaled therapy, subcutaneous epinephrine may be helpful.[111] Coronary artery disease is a relative contraindication to parenteral therapy.[112] Intravenous administration of beta agonists is not recommended. Several studies have demonstrated that inhaled therapy improves airflow greater with less toxicity compared with intravenous administration.[113-116] Combinations of inhaled and parenteral treatment have not been adequately evaluated.

IPRATROPIUM BROMIDE

Data generally support a benefit to adding ipratropium bromide to albuterol in the initial treatment of SAE.[117-119] Rodrigo and Rodrigo conducted a randomized trial of high and cumulative doses of ipratropium bromide and albuterol. In their study, combined albuterol, 120 μg, and ipratropium bromide, 21 μg per puff (in one inhaler), was compared to albuterol and placebo in 180 patients with acute asthma.[120] Four puffs were administered through an MDI with spacer every 10 minutes for 3 hours. Subjects who received combination therapy had 20.5% and 48.1% greater improvements in PEFR and FEV_1, respectively, compared with albuterol alone. The rate of hospitalization decreased significantly from 39% with albuterol alone to 20% with combination therapy. Subgroup analysis showed that patients most likely to benefit from high doses of ipratropium bromide were those with an FEV_1 less than 30% of predicted and symptoms for more than 24 hours before ED presentation. O'Driscoll and colleagues showed similar benefit to combination therapy, particularly in patients with PEFR less than 140 L/min at entry.[121] Garrett and colleagues randomized 338 asthmatics to a single nebulized dose of 0.5 mg of ipratropium bromide combined with 3.0 mg of salbutamol or to 3.0 mg of salbutamol alone.[122] Mean FEV_1 at 45 and 90 minutes was significantly higher with combined therapy. Karpel and colleagues studied 384 patients randomized to 2.5 mg of albuterol or to 2.5 mg albuterol mixed with 0.5 mg of ipratropium at entry and at 45 minutes.[123] At 45 minutes, there were significantly more responders in the ipratropium group; however, median change in FEV_1 from baseline did not differ between groups, and by 90 minutes there was no difference in the percentage of responders and median change in FEV_1 between groups and there was no difference in the number of patients requiring additional ED or hospital treatment. Lin and colleagues demonstrated that combination therapy resulted in greater improvement in PEFR than albuterol alone in 55 adult asthmatics.[124] In two other studies, combination therapy tended to improve outcome measures, but differences were not statistically significant.[125,126] In children, combination therapy decreases ED treatment time, albuterol dose requirements, and hospitalization rates.[119,127-129]

To the contrary, McFadden did not show benefit in PEFR, admission rate, or ED length of stay to combination ipratropium bromide and albuterol in the first hour of treatment.[130] Similarly, in children, Ducharme and Davis did not demonstrate benefit from combination therapy in their study of nearly 300 asthmatics with mild to moderate acute asthma.[131]

CORTICOSTEROIDS

The data are mixed regarding the benefits of systemic corticosteroids in the first few hours of treatment. Early data from McFadden and colleagues demonstrated no differences in physiologic or clinical variables in the first 6 hours in

38 patients receiving hydrocortisone hemisuccinate or placebo.[132] Similarly, Rodrigo and Rodrigo showed that early administration of corticosteroids does not improve pulmonary function in the first 6 hours of treatment.[133] These authors came to the same conclusion after an evidence-based evaluation of selected trials.[134] However, Littenberg and Gluck demonstrated that 125 mg of methylprednisolone given intravenously on arrival decreased admission rates compared with placebo.[135] Similarly, Lin and colleagues, studying the effects of 125 mg of methylprednisolone given intravenously on arrival in patients with a PEFR less than 50% predicted after albuterol, demonstrated improved PEFR after 1 and 2 hours.[136] A systematic review of 12 studies for the Cochrane database demonstrated that use of corticosteroids within 1 hour of arrival to the ED reduces the need for hospitalization and that benefits are greatest in patients with more severe asthma and those not previously taking corticosteroids.[137] Corticosteroids decrease the number of relapses in the first 7 to 10 days and the risk of asthma death.[138-141] In hospitalized patients, they speed the rate of recovery.[142,143]

Whether there is a dose-response relationship to systemic steroids in SAE is not clear. In one meta-analysis, Manser and colleagues found no therapeutic differences between low doses of corticosteroids (<80 mg/day of methylprednisolone or <400 mg/day hydrocortisone) and higher doses in the initial management of hospitalized asthmatics.[144] Emerman and Cydulka compared 500-mg and 100-mg doses of methylprednisolone in the ED, finding no benefit to higher-dose therapy.[145] Haskell and coworkers compared three doses of methylprednisolone (15 mg, 40 mg, and 125 mg) given intravenously every 6 hours for 3 days.[146] The high-dose group improved significantly by the end of the first day, the medium-dose group improved by the middle of the second day, and the low-dose group did not improve significantly by day 3. Bowler and colleagues found no difference between 50 mg of hydrocortisone given intravenously four times daily for 2 days followed by low-dose oral prednisone and 200 or 500 mg of hydrocortisone also administered four times daily for 2 days followed by higher doses of prednisone.[147]

The recommendation by the expert panel from the National Institutes of Health is to deliver 120 to 180 mg/day of either prednisone, methylprednisolone, or prednisolone in three or four divided doses for 48 hours and then 60 to 80 mg/day until the PEFR reaches 70% of predicted or the patient's personal best.[10] We recommend 60 mg of methylprednisolone (Solu-Medrol) (or its equivalent) every 6 hours by vein during initial management. Oral drug is as effective[148] but should be avoided in patients with gastrointestinal upset or in patients at risk for intubation.

Recent trials have demonstrated benefit to inhaled corticosteroids in acute asthma. Rodrigo and Rodrigo conducted a randomized, double-blind trial of 1 mg of flunisolide versus placebo combined with 400 μg of salbutamol every 10 minutes for 3 hours in 94 ED subjects.[149] They found that the PEFR and FEV_1 were approximately 20% higher in the flunisolide group, beginning at 90 minutes. This benefit may stem from steroid-induced vasoconstriction and decreases in airway wall edema, vascular congestion, and plasma exudation.[150] Rodrigo and Rodrigo also demonstrated therapeutic benefit from triple-drug therapy (flunisolide, albuterol, and ipratropium bromide) in high doses in patients not receiving systemic corticosteroids.[151]

To the contrary, Guttman and colleagues found no benefit from adding 7 mg of beclomethasone every 8 hours by MDI with spacer to nebulized salbutamol and systemic corticosteroids.[152] This group also demonstrated that beclomethasone (5 mg delivered by MDI) during the initial 4 hours of ED treatment did not confer added benefit to albuterol in adults with mild to moderately severe asthma.[153]

THEOPHYLLINE

Numerous studies have demonstrated that theophylline does not add to maximal doses of beta agonists in the first few hours of treatment and that theophylline increases the incidence of tremor, nausea, vomiting, and tachyarrhythmias.[154-160] In the meta-analysis by Parameswaran and colleagues, 15 studies in adults were analyzed demonstrating that intravenous therapy with aminophylline did not result in any additional bronchodilation compared with standard care with beta agonists, although there was a nonsignificant trend toward higher PEFRs in treated patients at 12 and 24 hours.[160]

Fewer studies demonstrate benefit to aminophylline use in SAE.[161-165] Some studies demonstrated that theophylline use in the ED resulted in fewer hospitalizations even though airflow rates were not different from placebo, raising the possibility that nonbronchodilating properties of theophylline may be important.[166,167] In one meta-analysis of aminophylline use in school-aged children, intravenous aminophylline was shown to improve FEV_1 by 6 to 8 hours, an effect that was maintained at 24 hours.[168]

MAGNESIUM SULFATE

Prospective trials have yielded conflicting results regarding the efficacy of magnesium sulfate ($MgSO_4$) as a bronchodilator in acute asthma. Several studies failed to show a benefit to the use of $MgSO_4$ added to standard therapies[169-173]; other studies have demonstrated that $MgSO_4$ improves spirometry or rates of admission.[174-176] In an attempt to shed further light on the use of $MgSO_4$, meta-analyses have been published,[177-179] but they reach different conclusions. One analysis by Rowe and colleagues of seven trials (five adult and two pediatric) involving 668 patients did not support routine intravenous use of $MgSO_4$ in all patients with acute asthma. However, $MgSO_4$ was found to be safe and effective in improving spirometry in asthmatics with severe acute exacerbations. Similarly, when 135 asthmatics were randomized to 2 g of intravenous $MgSO_4$ or placebo after 30 minutes and followed for 4 hours, hospital admission rates and FEV_1 were no different between treated patients and controls.[172] However, subgroup analysis showed that $MgSO_4$ decreased admission rates and improved spirometry in asthmatics with FEV_1 less than 25% predicted. Subsequently, a placebo-controlled, double-blind, randomized trial in 248 patients with FEV_1 less than 30% showed a small but statistically significant increase in FEV_1 after 240 minutes in the $MgSO_4$-treated group but no difference in hospitalization rates.[175] Additional evidence supporting benefit in severe disease comes from an uncontrolled study of five intubated asthmatics given magnesium.[180] In this study, patients were given high doses of $MgSO_4$ (10 to 20 g) over 1 hour, after which there was a significant decrease in peak airway pressure (43 to 32 cm H_2O) and in inspiratory flow resistance. $MgSO_4$ may also be of greater benefit in premenopausal

women because estrogen augments the bronchodilating effect of magnesium.[181]

$MgSO_4$ can also be administered by nebulized solution. Nannini and colleagues evaluated the efficacy of $MgSO_4$ (225 mg) versus normal saline as a vehicle for nebulized salbutamol in a randomized, double-blind, controlled trial of 35 patients in an ED.[182] At 20 minutes, patients who received $MgSO_4$ and salbutamol had an absolute increase in PEFR of 134 ± 70 L/min versus 86 ± 64 L/min in the saline and salbutamol group, a 57% greater percentage increase. More recently, Hughes and colleagues enrolled 52 patients with SAE in a randomized controlled trial of salbutamol mixed with 2.5 mL of isotonic $MgSO_4$ or isotonic saline on three occasions 30 minutes apart.[183] At 90 minutes, mean FEV_1 in the $MgSO_4$ group was 1.96 L and 1.55 L in the saline group (difference 0.37 L, $P = .003$).

LEUKOTRIENE MODIFIERS

Cysteinyl leukotrienes are elevated in asthmatic sputum compared with controls and higher in subjects studied within 48 hours of exacerbation.[184] Preliminary data demonstrating efficacy of the leukotriene receptor antagonist zafirlukast in acute asthma are available from a double-blind, randomized trial.[185] Two doses of zafirlukast (20 mg and 160 mg) administered orally were compared with placebo in 641 asthmatics after 30 minutes of standard treatment. Zafirlukast, 160 mg, decreased admission rates, relapses, and treatment failures. In another double-blind, placebo study of 20 patients not receiving systemic steroids, oral montelukast, 10 mg, resulted in a trend toward a shorter duration of stay and higher peak flows and fewer patients requiring aminophylline or corticosteroids.[186] More recently, Camargo and colleagues conducted a randomized, double-blind, parallel group trial in 201 acute asthmatics receiving standard therapy plus 7 mg or 14 mg of montelukast intravenously or placebo.[187] Montelukast improved FEV_1 over the first 20 minutes (14.8% vs. 3.6% with placebo). Benefits were seen within 10 minutes and lasted for 2 hours; both treatment doses were equivalent. Montelukast also tended to result in less beta agonist use and fewer treatment failures.

HELIOX

Heliox is a gas consisting of 20% oxygen and 80% helium (30:70% and 40:60% mixtures are also available). As the percent of helium decreases, so does the benefit of breathing this gas blend. Concentrations of helium less than 60% are ineffective, precluding its use in patients requiring significant supplemental oxygen. Heliox is slightly more viscous than air, but significantly less dense, resulting in a more than threefold increase in kinematic viscosity (the ratio of gas viscosity to gas density) compared with air. Theoretically, this property decreases the driving pressure required for gas flow by two mechanisms. First, for any level of turbulent flow, breathing low-density gas decreases the pressure gradient required for flow. Second, heliox decreases the Reynolds number, favoring conversion of turbulent flow to laminar flow.[188] Heliox does not treat bronchospasm or airway wall inflammation.

Heliox improves dyspnea, work of breathing, and arterial blood gases in upper airway obstruction.[189] In adult asthmatics treated in an ED, an 80:20 mix increased PEFR and decreased PP, suggesting improved airway resistance and work of breathing.[190] Similar results have also been published in children.[191] Other studies have failed to demonstrate a benefit.[192-194] In a recent meta-analysis for the Cochrane database of four randomized trials including 288 patients, Rodrigo and colleagues concluded that the evidence does not support the use of heliox in nonintubated asthmatics.[195] However, methodologic differences between studies and failure to control for concurrent upper airway obstruction (e.g., vocal cord dysfunction) limit conclusions. If heliox is effective, it may "buy time" for concurrent therapies to work and thereby avert the need for intubation in some cases. Of theoretical concern is the potential for heliox to mask worsening airflow obstruction, so that there may be less time (and no margin for error) to control the airway.

Whether heliox augments the bronchodilator effect of inhaled beta agonists compared with delivery in air is also unclear. Data are available demonstrating a benefit to heliox as a driving gas,[196] but there are also data to the contrary.[197]

ANTIBIOTICS

In their 2002 update, the expert panel from the National Institutes of Health did not recommend the use of antibiotics in asthma exacerbation unless there was fever with purulent sputum, evidence for pneumonia, or suspected bacterial sinusitis.[198] In a separate review of the literature, Graham recently selected 2 of 128 possible studies adequate for review, concluding that the role of antibiotics is difficult to assess.[199]

MECHANICAL VENTILATION

Noninvasive Positive Pressure

Noninvasive positive pressure by facemask is potentially useful in refractory patients—who are not in need of immediate airway control. In one study of 21 acute asthmatics with a mean PEFR of 144 L/min, nasal CPAP of 5 or 7.5 cm H_2O significantly decreased respiratory rate and dyspnea compared with placebo.[200] This benefit presumably stems from help overcoming the inspiratory threshold load created by auto-PEEP (see earlier).[201] Meduri and colleagues reported their observational experience with bilevel positive airway pressure (BiPAP) during 17 episodes of SAE.[202] In all but one patient (who subsequently required intubation), BiPAP improved dyspnea. BiPAP improved blood gases, heart rate, and respiratory rate, and only 2 patients required intubation. Soroksky and colleagues' pilot study of BiPAP in 15 patients with acute asthma compared with 15 controls receiving sham BiPAP for 3 hours demonstrated that BiPAP improved lung function and reduced need for hospitalization.[203]

Intubation

Respiratory arrest and impending respiratory arrest (e.g., extreme exhaustion and changes in mental status) mandate intubation. Oral intubation is preferred because it allows for a large endotracheal tube—important to decrease airway resistance and remove tenacious mucus plugs. Nasal intubation may be attempted in an awake patient with a difficult airway (e.g., short, obese patients), but nasal intubation necessitates a smaller endotracheal tube and may be complicated by polyps and sinusitis.

Postintubation Hypotension

The time immediately after intubation can be difficult for the patient with severe airflow obstruction. Care must be taken to stabilize the patient during this period through the thoughtful use of sedatives, paralytics, bronchodilators, intravenous fluids, and positive-pressure ventilation.

Immediate concerns are hypotension and pneumothorax. Hypotension has been reported in 25% to 35% of patients after intubation.[204] It occurs from a loss of vascular tone due to sedation, hypovolemia, tension pneumothorax, or overzealous ventilation. The latter results in dangerous levels of DHI when adequate time is not provided for exhalation. Clues to DHI include excessive effort during manual inflation, decreased breath sounds, hypotension, and tachycardia. A trial of hypopnea (2 to 3 breaths/min) or apnea in a preoxygenated patient is both diagnostic and therapeutic for DHI. When successful, hypopnea improves cardiopulmonary status within 30 to 60 seconds. Irrespective of clinical improvement, tension pneumothorax should be considered. Close inspection of the chest radiograph is mandatory because DHI may limit lung collapse. Because it causes preferential ventilation to the contralateral lung, unilateral pneumothorax increases the risk of bilateral pneumothoraces. Management of pneumothorax consists of hypoventilation, volume resuscitation, and tube thoracostomy (unilateral or bilateral as required).

Initial Ventilator Settings

During mechanical ventilation, the expiratory time, tidal volume, and severity of airway obstruction determine the level of DHI (Fig. 77-2). Because treatment of airway obstruction has been maximized in most intubated patients, expiratory time and tidal volume become important variables during ventilator management. Minute ventilation and inspiratory flow rates determine exhalation time.[205,206] At a set inspiratory flow, a drop in minute ventilation prolongs expiratory time and decreases DHI. To avoid dangerous levels of DHI, initial minute ventilation should be less than 115 mL/kg/min or approximately 8 L/min in a 70-kg patient.[207] This can be achieved with a respiratory rate between 12 and 14 breaths/min combined and a tidal volume between 7 and 8 mL/kg. The use of a low tidal volume avoids undue peak lung inflation, which may occur even with acceptably low minute ventilation.

Shortening the inspiratory time by use of a high inspiratory flow rate also prolongs expiratory time. We favor an inspiratory flow rate of 80 L/min, using a square or constant flow regimen. High inspiratory flow rates increase peak airway pressure by elevating airway resistive pressure, but peak airway pressure does not correlate with morbidity or mortality (see later). Rather it is the state of lung hyperinflation that predicts outcome, and any ventilator strategy that lowers peak airway pressure shortens expiratory time and worsens DHI. One concern is that high inspiratory flow rates in patients breathing in the assist-control mode will increase the respiratory rate and thereby decrease the expiratory time.[208]

There is little consensus regarding ventilator mode in acute asthma. In paralyzed patients synchronized intermittent mandatory ventilation (SIMV) and assist-controlled ventilation (AC) are equivalent. In patients triggering the ventilator, AC may increase minute ventilation but SIMV may be associated with increased work of breathing.[209,210] Volume-controlled (VC) ventilation is recommended over pressure-controlled (PC) ventilation for several reasons, including staff familiarity with its use. PC ventilation offers

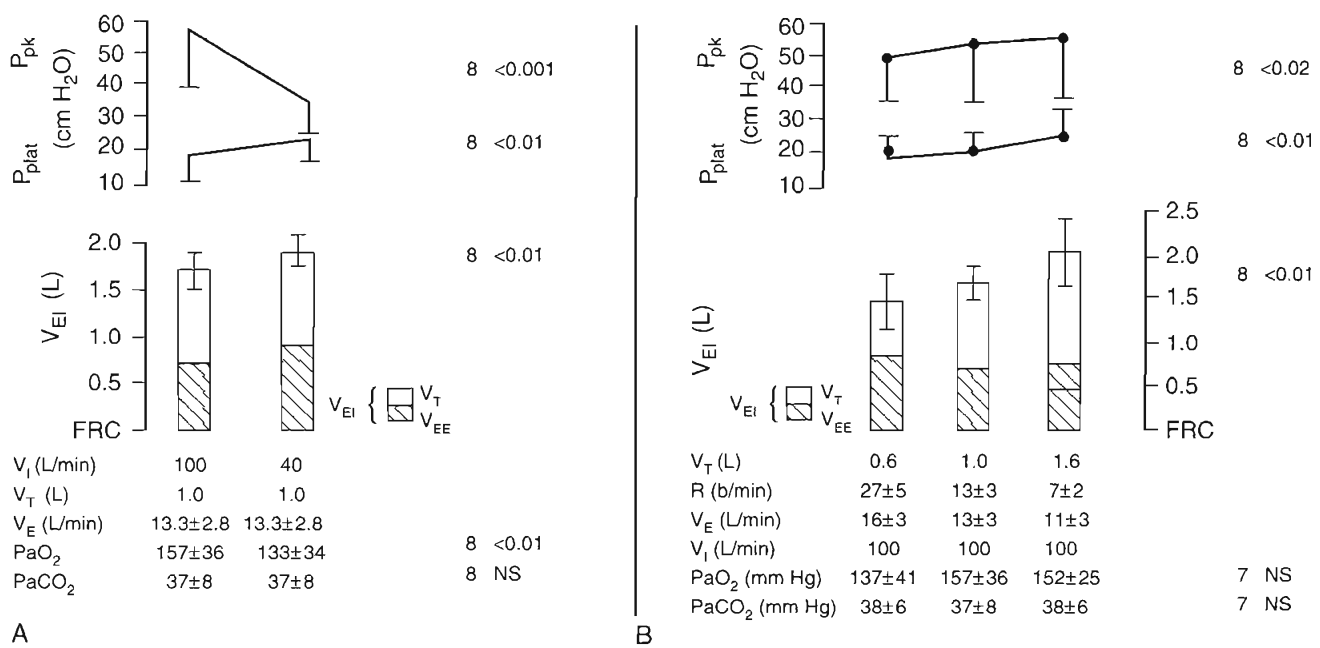

FIGURE 77–2. Effects of ventilator settings on airway pressures and lung volumes during normocapnic ventilation of eight paralyzed asthmatic patients. V_{EE}, lung volume at end expiration, V_{EI}, lung volume at end inspiration; Ppk, peak airway pressure; Pplat, end-inspiratory plateau pressure, V_E, minute ventilation, V_I, inspiratory flow. The numerals 7 and 8 are patient numbers. The numerals <0.001, <0.01, and <0.02 are p values. **A,** As inspiratory flow is decreased from 100 L/min to 40 L/min at the same V_E, Ppk falls but hyperinflation increases due to dynamic gas trapping. **B,** Dynamic hyperinflation is reduced by low respiratory rates and high tidal volumes (as long as V_E is decreased), but high tidal volumes result in high Pplat. (Reproduced with permission from Tuxen DV, Lane S: The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. Am Rev Respir Dis 1987;136:872.)

the advantage of limiting peak airway pressure to a predetermined set value (e.g., 30 cm H_2O). However, during PC ventilation tidal volume is inversely related to auto-PEEP and minute ventilation is not guaranteed. Also, PC requires a decelerating inspiratory flow pattern, which may shorten the expiratory time.

Ventilator-applied PEEP is not recommended in sedated and paralyzed patients because it may increase lung volume if used excessively.[211] In spontaneously breathing patients, low levels of ventilator-applied PEEP (e.g., 5 cm H_2O) decrease inspiratory work of breathing by decreasing the pressure gradient required to overcome auto-PEEP.

Assessing Lung Inflation

Determination of the severity of DHI is central to risk management and adjustment of ventilator settings. Numerous methods have been proposed to measure DHI. The volume at end-inspiration, termed V_{EI}, is determined by collecting expired gas from total lung capacity to functional residual capacity during 40 to 60 seconds of apnea. A V_{EI} greater than 20 mL/kg has been correlated with barotrauma.[207] Indeed, this is the only measure of DHI that has been shown to predict barotrauma (although it may underestimate air trapping if there are slowly emptying airspaces). The utility of this measure is limited by the need for paralysis and by staff who are unfamiliar with expiratory gas collection.

Alternate measures of DHI include the single-breath plateau pressure (Pplat) and auto-PEEP. Pplat is an estimate of average end-inspiratory alveolar pressures that is determined by stopping flow at end-inspiration. Auto-PEEP is the lowest average alveolar pressure achieved during the respiratory cycle. It is obtained by measuring airway-opening pressure during an end-expiratory hold maneuver. In the presence of auto-PEEP airway-opening pressure increases by the amount of auto-PEEP present. Persistence of expiratory gas flow at the beginning of inspiration (which can be detected by auscultation or flow tracings) also demonstrates auto-PEEP.[212]

Accurate measurement of Pplat and auto-PEEP requires patient-ventilator synchrony and absence of patient effort. Paralysis is generally not required for valid measurements. Unfortunately, neither measure has been validated as a predictor of complications. Pplat is affected by the entire respiratory system, including lung tissue and chest wall; thus, variations in DHI occur from patient to patient at the same pressure. Despite these limitations, experience suggests that when Pplat is less than 30 cm H_2O the outcome is generally good. Auto-PEEP can underestimate the severity of DHI possibly owing to poor communication between the alveoli and airway opening during mechanical ventilation.[213] In most cases, however, auto-PEEP less than 15 cm H_2O is acceptable.

Ventilator Adjustments

With the previous considerations in mind we offer an algorithm for the ventilator adjustments (Fig. 77-3). This algorithm relies on Pplat as the measure of lung hyperinflation and arterial pH as a marker of ventilation. If initial ventilator settings result in Pplat greater than 30 cm H_2O, respiratory rate should be decreased until this goal is achieved, even at the cost of hypercapnia. Fortunately, hypercapnia is well tolerated, even with arterial PCO_2 as high as 90 mm Hg, as long as a sudden rise in $PaCO_2$ does not occur.[214,215] Anoxic brain injury and myocardial dysfunction are contraindications to permissive hypercapnia because hypercapnia dilates cerebral vessels, decreases myocardial

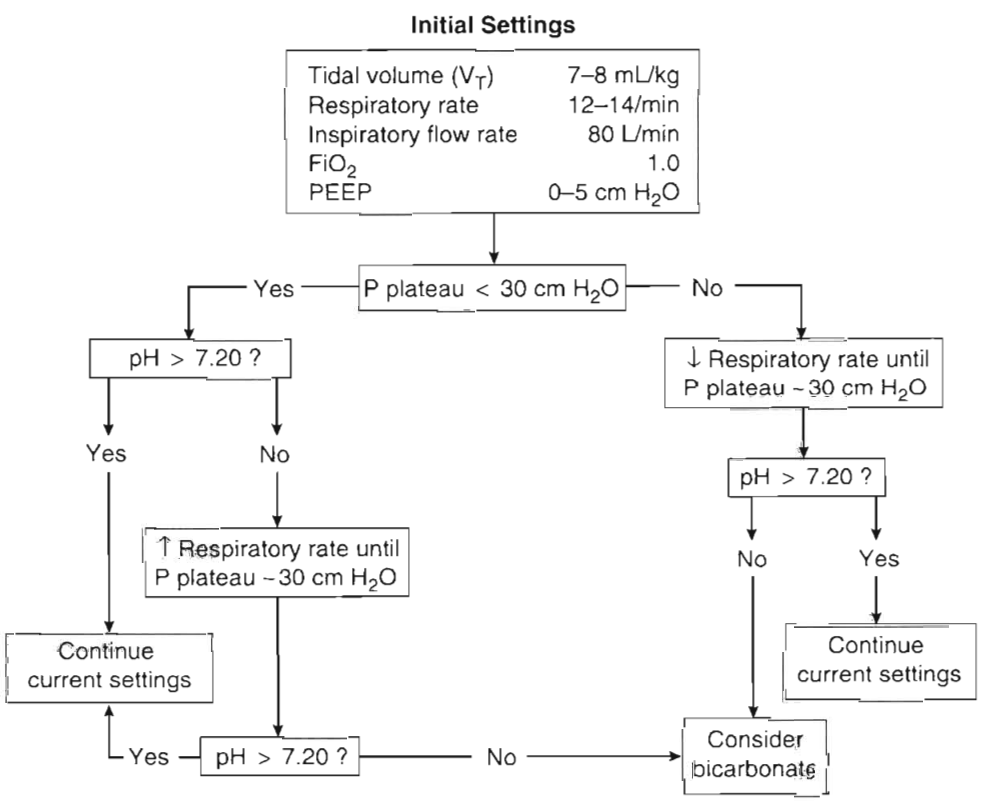

FIGURE 77-3. An approach to mechanical ventilation in acute severe asthma.

contractility, and constricts pulmonary vessels.[216] Lowering the respiratory rate may not increase $PaCO_2$ as expected if less DHI lowers dead space. If hypercapnia results in a blood pH of less than 7.20 and the respiratory rate cannot be increased because of the Pplat limit, we consider an infusion of sodium bicarbonate, although this has not been shown to improve outcome.[217] If Pplat is less than 30 cm H_2O and pH is less than 7.20, the respiratory rate is increased until Pplat nears 30 cm H_2O.

Sedation and Paralysis

Sedation improves comfort, safety, and patient-ventilator synchrony. This is particularly important when hypercapnia stimulates respiratory drive. In patients who can be extubated within hours (e.g., those with sudden-onset asthma), propofol is attractive because it can be titrated to a deep level of sedation and allow for rapid reversal after discontinuation.[218] Benzodiazepines, such as lorazepam and midazolam, are less expensive alternatives.[219] Time to awakening after discontinuation of these drugs is less predictable than with propofol.

To provide amnesia, sedation, analgesia, and suppression of respiratory drive, a narcotic can be added by continuous infusion to either propofol or a benzodiazepine.[220] Morphine and fentanyl are the two most commonly used narcotics. Fentanyl has a quicker onset of action and is slightly more expensive than morphine, although the magnitude of this difference is small. Daily interruption of sedatives avoids undue drug effects.[221]

Ketamine, an intravenously administered anesthetic with sedative, analgesic, and bronchodilating properties, is reserved for intubated patients with severe bronchospasm despite the use of standard therapies.[222-224] Ketamine must be used with caution because of its sympathomimetic effects and ability to cause delirium.

When safe and effective mechanical ventilation cannot be achieved by sedation alone, consideration should be given to short-term muscle paralysis. Short- to intermediate-acting agents include atracurium, *cis*-atracurium, and vecuronium. Pancuronium is a less expensive alternative, but it lasts longer and may cause unwanted tachycardia. Pancuronium and atracurium both release histamine, but the clinical significance of this property is doubtful.[225] In our ICU we prefer *cis*-atracurium because it is essentially free of cardiovascular effects, does not release histamine, and does not rely on hepatic and renal function for clearance.

Paralytics may be given intermittently by bolus or continuous intravenous infusion. If a continuous infusion is used, a nerve stimulator should be used or the drug should be withheld every 4 to 6 hours to avoid drug accumulation and prolonged paralysis. Paralytics should be stopped as soon as possible to decrease the risk of postparalytic myopathy.[226-228] Acute myopathy is rare in patients paralyzed for less than 24 hours. Most patients with postparalytic myopathy recover, but there may be significant disability.

Administration of Bronchodilators during Mechanical Ventilation

Data from controlled trials are needed to determine the efficacy of bronchodilators in intubated asthmatics and to provide evidence for or against current clinical recommendations.[229] One consistent observation is that intubated patients require higher drug dosages to achieve a clinical effect. Indeed in some intubated asthmatics a clinical effect may not be apparent at all. This may be because intubated patients are more likely albuterol nonresponders (see earlier) and because albuterol is delivered inadequately. In one study, only 2.9% of a radioactive aerosol delivered by nebulizer was deposited in the lungs of mechanically ventilated patients.[230] In another study, the efficacy of albuterol delivered by MDI via a simple inspiratory adapter (no spacer) was compared with nebulized albuterol in mechanically ventilated patients.[231] Using the peak-to-pause pressure gradient at a constant inspiratory flow to measure airway resistance, the authors found no effect (and no side effects) from the administration of 100 puffs (9.0 mg) of albuterol. However, albuterol delivered by nebulizer to a total dose of 2.5 mg reduced the inspiratory flow-resistive pressure 18%. Increasing the nebulized dose to a total of 7.5 mg further reduced airway resistance in 8 of 10 patients but caused side effects half the time.

When MDIs are used during mechanical ventilation, the use of a spacing device on the inspiratory limb of the ventilator improves drug delivery.[232] In general, nebulizers should be placed close to the ventilator and in-line humidifiers should be stopped during treatments. Inspiratory flow should be reduced to approximately 40 L/min during treatments to minimize turbulence, although this strategy may worsen DHI and should be time limited.[231] Patient-ventilator synchrony helps to optimize drug delivery.

Regardless of whether an MDI with spacer or nebulizer is used, higher drug dosages are required and the dosage should be titrated to achieve a fall in the peak-to-pause airway pressure gradient. When no measurable drop in airway resistance occurs, other causes of elevated airway resistance such as a kinked or plugged endotracheal tube should be excluded. Bronchodilator nonresponders should be considered for a drug holiday.

Other Considerations

Rarely, the aforementioned strategies are unable to stabilize the patient on the ventilator. In these situations, consideration should be given to other therapies. Halothane and enflurane are general anesthetic bronchodilators that can acutely reduce peak pressure and $PaCO_2$.[233,234] These agents are associated with myocardial depression, arterial vasodilation, and arrhythmias, and their benefits do not last after drug discontinuation. Heliox delivered through the ventilator circuit also decreases peak pressure and $PaCO_2$.[235] However, safe use of heliox requires significant institutional expertise and planning. Ventilator flowmeters (which are gas-density dependent) must be recalibrated to low density gas, and a spirometer should be placed on the expiratory port to measure tidal volume. A trial of heliox in a lung model is recommended before patient use.

Strategies to mobilize mucus such as chest physiotherapy, mucolytics, or expectorants have not proved to be efficacious in controlled trials. Bronchoalveolar lavage, on the other hand, using either saline or acetylcysteine may be useful in nonintubated patients.[236-238] This procedure is theoretically risky because the presence of a bronchoscope increases expiratory airway resistance and may provoke bronchospasm.

Extubation

Weaning and extubation criteria have not been validated for patients with acute asthma. One approach is to perform a spontaneous breathing trial once (1) $PaCO_2$ normalizes at

a minute ventilation that achieves a safe level of DHI, (2) airway resistance is less than 20 cm H_2O, (3) the patient follows commands, and (4) neuromuscular weakness has not been identified. Patients with labile asthma may meet these criteria within hours of intubation, but more often 24 to 48 hours of treatment is required. We extubate as soon as possible because the endotracheal tube may aggravate bronchospasm. After extubation, observation in an ICU is recommended for an additional 12 to 24 hours. During this time the focus can switch to safe transfer to the ward and outpatient management.

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In this study, the factors predicting admission of asthmatic patients to the hospital are reviewed. Whereas many of the factors, such as severity of airflow limitation, are not surprising, other more subtle findings on history and physical examination also have predictive value.

Chapter 78
CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Peter M. A. Calverley

KEY POINTS

1. **The prognosis of patients with chronic obstructive pulmonary disease (COPD)** admitted to the ICU is better than commonly believed.
2. The **burden of symptomatic COPD** is likely to rise for several decades, despite an effective smoking cessation program.
3. **Small changes in forced expiratory flow** are associated with significant impairment in lung mechanics, particularly airway closure and dynamic hyperinflation, and worse gas exchange.
4. **Common upper respiratory tract pathogens and respiratory viruses precipitate most exacerbations of COPD.** Treatment aimed at these agents is useful, but it is not as important as improving lung emptying and maintaining gas exchange until the acute insult resolves.
5. **Oral and intravenous corticosteroids shorten the duration of an exacerbation and reduce the risk of relapse.** However, high-dose treatment beyond 2 weeks provides no advantage and actually poses a risk, especially in ventilated patients.
6. **Maintaining oxygenation is relatively easy, but there are risks** of carbon dioxide retention and acidosis if high-flow oxygen is administered. An oxygen saturation between 91% and 93% ensures adequate tissue oxygen delivery if the cardiac output is stable.
7. **Respiratory acidosis is a poor prognostic marker** in COPD exacerbations and a strong indicator of the need for assisted ventilation.
8. **Unless contraindicated, noninvasive ventilation is the safest and most effective way of managing acute respiratory failure.** More acidotic patients should be managed in an ICU facility with the option of intermittent positive-pressure ventilation if noninvasive ventilation fails.
9. **COPD patients meet conventional weaning criteria less frequently than other ICU patients do,** but they are more likely to wean successfully when they do meet the criteria.
10. **Seriously ill patients should be encouraged to make advance directives,** particularly after an ICU admission involving any form of ventilatory support.

Chronic obstructive pulmonary disease (COPD) is a major cause of death and disability worldwide and is one of the most common reasons for ICU admission. Several monographs review this complex disorder in some detail.[1,2] The intensivist's view of COPD is predominantly physiologic, focusing on the impact of disrupted function on the individual's normal homeostatic mechanisms. Although many important insights that have shaped our understanding of COPD have come from ICU studies, other aspects of this disorder must be considered if a rational approach to COPD management is to be developed.

Access to ICU care for sick COPD patients remains relatively inequitable among different health care systems. In North America and parts of western Europe, most patients are offered ICU care, but in other relatively developed health care systems, such as in the United Kingdom, this is not the case. Even physicians in the same health care system differ significantly in their selection of patients for ICU referral.[3] These choices may be influenced by local resource availability, but they are also conditioned by the generally pessimistic view of the outcome achievable with this treatment intervention. However, poor response to treatment is not universal, and extended periods of positive-pressure ventilation are not invariably required to successfully manage patients with COPD.[4] Nevertheless, intensivists often take a particularly bleak view of the prognosis of COPD patients compared with others entering their units. Inevitably, value judgments about the worth of an individual's life come into play, especially when resources are limited. However, such decisions should not be made in the emergency room without sufficient medical information or a proper discussion with the family. Supportive therapies should be offered until it is clear what the patient's wishes are and what the likely outcome of treatment will be.

This chapter reviews some of the relevant pathophysiology of COPD requiring ICU admission, considers the common reasons for such admissions, reviews the treatment options to support the patient and shorten the duration of the illness, and considers the role of assisted ventilation.

DEFINITION AND NATURAL HISTORY

Although the most appropriate definition of COPD has been debated in the wider pulmonary community, it has less of an impact in the context of ICU care, where acute hospitalization is usual only in cases of severe and well-established disease. The currently favored definition, developed by the global initiative for chronic obstructive lung disease, is as follows: "Chronic obstructive pulmonary disease (COPD) is a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive

and associated with an abnormal inflammatory response of the lungs to noxious particles or gasses."[5]

The emphasis here is on incompletely reversible airflow obstruction that is persistent and progressive. Symptoms and disability usually parallel these processes, although some individuals can apparently cope with a severe degree of airflow limitation without seeking medical help. Such patients finally present to the emergency room when they develop a severe exacerbation of COPD. In this situation, it is wisest to offer ventilatory support until the patient has at least had a chance to improve with conventional medical therapy. More common is a patient whose progressive illness is accompanied by repeated exacerbations, events that identify an accelerated decline in both lung function and health status.[6,7] Such patients have often been hospitalized previously, and their response to treatment is usually clearly established.

The usual inhaled particles or gases that produce COPD are a complex mixture of hydrocarbons and particulates derived from tobacco smoke. These are the principal causes of COPD in the United States and western Europe,[8,9] although other factors, such as poor lung function during childhood, bronchial hyperresponsiveness, and low birth weight, may also be important. The associated inflammatory changes, which persist when smoking stops,[10] are thought to explain the airway and parenchymal destruction and fibrosis within the lung, although this has not been conclusively established as the only mechanism.

The natural history of COPD explains why the number of patients presenting for ICU care has not diminished in the last 3 decades, as might be expected given the overall reduction in tobacco consumption in Western countries. This is illustrated by the classic study of Fletcher and Peto (Fig. 78-1).[11] Although the rate of decline of lung function is reduced in individuals who stop smoking, the lung function already lost is never regained, and even if the rate of decline of lung function returns to normal, these patients are still more likely to experience disability as they age. Thus, in an aging population that contains many former smokers, a significant number will still develop the complications of COPD that require ICU care. The situation is complicated by the steadily rising number of women who smoke, who appear to be at least as susceptible as men to the adverse effects of tobacco.[12] Thus, the initial reduction in new cases of COPD is partially offset by the increased incidence of women with significant symptoms.

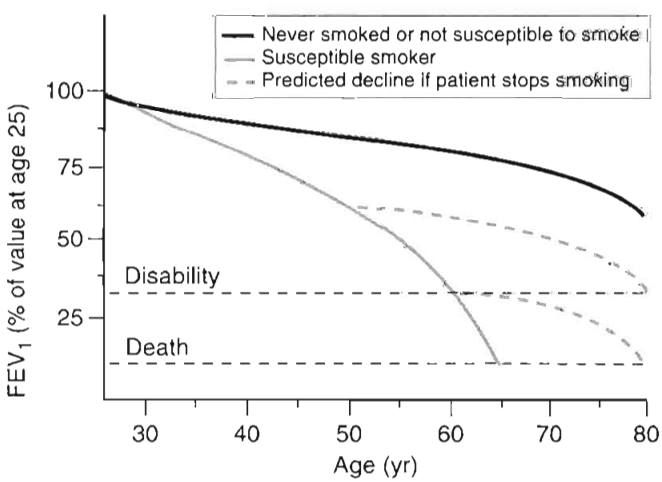

FIGURE 78–1. Natural history of chronic obstructive pulmonary disease and the effect of smoking cessation. Compared with lung function standardized to age 25, smokers show an accelerated rate of decline in forced expiratory volume (FEV_1), which returns to more normal values when they stop smoking. However, they are operating at a lower FEV_1 than that predicted for their age, and the physiologic decline continues. This explains why older ex-smokers can present to the ICU with severe disease despite years of abstinence. (Adapted from Fletcher C, Peto R: The natural history of chronic airway obstruction. BMJ 1977;1:1645-1648.)

PATHOLOGY

The pathologic features of COPD depend on the stage of the illness and the part of the lung examined.[13] Central airways show mucous gland hypertrophy and goblet cell metaplasia, whereas more peripheral airways show variable combinations of smooth muscle hypertrophy, peribronchial fibrosis, luminal occlusion by mucus, and enlarged lymphoid follicles.[14] Alveoli are often but not invariably enlarged by the loss of alveolar walls, with an attendant loss of support for the small noncartilaginous airways in this region of the lung. There is evidence of persistent inflammation, with neutrophils in the airway lumen and macrophages in the airway wall. $CD8^+$ T lymphocytes are more prominent in this response than in bronchial inflammation of an asthmatic type, although intermediate states appear to exist.[15,16] Inflammatory cells are also present adjacent to breaks in the alveolar wall.[17] Overall, as the clinical and spirometric severity of the disease increases, so do the numbers of each cell involved in the inflammatory process.[18] Data on exacerbations, though limited, support an increased role for neutrophils and, surprisingly eosinophils.[19]

PHYSIOLOGY

The pathologic changes just described combine to produce the characteristic diagnostic finding of reduced forced expiratory flow at a given lung volume (FEV_1), which is usually assessed on a time base as an FEV_1/forced vital capacity (FVC) ratio of less than 0.7. Technically, this should be 70% of the age-adjusted normal value for this ratio, because lung elastic recoil declines with age, even in healthy individuals. Use of the uncorrected ratio tends to overdiagnose COPD among the very elderly.[20] In practice, however, this does not cause problems for COPD patients admitted for ICU care, because they are invariably more severely affected.

COPD affects all aspects of lung function, but its primary impact is a change in lung mechanics. This is traditionally analyzed in terms of the static (no flow) and dynamic (flow) properties of the respiratory system.[21] Because chest wall mechanics are believed to be normal in COPD (although they are seldom measured directly), changes in the pressure-volume characteristics of the respiratory system are determined by alterations in lung compliance, often attributed to the loss of elastic recoil due to emphysema. How large a role this plays in changes in tissue compliance is not known. The resulting steeper slope, early-onset inspiratory plateau, and increase in end-expiratory lung volume are typical of the pressure-volume relationships in patients with COPD. Changes in end-expiratory lung volume and increases in residual volume change chest wall geometry to favor a lower, flatter diaphragm and a more horizontal rib cage; these changes, in turn, impair the inspiratory muscles' ability to develop pressure, and increase the overall work of breathing.[22] Expiratory muscle activation is common in more severe COPD,[23,24] even at rest, and provides a useful clinical marker of respiratory distress. Flattening of the diaphragm redirects the axis of shortening of

the skeletal muscle and often produces paradoxical in-drawing of the lower thoracic rib cage (so-called Hoover's sign), which becomes more evident as pulmonary hyperinflation and respiratory drive to breathe rise.

The dynamics of the respiratory system are influenced by these static properties but also differ significantly between inspiration and expiration. Maximum inspiratory flow is affected by inspiratory resistance, as well as by the inspiratory muscles' ability to develop pressure (and thus indirectly by chest wall geometry). Maximum expiratory flow is influenced by expiratory pressure generation and, more importantly, by the onset of volume-related airflow limitation, best described by the maximum expiratory flow-volume loop. As lung volume falls during expiration, airways close or become flow limited; hence, the flow at a specific lung volume is reduced. Although an assessment of flow (FEV_1) relative to total volume change during expiration (FVC) is useful in defining COPD, an assessment of tidal flow limitation is more helpful in determining the degree of dyspnea experienced by the patient.[25] More attention is now being paid to the determination of expiratory flow limitation under tidal conditions. In the past, detection was difficult, involving invasive measurements or reliance on body plethysmography, which tended to overestimate the incidence of tidal expiratory flow limitation. The development of the negative expiratory pressure test and, more recently, within-breath variation in respiratory system impedance has changed this.[26] In general, the lower the FEV_1, the greater the likelihood that expiratory flow limitation is present. However, some COPD patients are not flow-limited on every breath and regulate their end-expiratory lung volume to try to minimize this. When respiratory drive rises (e.g., during exercise), during disease exacerbations, or when minute ventilation has to increase to maintain gas exchange during ventilator weaning, this resting variation in expiratory lung volume is likely to decrease. If expiratory flow and hence tidal volume are to increase, end-expiratory lung volume must rise; this further increases the work of breathing and the sensation of respiratory distress. This process, described as dynamic hyperinflation, has been clearly demonstrated during exercise[27] and can be lessened by bronchodilator treatment, which aids lung emptying.

In the ICU, where the first observations about dynamic hyperinflation were made,[28] the same constraints occur. Patients have a high respiratory drive during weaning and adopt a rapid, shallow breathing pattern (see later). Total respiratory muscle work increases, in part because of the increased operating lung volumes, but also because of the presence of intrinsic positive end-expiratory pressure (PEEPi). This represents the pressure that must be developed to overcome residual expiratory driving pressure before inspiratory flow can begin. Calculating the size of this variable is fraught with technical difficulties beyond the problems of accurate placement of the balloon catheter system in intubated patients. Several methods have been proposed that correct for the effects of coexisting abdominal muscle activation, with recent work favoring a correction based on the total decay of gastric pressure.[29] However, the need to compute this variable in clinical practice has been questioned.[30]

What is clear is that the overall impairment of mechanical function in COPD is substantial and that both static and dynamic properties interact—a concept best captured by the time constant of the respiratory system, which is the product of the total respiratory system resistance in compliance. This is greatly lengthened in COPD and helps explain why lung emptying is delayed and dynamic hyperinflation occurs. There is substantial evidence of regional inhomogeneity in more severe COPD. Differences in the regional time constants explain why COPD patients are prone to barotrauma during mechanical ventilation, despite seemingly acceptable peak inspiratory pressures, as well as why gas exchange can be quite disordered in this population (see later).

GAS EXCHANGE

Arterial hypoxemia is common in COPD but becomes clinically significant only when the partial pressure of oxygen in arterial blood (PaO_2) falls below 60 mm Hg, a problem largely confined to patients with an FEV_1 below 35% of their predicted value. It arises predominantly due to ventilation-perfusion mismatching, often worsens during exercise, and is readily corrected by a small increase in the inspired oxygen concentration, unless the situation is made worse by secretion retention or severe pneumonia.[31] Arterial hypercapnia is seen in some but not all hypoxemic patients who are clinically stable, but it is more frequent, at least temporarily, in hospitalized individuals.[32] A combination of ventilation-perfusion mismatching due to an increase in physiologic deadspace and a degree of effective alveolar hypoventilation explains this phenomenon (see later). Acute rises in the partial pressure of arterial carbon dioxide ($PaCO_2$) precipitate respiratory acidosis, a more reliable guide to prognosis and the need for ventilation than the $PaCO_2$ itself.[33,34]

CONTROL OF BREATHING

Despite years of study, there is no conclusive evidence that ventilatory control is abnormal in COPD patients. However, the response to sustained mechanical loading appears to be variable in healthy subjects[35] and may explain why some individuals adopt the breathing patterns they do. Traditional techniques of studying respiratory control, which involve stimulation with exogenous CO_2 or nitrogen, suggested that respiratory drive was reduced. However, studies using mouth occlusion pressure techniques or recording the electrical activation of inspiratory muscles suggest that respiratory drive is generally high, even in those who tolerate relatively high levels of CO_2.[36-38] Studies of breathing pattern have been more instructive. In general, the lower the tidal volume, the higher the $PaCO_2$.[39] This is because the ratio of deadspace (its fixed, predominantly anatomically determined volume) to tidal volume increases as the latter is reduced. Small tidal volumes are accompanied by an increased respiratory frequency, to maintain the somewhat higher than normal level of minute ventilation. The resulting shortening of inspiratory time is also associated with hypercapnia.[39] The system appears to be regulated to minimize peak inspiratory pressure generation, even at the cost of impaired gas exchange. There are theoretical reasons for believing that this is both energy efficient and likely to minimize the occurrence of inspiratory muscle fatigue.[40] This also explains the usefulness of rapid, shallow breathing as an index of weaning failure when neuromechanical coupling in the respiratory system is under considerable stress.[41]

PULMONARY CIRCULATION

In the past, considerable attention was paid to the determination of pulmonary artery pressure in COPD patients, but this

is now thought to be less important. Undoubtedly, pulmonary artery pressure increases by day and at night[42] in hypoxemic COPD patients, reflecting a combination of hypoxic vasoconstriction and pulmonary vascular remodeling. How important this is in the daily limitation of exercise reported by these patients is not clear, but it is known that treatment with domiciliary oxygen prevents disease progression[43] and may even reduce pulmonary artery pressure. More specific attempts at therapy both inside and outside the ICU have been unsuccessful, usually resulting in worsening of ventilation-perfusion mismatching, which is thought to be clinically unacceptable.[44] In general, assessment of pulmonary hypertension has fallen out of favor as part of a routine evaluation in COPD patients, but its occurrence is important to note when interpreting changes in central venous pressure in instrumented patients.

SYSTEMIC EFFECTS

There is good evidence that systemic (extrapulmonary) factors are important in COPD. Patients with a reduced body mass index die sooner than better-nourished individuals with a similar degree of pulmonary function impairment, although those who can gain weight fare better.[45] There are data to show that peripheral muscle function is impaired,[46] fiber type is altered,[47] and exercise is associated with increased oxidative stress.[48] This has led to the concept of a specific COPD myopathy,[49] although how much of this reflects inactivity and the effects of impaired oxygen delivery during exercise has yet to be established. There are data suggesting altered oxidative metabolism in circulating lymphocytes[50] and increased concentrations of tumor necrosis factor, which may predispose to cachexia in some cases.[51] Whether one or several inflammatory pathways are involved in producing these diverse effects is not clear, but their presence is generally a marker of a poorer prognosis and can lead to specific problems in the ICU.

EXACERBATIONS

A recent consensus conference defined an exacerbation of COPD as a sustained worsening of the patient's condition from the stable state, beyond normal day-to-day variation, that is acute in onset and necessitates a change in regular medication.[52] The key feature here is the sustained change from usual daily symptoms. The operational requirement for a change in treatment is more arbitrary but is almost always present in patients referred for ICU care. Disease exacerbation is the principal cause of ICU admission with COPD, and patients commonly have or are at risk of developing significant respiratory failure, defined as a PaO_2 below 60 mm Hg with or without an increase in $PaCO_2$.[53] The most common causes of exacerbation are listed in Table 78-1. Viral and bacterial infections are both relevant,[54] with rhinoviruses commonly reported in most series; *Haemophilus influenzae* and *Streptococcus pneumoniae* are the principal microbial pathogens.[55] Some patients, particularly those with a regular cough and green sputum production, develop persistent lower respiratory tract colonization, making the interpretation of qualitative microbiology difficult.[56] Usually, there is an increase in the absolute number of colony-forming units of microorganisms in these patients during exacerbations, reflecting an increased burden of infection, although more subtle changes have been reported involving the introduction of a different serotype of *H. influenzae*.[57] Not all exacerbations have an infectious precipitant, and changes in the degree of atmospheric pollution can precipitate events in some patients.[58] How frequently individuals develop exacerbations after exposure to a specific precipitating event is not clear, although the likelihood of meeting the consensus definition rises as spirometric impairment worsens.[59]

The physiologic consequences of increased airflow obstruction secondary to increased inflammation within the bronchial tree are summarized in Figure 78-2. Whatever the precipitant, the key event appears to be a change in lung mechanics. Previously, attention focused on alterations in respiratory system resistance, but more recent data emphasize that airway narrowing and closure may be more important, particularly by producing changes in operating lung volumes (see earlier). This may explain why the small changes in pulmonary function that accompany exacerbations can be associated with substantial deterioration in gas exchange and clinical well-being, leading to hospitalization.

TABLE 78–1. CAUSES OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATION

New infection
Bacterial (*Haemophilus influenzae, Streptococcus pneumoniae, Moraxella haemophilus*)
Change in an existing strain (e.g., *H. influenzae*)
Viral (influenza, rhinovirus, respiratory syncytial virus)
Atmospheric pollution
Sulfur dioxide, oxides of nitrogen
Temperature change
Often related to pollution episodes
Intercurrent illness*
Pneumonia, pulmonary embolus, pneumothorax
Postoperative
Especially after upper abdominal surgery

*Clinical presentation is dominated by the primary illness, but respiratory failure can occur.

CLINICAL FEATURES

Key clinical features of the acute presentation are summarized in Table 78-2. In addition to obtaining an appropriate history and performing a physical examination, it is necessary to assess the degree of abnormal gas exchange and the presence of acidosis by measuring the arterial blood gases. In the context of an exacerbation, more direct measurements of lung mechanics are usually impractical, and the severity of the mechanical problem is evaluated indirectly by its effect on gas exchange. An urgent chest x-ray is useful for identifying specific precipitating factors, particularly alveolar shadowing due to infection, the presence of a pneumothorax, or radiographic features of pulmonary edema. The last is especially important, because it is commonly associated with hypercapnic respiratory failure—the combination of an increased ventilatory drive and poor perfusion of respiratory muscles, together with further impairment of ventilation-perfusion matching favoring CO_2 retention. In this context, an electrocardiogram is invaluable to screen for both underlying ischemic heart disease and rhythm disturbances. If major thromboembolic events are suspected on clinical grounds, quantitative D-dimer and urgent helical computed tomography scans with intravenous contrast to visualize the pulmonary circulation are the best way to establish their

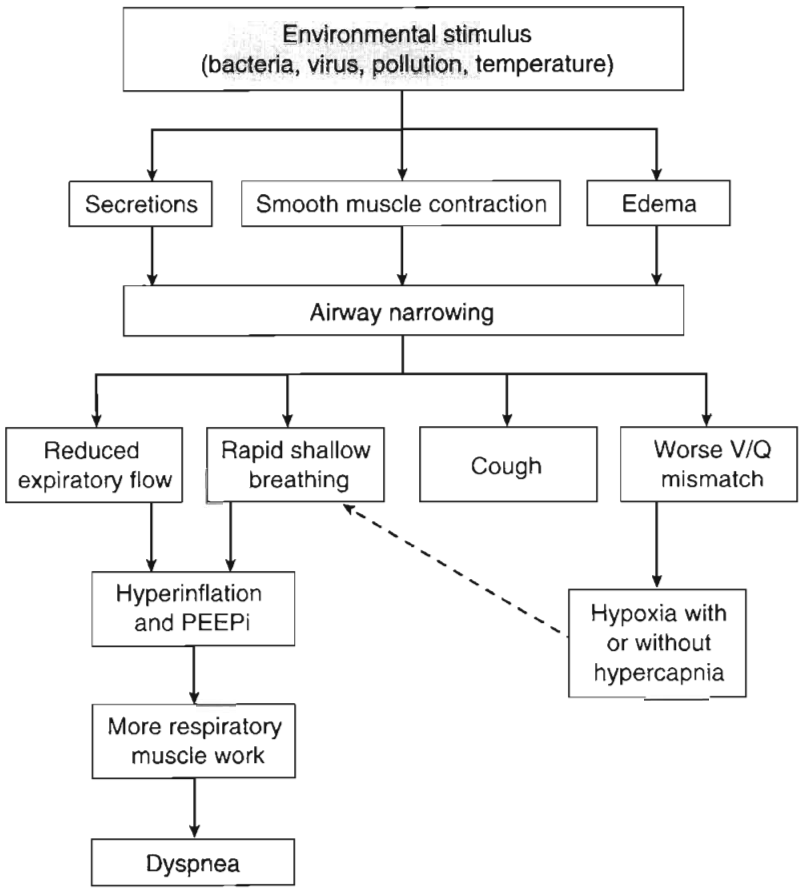

FIGURE 78–2. Schematic presentation of the principal physiologic changes that accompany an exacerbation of chronic obstructive pulmonary disease. Note that deterioration in one area tends to produce worsening in other areas and leads to a downward spiral in functional abnormality. PEEPi, intrinsic positive end-expiratory pressure; V/Q, ventilation-perfusion.

existence. Reliance on isotope ventilation-perfusion scanning is particularly prone to overdiagnosis in these patients and should be avoided. Simple laboratory tests such as the hemoglobin and white cell count can be valuable guides to the need for oxygenation and the likelihood of coexisting sepsis.

Exacerbation of airway inflammation is not the only reason for the deterioration of postoperative COPD patients, who are at significant risk after any type of surgery. This may reflect the consequences of anesthesia and impaired secretion clearance, the risks of lower respiratory tract infection after intubation, or the effects of surgery itself. Both pain and the drugs administered to relieve it are likely to depress ventilation in these patients. Thoracic and upper abdominal surgery impairs the function of the inspiratory and expiratory muscles, respectively. In those with severe COPD, abdominal muscle activation is an important involuntary technique to "share" the work of breathing between the inspiratory and expiratory muscles; impairment of abdominal muscle activation commonly increases the degree of breathlessness and may precipitate respiratory muscle fatigue. Persistent smoking before elective procedures should be discouraged, because this further compromises the already reduced compensatory mechanisms in COPD patients. In this setting, it is not surprising that respiratory failure develops in a significant number of individuals with severe disease, necessitating ICU care.

TABLE 78–2. CLINICAL FEATURES OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATION

Sustained increase in dyspnea*
Increased cough (with or without sputum)*
Increased sputum volume or purulence*
Symptoms of upper respiratory tract infection (variable and should be accompanied by a major symptom)
Fever (infrequent in the absence of pneumonia)
Cyanosis (with advanced disease)
Tachypnea
Pursed lip breathing
Accessory muscle use (including abdominals)
Pulmonary overinflation (reduced cricoid distance, Hoover's sign, resonant percussion over the heart)
Tachycardia
Boundary pulse
Hypotension†
Flapping tremor†
Impaired level of consciousness†

*Major symptom.
†Severe illness.

ICU REFERRAL

The need for mechanical ventilation is the primary reason for ICU referral among COPD patients. Although the various indications for mechanical ventilation (Table 78-3) vary in frequency from institution to institution, they represent the most common causes for ICU admission and have been acknowledged as such in a number of treatment guidelines.[5,60]

Before referring a patient for ICU care, and especially for any form of ventilatory support, it is important to determine what degree of intervention is appropriate. Advance

TABLE 78–3. INDICATIONS FOR INVASIVE MECHANICAL VENTILATION

Severe dyspnea, with use of accessory muscles and paradoxical abdominal motion
Respiratory frequency >35 breaths/min
Life-threatening hypoxemia (PaO_2 <40 mm Hg or PaO_2/FiO_2 <200 mm Hg)
Severe acidosis (pH <7.25) and hypercapnia ($PaCO_2$ >60 mm Hg)
Respiratory arrest
Somnolence, impaired mental status
Cardiovascular complications (hypotension, shock, heart failure)
Other complications: metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion
Noninvasive positive-pressure ventilation failure (or exclusion criteria)

FiO_2, inspired oxygen fraction; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood.

directives are becoming increasingly common among COPD patients, particularly in the United States. These are specific orders about the level of intervention desired by the patient, informed by discussions with his or her physician. These difficult and potentially upsetting discussions are necessary when patients are approaching the terminal phase of an illness, and they should be encouraged as a routine practice, particularly in those who have already been admitted to an ICU and have a clear idea of what therapy involves. However, it is important to ensure that such interviews are conducted when the patient is clinically stable and capable of making rational judgments about what the future holds. We still have some way to go before this important aspect of care becomes a routine part of our clinical practice.

PRINCIPLES OF TREATMENT

Four general principles guide the management of COPD patients presenting acutely to the ICU, and each should contribute to shortening the duration of illness and stabilizing the patient physiologically until either the natural course of the disease or the effects of therapy lead to its resolution.

TREAT PRECIPITATING FACTORS

Bacterial infection is the most common reason for ICU admission in COPD patients. Infection confined to the airways can be managed with broad-spectrum antimicrobials, provided the patient is capable of swallowing and has reasonable gastrointestinal absorption. Otherwise, intravenous therapy is required; this is usually the case in patients sick enough to merit ICU admission. Radiographic evidence of pneumonia likely requires a broadening of the antibiotic spectrum, but whether the infection is confined to the airways or involves the alveoli, antibiotic therapy should follow locally established guidelines designed to minimize the development of resistance within the ICU and to address known patterns of drug resistance in the community and the hospital. Broad-spectrum penicillins or, more commonly, cephalosporins are usually recommended, often with an intravenous macrolide. Some advocate the prophylactic use of quinolone in COPD patients in the ICU,[61] but this practice requires confirmation before being accepted as universally effective. Colonization with methicillin-resistant *Staphylococcus aureus* is still a frequent problem and requires particular vigilance in the selection of antibiotics. Likewise, excessive use of broad-spectrum agents can produce superinfection, such as *Clostridium difficile* diarrhea. This can be particularly distressing in a patient with severe COPD and a low body mass index and requires early identification and appropriate therapy.

The role of antiviral drugs, such as the neuraminidase inhibitors, in the management of acutely ill COPD patients remains to be determined. In some cases in which deterioration is extremely rapid, there may be some advantage in introducing these expensive agents, although the opportunity to maximize their ability to shorten the duration of the illness may have been lost by the time the patient reaches the hospital.

For those with postoperative pain, epidural anesthesia is frequently helpful, as it permits adequate analgesia without the unwanted ventilatory depressant effects noted earlier. Prophylaxis for pulmonary embolism should follow established guidelines in other high-risk groups managed in the ICU setting.

REDUCE LUNG VOLUME AND INCREASE EXPIRATORY FLOW

Agents that improve lung emptying, commonly by increasing airway caliber or preventing airway closure, interfere with the vicious circle of pulmonary hyperinflation described in Figure 78-2. This has been demonstrated in stable patients using exercise as a model of hyperinflation,[62] but the data in spontaneously breathing COPD patients during exacerbations are much less satisfactory. Nonetheless, treatment with regular but high doses of short-acting nebulized beta agonists, such as albuterol or ipratropium (2.5 to 5 mg or 250 to 500 μg, respectively), is usually recommended. There is no clear evidence that one drug is better than the other,[63] and combination therapy is commonly used. The outcomes of the few studies conducted in this setting were based on FEV_1 rather than symptoms or lung volume change. Intravenous theophylline, or one of its derivatives, is often added to these regimens, but there are few data to support doing so.[64]

REDUCE PULMONARY INFLAMMATION

Several randomized, controlled trials have shown that oral corticosteroids shorten the duration of hospitalization and accelerate improvement of post-bronchodilator FEV_1 during an exacerbation of COPD.[65,66] Patients randomized to treatment with oral corticosteroids were less likely to relapse during the subsequent month and showed a number of other benefits, although these did not always reach statistical significance.[67] There does not appear to be any additional benefit from using particularly high doses of corticosteroids or prolonging treatment beyond 10 days to 2 weeks. In the ICU, corticosteroid treatment is often given peremptorily to patients on ventilators; caution should be exercised, however, because these individuals are often at risk for relatively acute-onset corticosteroid myopathy.[68] If corticosteroid therapy has been maintained for a longer-than-normal period, or if courses of oral corticosteroids to treat less serious exacerbations have been given more frequently, a tapered dose-reduction plan should be introduced. Otherwise, treatment can be discontinued at the end of the normal 10 to 14 days. Patients given this therapy may benefit from subsequent treatment with inhaled corticosteroids,[69] but they should be evaluated for significant side effects. Osteoporosis is

particularly common in COPD patients, whether they receive corticosteroid treatment or not, and it is probably worth identifying in any individual who requires ICU care.[70]

MANAGE GAS EXCHANGE

It is relatively easy to improve oxygenation in an uncomplicated exacerbation of COPD.[71] Raising the inspired oxygen concentration to 28% to 35% is usually sufficient to achieve a PaO_2 greater than 90 mm Hg. However, this is often accompanied by an undesirable increase in $PaCO_2$, with its accompanying respiratory acidosis. This impairs respiratory muscle function, at least during loaded breathing,[72] and often precedes more serious clinical deterioration, including impairment of consciousness. The reasons for this effect have been debated for many years, with some advocating a reduction in respiratory drive from the carotid chemoreceptors, and others citing a worsening ventilation-perfusion match as the cause.[71] Each view has evidence to support it, but the actual cause is likely a combination of both problems, with ventilation-perfusion mismatching being particularly important in severely ill patients, and hypoventilation playing a larger role in those not yet sick enough to require intubation.[73]

Although the phenomenon of oxygen-induced hypercapnia has been recognized for decades, it remains a real problem. In one large center in the United Kingdom, 34% of individuals showed evidence of oxygen-induced hypercapnia.[34] The use of high-flow oxygen in the emergency room is widespread, as is the false sense of security provided by a high pulse oxygen saturation. Many intensivists have legitimate concerns about the failure to adequately oxygenate COPD patients with compromised circulation, along with the attendant risk of unanticipated mortality. However, the solution is to carefully consider the risks of excessive or insufficient oxygen in a given individual, rather than to slavishly adhere to one view or the other. Patients whose problems are predominantly due to COPD and who have a normal hemoglobin and preserved cardiac output can maintain adequate tissue oxygen delivery with an oxygen saturation as low as 85%, and they will do quite well if an arterial oxygen saturation (SaO_2) of 90% to 93% is maintained. The modest increase in inspired oxygen needed to achieve this (often 24% to 28%) is accompanied by less hypercapnia and may avoid the need for ventilatory support. However, if cardiac output is impaired (reduced blood pressure, poor peripheral circulation) or the metabolic demands of the tissue are increased (e.g., in sepsis secondary to pneumonia), a higher SaO_2 will be required to ensure that there is sufficient oxygen delivery; in this case, the consequences of any resultant hypercapnia, including the need for ventilatory support, must be accepted.

Oxygen can be delivered accurately by facemask, using the Venturi principle of entraining room air into the mask. This is a precise method of giving a known inspired oxygen concentration to COPD patients,[74] but many patients dislodge facemasks and are unlikely to keep nasal prongs in place.[75] Nasal prongs allow the patients to speak and drink, but the inspired oxygen fraction (FiO_2) is more variable, and it may be necessary to monitor arterial blood gases more frequently. Institutions where nebulizers are used to deliver bronchodilator drugs should be cautious about nebulizing these drugs using wall oxygen, because this can produce severe hypercapnia. A better policy is to nebulize in air, with the patients keeping their nasal cannulas in place.

For many years, respiratory stimulants were used to waken semiconscious patients and permit physiotherapy and other forms of suction, but this approach was never tested scientifically and must be viewed with some skepticism today. There are data that continuous infusion of the nonspecific ventilatory stimulant doxapram can lower $PaCO_2$ values and allow a higher inspired oxygen to be delivered,[76] and groups have recommended this as a way of deferring the need for positive-pressure ventilation.[60] The advent of nasal positive-pressure ventilation has changed this approach, and the only study that directly compared the effects of doxapram and this modality in COPD concluded that patients did better with noninvasive ventilation and were less likely to deteriorate.[77] If chemical ventilatory stimulants are used, they should be considered a short-term means of sustaining the patient until a more appropriate method of ventilation can be instituted. Ultimately, some kind of mechanical ventilatory support is the best way to address the problems of hypercapnia.

NONINVASIVE VENTILATION

This topic is reviewed in detail in Chapter 68, but some key issues relevant to COPD are worth emphasizing. Many of the data supporting the use of noninvasive ventilation were obtained in patients with hypercapnic respiratory failure due to COPD exacerbation, and several excellent reviews have analyzed these data.[78,79]

Noninvasive ventilation has a number of potentially beneficial effects in COPD. Intuitively, it seems reasonable to expect that it would increase tidal volume, improve CO_2 elimination, and hence reduce respiratory drive. Studies of gas exchange using a multiple inert gas elimination methodology confirmed that CO_2 elimination is increased but overall ventilation-perfusion mismatch is not changed during noninvasive ventilation.[80] A more important effect is the unloading of the respiratory muscles, which are often close to fatigue conditions in severe episodes of respiratory failure. By assuming some of the additional work required to overcome intrinsic PEEP, noninvasive ventilation directly reduces the drive to breathe, and the respiratory rate falls, a good prognostic feature. Data from randomized, controlled trials suggest that there is a mean fall of 3.1 breaths per minute (95% confidence interval 4.3 to 1.9).[78] This allows more effective emptying of the lungs and less dynamic hyperinflation. The resulting improvement in the intensity of breathlessness is usually a much earlier sign of successful noninvasive ventilation treatment in COPD than are changes in blood gas tensions, which often lag behind evidence of clinical improvement.

Evidence-based reviews provide a reasonable series of recommendations based on the relative effectiveness of noninvasive ventilation. Key points, including the number of patients needed to be treated to prevent one significant event or complication, are shown in Table 78-4. Noninvasive ventilation is associated with less treatment failure, lower mortality, fewer complications, and a lower intubation rate compared with conventional medical treatment. It reduces the ICU or hospital stay by approximately 3 days and favorably influences gas exchange. Thus, pH increases by a mean value of 0.03 (0.02 to 0.04), $PaCO_2$ falls by 3 mm Hg (5.9 to 0.23 mm Hg), and PaO_2 rises by 2 mm Hg (−2 to +6 mm Hg). The lower rate of nosocomial pneumonia associated with noninvasive ventilation is a particular advantage.

These data support the use of noninvasive ventilation as a first-line treatment in patients with exacerbations of

TABLE 78–4. EFFICACY OF NONINVASIVE VENTILATION COMPARED WITH USUAL CARE

Outcome	Number of Patients Studied	Relative Risk (95% Confidence Interval)	NNT
Treatment failure	529	0.51 (0.38-0.67)	5
Death	523	0.41 (0.26-0.64)	8
Intubation	546	0.42 (0.31-0.59)	5
Complications	143	0.32 (0.18-0.56)	3

NNT, number needed to treat—the number of patients who must be treated to prevent this outcome in one individual.

COPD and moderate respiratory acidosis (pH <7.35) despite medical treatment. In general, most patients with pH in the range of 7.3 to 7.35 survive without noninvasive ventilation, although the number patients needed to prevent one exacerbation is still only 10.[81] As acidosis becomes more severe, the benefits of noninvasive ventilation become greater; this treatment should be encouraged in anyone with a pH less than 7.3. In patients with more severe acidosis (pH <7.25), the benefit is less clear, and results in different trials suggests that such patients have a better outcome if they are managed in the ICU with mechanical ventilation and intubation; however, these trials are influenced by selection bias. In clinical practice, it is reasonable to offer a trial of noninvasive ventilation unless the patient has some of the established contraindications to this treatment (Table 78-5). Even then, there are occasions when noninvasive ventilation is appropriate first-line therapy, for example, if a patient does not wish to be intubated (as indicated in an advance directive) or has a "ceiling of treatment" determined by his or her prior health status.

Treatment failure, which occurs in approximately 30% of cases,[82] reflects an inability to adapt to noninvasive ventilation or progression of the underlying disease. Although early failure may reflect rapid clinical deterioration, such as worsening of oxygenation toward progressive consolidation, it is more often due to the patient's inability to synchronize with the ventilator and thus effectively offload the respiratory muscles. Failure to trigger the machine or excess trigger sensitivity can lead to problems of coordination between patient and machine. Air leakage can be a problem when facemasks are used, the usual approach in patients with COPD. Reducing rather than increasing inspiratory positive airway pressure often lessens this complication and allows better patient-ventilator coordination. Some patients develop hypercapnia, occasionally due to rebreathing in the mask, but more often due to ineffective cough and retained secretions. Conversion to a nasal mask and chinstrap allows more effective cough, without loss of ventilator support. Late failure (after 48 hours or more of noninvasive ventilation), suggested by worsening acidosis, is a poor prognostic sign; it usually reflects deterioration caused by the underlying lung disease. If this occurs, the institution of invasive positive-pressure ventilation needs to be considered.[83] Patients treated in this way may have a better prognosis, although the interpretation of data is difficult, given the nonrandomized design of the relevant study.[83] What is clear is that extending the period of noninvasive ventilation in a patient with physiologic evidence of deterioration is not likely to produce a successful result.

In addition to its role in the acute phase of respiratory failure, noninvasive ventilation can be valuable as a "bridge" in helping patients wean from intermittent positive-pressure ventilation. In an important multicenter, prospective trial, Nava and colleagues randomized people who had failed a T-piece weaning trial to either noninvasive ventilation or further mechanical ventilation.[84] Noninvasive ventilation was associated with fewer days of ventilatory support (10.2 versus 16.6, respectively), shorter ICU stay (15.1 versus 24 days), less nosocomial pneumonia, and a better 60-day survival (92% versus 72%). These results were achieved in a unit with a lot of experience with noninvasive ventilation. As this technique is used more often, both inside and outside the ICU setting, it is likely that noninvasive ventilation will yield good results and will become a more standard approach than is currently the case.

TABLE 78–5. CONTRAINDICATIONS TO NONINVASIVE VENTILATION

Impaired consciousness (unless oxygen induced)
Confusion, agitation
Significant risk of vomiting
Profound hypoxemia
Excessive secretions
Facial or upper airway trauma or surgery

MECHANICAL VENTILATION

Practical aspects of intermittent positive-pressure ventilation are reviewed in detail elsewhere in this book. This treatment should be considered when noninvasive ventilation is not appropriate (see Table 78-5) or has failed. Patients with a pH below 7.25 are more likely to require this therapy. Persistent significant hypoxemia despite treatment, hypotension, and impaired mental state are all predictors of imminent respiratory arrest and the need for intermittent positive-pressure ventilation.

The major risk during intubation is hypotension. This reflects a combination of problems, including reduced venous return secondary to positive intrathoracic pressures, direct vasodilatation, and reduced sympathetic tone produced by the anesthetic agents. Reoxygenation of the patient with rapid-sequence induction of anesthesia is recommended, and this is normally accompanied by cricoid pressure to reduce the risk of aspiration, although the benefits of this technique remain unclear.[85] Short-acting muscle relaxants are usually used. Because of concerns about the risk of hyperkalemia, nondepolarizing drugs are often preferred in this circumstance. Hypotension is normally combated with fluid replacement, and if it is persistent, it is sensible to disconnect the endotracheal tube from the ventilator and allow the patient to return to a true end-expiratory lung volume before resuming ventilation.

VENTILATION STRATEGIES

A wide range of ventilation strategies have been advocated for use in COPD, each with its own proponents; none has shown a clear advantage over its competitors, however. Familiarity with the equipment in the context of COPD patients is probably more important than the relatively

TABLE 78–6. MODES OF VENTILATION

Mode	Method	Comment
Assist-control	Preset tidal volume, patient triggered with backup rate	Patient still performs substantial work of breathing; dynamic hyperinflation worsens this
Spontaneous intermittent mandatory ventilation	Preset number of breaths of a preset volume—patient does the rest	Patient still makes an effort during part of machine breath—involves more patient work, especially at low respiratory rates
Pressure support ventilation	Pressure set to augment each inspiration—tidal volume depends on patient effort, pulmonary mechanics, and pressure applied	Basis of noninvasive ventilation therapy; pressure titrated to a respiratory rate below 27 breaths/min; asynchrony with machine breaths a problem at high pressures
Proportional assist ventilation	Flow and volume generated proportional to patient effort	Experimental technique; requires accurate measurement of elastance and resistance + an intact drive to breathe; proven effective in COPD patients

minor differences between ventilator modes. The most commonly used approaches, together with their proposed advantages, are summarized in Table 78-6.

SETTINGS

In general, a combination of a relatively low respiratory rate, prolongation of the expiratory time, and limited tidal volume increases the risks of barotrauma, reduces the degree of dynamic hyperinflation, and allows better synchronization between machine-delivered breaths and the patient's own lengthened respiratory time constants. In the United Kingdom, patients are commonly paralyzed for the first 12 to 24 hours of intermittent positive-pressure ventilation to heighten ventilator synchrony and stabilize gas exchange. Although a degree of permissive hypercapnia is usual with this regimen, it is generally well tolerated. Typical ventilator settings are a tidal volume of 8 to 12 mL/kg, a frequency of 10 to 14 breaths per minute, and an inspiratory-expiratory ratio of 1:2.5 or 1:3. Increasingly, pressure control ventilation is used; with this method, the respiratory flow more closely resembles the patient's own spontaneous breathing pattern, and there is more equal ventilation of all lung units rather than preferential ventilation of those with the highest compliance, as occurs during volume cycle ventilation. The optimal extrinsic PEEP remains contentious in this setting, as there is a risk of inducing hyperinflation if too much pressure is added. In general, 5 cm H_2O of PEEP is probably sufficient to overcome intrinsic load without risking passive hyperinflation. The difficulties of assessing this variable have already been considered.

ASSISTED VENTILATION AND WEANING

As acidosis resolves and oxygen requirements fall, it is possible to reduce the degree of sedation and allow the patient to make some contribution to ventilation before weaning. Several modes of ventilatory support are available in these circumstances, and again, there is no specific advantage of one over another.[86,87] There is an impression, however, that reliance on spontaneous intermittent mandatory ventilation prolongs subsequent weaning. Although not universally accepted, there are good data supporting the use of spontaneous breathing trials in patients who are clinically stable, to determine when they are ready to wean.[87-89] The ability to sustain ventilation in the absence of increasing CO_2, worsening acidosis, or clinical distress (reflected by an increase in blood pressure, heart rate, or restlessness) is generally agreed to be a predictor of future weaning success. Although COPD patients are less likely to achieve these goals as early as other ICU patients, the re-intubation rate in those who do meet these criteria is low.[88,89] Unfortunately, breathing through the ventilator on a continuous positive airway pressure circuit may be associated with significant increases in inspiratory resistance,[90] and it is sensible to use pressure support to offset some of this additional respiratory work. This reflects the necessity of identifying patients who can be weaned using the ventilator alone and those who need more prolonged support. In the latter circumstance, weaning supported by noninvasive ventilation is particularly helpful.

A variety of predictors of weaning success have been developed to try to identify when successful weaning will occur. Unfortunately, none has proved entirely reliable, and relatively few have been assessed prospectively. An empirical approach based on the criteria listed in Table 78-7 is widely used. An aggressive policy toward weaning is justified in COPD patients, because an inability to wean is invariably associated with a worse prognosis and prolonged ventilation.

NONVENTILATORY ISSUES

Therapy employed in spontaneously breathing patients is still required in those undergoing mechanical ventilation. High-dose nebulized bronchodilators are commonly used, singly and in combination,[91,92] although it is important to pay attention to the details of drug delivery. Drug deposition within the ventilator circuit and endotracheal tube can lead to a significant loss of effective drug.[93] When using a nebulized drug, the nebulizer should be placed in the inspiratory line,

TABLE 78–7. CRITERIA FOR WEANING FAILURE

Increasing hypercapnia or worsening hypoxemia (<55 mm Hg)
pH <7.32
Increased respiratory rate, >35 breaths/min
Increase in heart rate or blood pressure by 20% of baseline
Agitation, sweating, or impaired consciousness

at least 30 cm from the endotracheal tube; this allows the tubing to act as a spacer device and increases the respirable fraction.[93] If a metered dose inhaler is used instead, it should always be given with some form of spacer device, for the same reason. Parenteral corticosteroids are commonly administered. This is not without hazard, particularly because of the real risk of myopathy (see earlier). As noted previously, there does not seem to be any advantage in giving high doses, nor should the period of treatment extend beyond 5 days.

Clearance of secretions is important in ventilated patients, and it is essential that the patient's hydration state be maintained. Whether specific mucolytic drugs such as *N*-acetylcysteine are helpful is unclear, and no good scientific studies to support or reject their use are available. Introduction of a mini-tracheostomy often facilitates secretion clearance without compromising subsequent weaning. For patients requiring longer periods of ventilation, a formal tracheostomy is needed; the introduction of a speaking valve or fenestrated tube permits speech and improves patient communication and morale.

The benefits of nutritional support are unclear, although it is obviously needed in patients who are catabolic and poorly nourished. However, concerns about providing an excessive metabolic CO_2 load are unfounded. Simple nursing measures are often surprisingly effective; in particular, keeping the patient's head elevated prevents nosocomial pneumonia and is more effective than other approaches, such as gut sterilization, in patients with COPD.

PROGNOSIS

The prognosis following an exacerbation of COPD is better than the gloomy outlook proposed by some physicians. Nonetheless, patients who experience exacerbations appear to have a more severe clinical course than those who do not, and they report a worse overall quality of life.[94] Mortality after an ICU admission is significant, at least in North American series.[95] Ten percent to 15% of such subjects die as inpatients; over the next 2 years, 30% to 60% of patients die. Patients with a low FEV_1, significant comorbidity, and a particularly poor performance status at home have the worst outlook.[96] These factors should be considered when decisions about the requirement for ventilatory support are made. It is important to discuss these issues with a patient who has recovered from a severe exacerbation so that he or she can make an informed judgment about future treatment. This is best done away from the immediate ICU environment, after the patient's normal performance status has been reestablished. Anecdotal evidence suggests that some individuals deteriorate significantly after a major exacerbation and never regain their previous sense of well-being. Because it can take a number of months before this new stable state is achieved, it makes sense for these patients' long-term caregivers to review their ICU needs. In patients with severe disease—and certainly anyone who has required ICU admission or ventilation—this should be an essential part of their continuing care.

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Chapter 79

PULMONARY EMBOLISM

Graham F. Pineo • Russell D. Hull

KEY POINTS

1. **The clinical diagnosis of deep venous thrombosis** (DVT) is highly nonspecific because none of the symptoms or signs is unique and each may be caused by nonthrombotic disorders.
2. **The clinical presentation of pulmonary embolism** (PE) depends on the size, location, and number of emboli and on the patient's underlying cardiorespiratory reserve.
3. There is evidence that the **prognosis for long-term survival and recurrent venous thromboembolism** (VTE) is worse with patients presenting with PE as opposed to DVT.
4. Multiple studies indicate that in more than one half of all patients with clinically suspected PE **the diagnosis is not confirmed by objective testing.**
5. **Determining the clinical probability of VTE** and the use of various forms of D-dimer to rule out VTE have been incorporated into diagnostic algorithms for the diagnosis and management of VTE.
6. Further studies are required to fully identify **the role of spiral CT in the diagnosis of PE.**
7. **Efficacy of heparin therapy** depends on achieving a critical therapeutic level of heparin within the first 24 hours of treatment.
8. **Low-molecular-weight heparin (LMWH) replaced intravenous unfractionated heparin** in the initial management of patients with VTE.
9. Safer and more effective anticoagulant therapy is required for the **treatment of VTE in patients with cancer.**
10. At this time, there is **no justification for the use of the lesser intensive warfarin program.**
11. Until the proper randomized clinical trials have been carried out, **thrombolytic therapy should only be used for patients with massive PE complicated by shock.**
12. **Routine insertion** of inferior vena cava filters in patients with free-floating thrombi cannot be supported.

Venous thromboembolism (deep venous thrombosis [DVT], pulmonary embolism [PE], or both [VTE]) usually complicates the course of sick, hospitalized patients but may also affect ambulant and otherwise apparently healthy individuals.[1-3] PE remains the most common preventable cause of hospital death and is responsible for 150,000 to 200,000 deaths per year in the United States. Most patients who die of PE succumb suddenly or within 2 hours of the acute event before therapy can be initiated or can take effect.[4] Effective prophylaxis against VTE is now available for most high-risk patients.[5-7] Prophylaxis is more effective in preventing death and morbidity from VTE than is treatment of the established disease.

PATHOPHYSIOLOGY

Venous thrombi are composed predominantly of fibrin and red cells and have a variable platelet and leukocyte component. The formation, growth, and dissolution of venous thromboemboli represent a balance between thrombogenic stimuli and protective mechanisms. The factors that predispose to the development of venous thromboemboli are venous stasis, activation of blood coagulation, and vascular damage. The protective mechanisms that counteract these thrombogenic stimuli include (1) the inactivation of activated coagulation factors by circulating inhibitors (e.g., antithrombin III, α_2-macroglobulin, α_1-antitrypsin, and activated protein C); (2) clearance of activated coagulation factors and soluble fibrin polymer complexes by the reticuloendothelial system and by the liver; and (3) dissolution of fibrin by fibrinolytic enzymes derived from plasma and endothelial cells and digestion of fibrin by leukocytes.

Various risk factors predispose to the development of venous thromboembolism (Table 79-1).[2,8,9]

PE originates from thrombi in the deep veins of the leg in 90% or more of patients.[10-14] Other, less common sources of PE include the deep pelvic veins, the renal veins, the inferior vena cava, the right ventricle, and the axillary veins. Most clinically important PE arise from thrombi in the popliteal or more proximal deep veins of the leg. PE occurs in 50% of patients with objectively documented proximal DVT; many of these emboli are asymptomatic.[10] Usually, only part of the thrombus embolizes, and 50% to 70% of patients with angiographically documented PE have detectable DVT of the legs at the time of presentation.[11] The clinical significance of PE depends on the size of the embolus and on the cardiorespiratory reserve of the patient.

TABLE 79–1. FACTORS PREDISPOSING TO VENOUS THROMBOEMBOLISM

Clinical Risk Factors	Inherited or Acquired Abnormalities
Surgical and nonsurgical trauma	Activated protein C resistance
Previous venous thromboembolism	Hyperhomocystinemia
Immobilization	Prothrombin 20210A
Malignant disease	Protein C deficiency
Heart disease	Protein S deficiency
Leg paralysis	Antithrombin-III deficiency
Age > 40 years	Dysfibrinogenemia
Obesity	Heparin-induced thrombocytopenia
Estrogens	

CLINICAL FEATURES

The clinical features of DVT include leg pain, tenderness and swelling, a palpable cord, discoloration, venous distention, prominence of the superficial veins, and cyanosis. The clinical diagnosis of DVT is highly nonspecific because none of the symptoms or signs is unique, and each may be caused by nonthrombotic disorders. Patients with relatively minor symptoms and signs may have extensive DVT, whereas those with florid leg pain and swelling, suggesting extensive DVT, may have negative results on objective testing. Thus, objective testing is mandatory to confirm or exclude a diagnosis of DVT.[12-15]

The location of the initial DVT has an impact on the incidence of recurrence; thus the presence of an iliofemoral vein thrombosis was shown to have a higher rate of recurrent VTE compared with popliteal vein thrombosis.[16,17] Also, there is a high correlation between venographic results as measured by the Marder score in recurrence of VTE.[18]

The clinical presentation of PE depends on the size, location, and number of emboli and on the patient's underlying cardiorespiratory reserve. The clinical manifestations of acute PE generally can be divided into several syndromes that overlap considerably: (1) transient dyspnea and tachypnea in the absence of other associated clinical manifestations; (2) pulmonary infarction or congestive atelectasis (also known as ischemic pneumonitis or incomplete infarction), which includes pleuritic chest pain, cough, hemoptysis, pleural effusion, and pulmonary infiltrates on the chest radiograph; (3) right ventricular failure associated with severe dyspnea and tachypnea; (4) cardiovascular collapse with hypotension, syncope, and coma (usually associated with massive PE); and (5) less common and highly nonspecific clinical features, including confusion and coma, pyrexia, wheezing, resistant cardiac failure, and unexplained arrhythmia.

There is evidence that the prognosis for long-term survival and recurrent VTE is worse with patients presenting with PE as opposed to DVT.[19] This may be reason to treat patients presenting with PE more aggressively in the future, but at the present time the anticoagulant management is identical. Various studies have attempted to identify risk factors for recurrent VTE, including fatal PE in patients presenting with an initial PE.[20-22]

Factors contributing to recurrent VTE include length of an initial hospitalization, presence of cancer, older age at hospitalization for multiple injuries, or surgery within 3 months.[20] Risk factors for an adverse outcome include factors such as age older than 70, hypotension, congestive heart failure, chronic obstructive pulmonary disease, cancer, the presence of a DVT, and right ventricular hypokinesis on echocardiography. Evidence of right ventricular damage in the form of an elevated troponin-T level may also have prognostic significance.[23,24]

It is now widely accepted that the clinical diagnosis of PE is highly nonspecific. Multiple studies indicate that in more than half of all patients with clinically suspected PE the diagnosis is not confirmed by objective testing.[9,14-16] Therefore, objective testing is mandatory to confirm or exclude the presence of PE.[25-28]

DIAGNOSIS OF PULMONARY EMBOLISM

The differential diagnosis of PE is wide, depending on the clinical scenario, and includes pneumonia, pneumothorax, pulmonary edema, pericarditis, rib fracture, and myocardial infarction. Various ancillary tests, such as chest radiograph, arterial blood gas determination, electrocardiography, and laboratory tests such as serum lactate dehydrogenase have a role in the diagnosis of VTE, but they all lack sensitivity and specificity for PE. The main role of these tests is to rule out other conditions that may mimic PE, such as acute myocardial infarction or pneumothorax.[28] The key tests for the diagnosis of PE include ventilation-perfusion lung scanning, spiral computed tomography (spiral CT), pulmonary angiography, and objective tests for proximal DVT.[28] Echocardiography may be useful for both diagnosis and prognostication, and there is increasing evidence that magnetic resonance angiography (MRA) may also have a useful role in the diagnosis of PE.

In recent years, numerous studies have shown that use of standardized clinical assessments for determining the clinical probability of VTE and the use of various forms of D-dimer to rule out VTE have been incorporated into diagnostic algorithms for the diagnosis and management of VTE.[29-33] The most thoroughly validated clinical models are those of Wells[31] and Wicki[32] and their colleagues. It is now clear from prospective studies that clinical assessment can stratify the probability of PE in a wide spectrum of patients both in the emergency department and in hospital. Thus, the problem of PE is expected to be less than 10% in patients with a low clinical probability, around 25% for those with an intermediate probability, and greater than 60% for patients with a high clinical probability of PE.

Performance of a quantitative D-dimer alone or in conjunction with assessment of probability further enhances the diagnostic approach.[34,35] The D-dimer is formed when cross-linked fibrin undergoes lysis by plasmin. The elevated levels can be found in numerous conditions in addition to VTE. Thus, conditions such as infection, cancer, surgery, trauma, and increasing age will produce elevated levels of D-dimer. Therefore, this assay is only useful if the test is negative. In such circumstances it can be used to exclude VTE. Numerous assays for D-dimer have been tested, but quantitative tests with a rapid turnaround, such as enzyme-linked immunosorbent assays or latex agglutination assays, have proven to be the most useful.[34-38] These tests have been shown to have an extremely high negative predictive value and in conjunction with clinical probability assessment may be used to exclude further diagnostic testing in a large number of patients presenting with suspected VTE.[36,38]

OBJECTIVE TESTS FOR THE DIAGNOSIS OF PULMONARY EMBOLISM

Ventilation-Perfusion Lung Scanning

Perfusion lung scanning is the key diagnostic test for patients with suspected PE. A normal perfusion scan result excludes clinically important PE.[39-41] An abnormal perfusion scan result, however, is nonspecific and may occur in conditions that produce either increased radiographic density (e.g., pneumonia, atelectasis, and pleural effusion) or regional reduction in ventilation (e.g., chronic obstructive lung disease, acute asthma, bronchial mucus plugs, and bronchitis, all of which are frequently associated with normal radiographic results).

Ventilation imaging was introduced to improve the specificity of an abnormal perfusion scan result by differentiating embolic occlusion of the pulmonary vasculature from perfusion defects occurring secondary to a primary disorder of ventilation.[42-44] This basic premise that perfusion defects that ventilate normally [ventilation-perfusion mismatch] are due to PE, whereas matching ventilation-perfusion abnormalities are due to other conditions, has been shown to be incorrect by prospective clinical trials.[41,45]

Ventilation lung scanning is helpful only if the perfusion defect is segmental or greater and is associated with ventilation mismatch; such patients have a high probability (86%) of PE confirmed by pulmonary angiography.[11,41-45] Abnormal findings on lung scans, such as matching ventilation-perfusion defects (either segmental or subsegmental, so-called low-probability), subsegmental defects with ventilation mismatch, or perfusion defects that correspond to an area of increased density on chest radiography (indeterminate perfusion scan), are associated with a 20% to 40% frequency of PE.[11,41,45] These scan patterns are nondiagnostic. Further investigations, including pulmonary angiography and objective tests for DVT, are therefore required in patients who have nondiagnostic ventilation-perfusion scan findings.[11,27,41,45,46] Pulmonary angiography, or venography, or both should be used when other approaches are unavailable or inconclusive. The morbidity associated with these tests is substantially less than that arising from unnecessary anticoagulant therapy and inappropriate hospitalization.

Pulmonary Angiography

Pulmonary angiography is the accepted diagnostic reference standard for PE.[47-49] The diagnosis is established if an intraluminal filling defect is constant on multiple films or if abrupt termination (cut-off) of a vessel greater than 2 to 5 mm in diameter occurs and is constant on multiple films.[47,48] Other abnormalities, such as oligemia, vessel pruning, and loss of filling of small vessels, are nonspecific and occur in many conditions, including pneumonia, atelectasis, bronchiectasis, emphysema, and pulmonary carcinoma.[47,48]

In recent years, the diagnostic resolution of pulmonary angiography has markedly improved, and the risk to the patient decreased, by the use of selective catheterization and repeated injections of small volumes of dye. This technique is safe in the absence of severe chronic pulmonary hypertension or severe cardiac or respiratory decompensation.[50] Clinically significant complications, including tachyarrhythmias, endocardial or myocardial injury, cardiac perforation, cardiac arrest, and hypersensitivity reactions to contrast medium, occur in up to 3% to 4% of patients.[47,50]

Spiral CT

Spiral CT (also known as helico or continuous volume CT) has come into wide use for the diagnosis of PE. A single breath hold of 15 to 20 seconds allows a full lung examination to be carried out. Abnormalities other than PE (identified intraluminal filling defects) that may be causing the symptoms and signs suggestive of PE can also be identified, which is an advantage of spiral CT.[51,52] These conditions include malignancy, pleural disease, postoperative changes, pneumonia, cardiac disease, and pulmonary fibrosis. The technology for spiral CT is rapidly changing with its new multichannel equipment that permits full-lung scanning with a single breath hold of approximately 5 seconds.[51,52]

The use of spiral CT has gained popularity in clinical practice without adequate assessment. Two systematic reviews of the literature up to the year 2000 indicated that the sensitivity of spiral CT for isolated subsegmental PE was in the range of 30%.[53,54] Thus, although the sensitivity of spiral CT for large PE was acceptable, the authors recommended caution in using anticoagulant treatment in patients with negative results on spiral CT. Indeed, an initial prospective follow-up of patients with suspected PE with negative studies on spiral CT and negative venous ultrasound indicated that up to 5% may have VTE in follow-up, including fatal PE.[55]

The changing technology for spiral CT requires ongoing assessment. Indeed, two management studies in which more modern equipment for spiral CT was used in conjunction with bilateral leg ultrasound indicated it was safe to withhold anticoagulant therapy in the patients with negative studies, particularly if they had low or moderate pretest clinical probability.[56-59] One further advantage of spiral CT is that the venous system can be studied down to the popliteal veins with a single infusion of contrast medium. Studies comparing spiral CT venography and ultrasonography illustrate that the test has a high sensitivity and specificity.[60,61]

Further studies are required to fully identify the role of spiral CT in the diagnosis of PE. Indeed, the second Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED II) is designed to assess the role of spiral CT in comparison with ventilation-perfusion lung scanning, ultrasonography of the legs, pulmonary angiography, and venography in more than 1000 patients presenting with suspected PE. This multicenter study, which is funded by the National Institutes of Health, has completed enrollments and will be reported in the near future.[62]

Echocardiography

The value of echocardiography has been firmly established and has four main advantages:

1. It is noninvasive and easily available.
2. It can exclude other causes of cardiogenic shock (e.g., extensive left ventricular infarction, pericardial tamponade, or dissecting aortic aneurysm).
3. It allows an estimate of pulmonary artery pressure and so provides information on the severity of pulmonary artery obstruction.[63-69]
4. It can be used serially to assess response to treatment.

Echocardiographic findings are not specific and reflect the response of the right side of the heart to acute pulmonary artery hypertension. They consist of distention of the

pulmonary artery trunk, right ventricular (RV) dilation and hypokinesis, reduced left ventricular (LV) size, an increased RV to LV diameter, diastolic and systolic flattening of the interventricular septum, and paradoxical systolic wall motion.[63] This pattern is mimicked, in particular, by RV infarction associated with LV dysfunction.

Scoring systems have been developed that correlate well with the angiographic severity index, and the value of serial echocardiography has been demonstrated in patients treated with thrombolytic agents. Rarely, RV thrombus may be visualized, a clinical situation associated with a high mortality rate, with 30% of such patients succumbing as a result of massive pulmonary thromboembolism.

There are several limitations to the applications of echocardiography. At least 40% of the pulmonary vascular bed needs to be obstructed to produce detectable features. Coexistent cardiorespiratory disease also limits its value because of the nonspecific nature of the abnormalities and because imaging via the transthoracic route may be difficult. Transesophageal echocardiography may be valuable in this situation, particularly in making a full hemodynamic assessment in the shocked, intubated patient.[67-69]

Magnetic Resonance Angiography

MRA has been compared with pulmonary angiography and spiral CT for the diagnosis of PE in patients in whom the diagnosis is suspected.[70,71] During one study, the sensitivity of 77% was found and this varied with the subsegmental, segmental, or central or lobar embolism on pulmonary angiography. Specificity, however, was 98%.[70] Oudkerk and coworkers suggest that MRA could become part of the diagnostic strategy for PE,[70] although this diagnostic modality requires further study. MRA may have obvious advantages for patients for whom the risk of pulmonary angiography is high or for the diagnosis of VTE in pregnancy.

DIAGNOSIS AND TREATMENT OF PULMONARY EMBOLISM BASED ON OBJECTIVE TESTING FOR PROXIMAL DEEP VEIN THROMBOSIS

At least 80% of patients with PE have thrombi originating in the lower leg veins.[10,11,13] Because of the diagnostic inaccuracy of noninvasive tests for PE, particularly in patients with nondiagnostic lung scan results, the concept of using objective tests for the detection of proximal DVT in the legs was developed in patients suspected of having PE.[25-27] This combined strategy for the diagnosis and treatment of PE or DVT (i.e., VTE) has been applied in prospective clinical trials.[72]

Noninvasive tests such as compression ultrasonography have advantages because they are free of morbidity and are readily repeatable. For patients presenting with acute PE, compression ultrasonography of the proximal veins is positive in approximately 50% of patients. Venography is positive in approximately 70% of patients. The fact that approximately 30% of such patients with angiographically documented PE have negative venography indicates that either the thrombosis that had been present in the legs has embolized to the lung or the PE may have originated from a source other than the deep veins in the legs.[11,36-38,73-76]

In patients with a nondiagnostic lung scan and a negative two-point compression ultrasound of both legs, particularly in the presence of a low to moderate pretest clinical probability and a negative D-dimer, there is a very low likelihood of developing VTE in follow-up.[35-38] However, patients with a high clinical probability for pulmonary embolus or a previous history of VTE require further studies such as venography or pulmonary angiography.[36] As an alternative, repeat ultrasonography at 7 days may be performed.[74]

DIAGNOSTIC ALGORITHMS

In a typical algorithm, patients with a low or moderate clinical probability undergo D-dimer testing. If the test is negative no further studies are required. If the D-dimer test is positive, ventilation-perfusion scanning is carried out. Those with a normal ventilation-perfusion scan have no further studies and PE is excluded. Patients with a high-probability lung scan are treated. Patients with a nondiagnostic lung scan undergo ultrasound study of the legs: those who are positive are treated, whereas those who are negative have no further studies or have a repeat test in 1 week. Patients with low probability for PE who have a high probability lung scan should undergo spiral CT or pulmonary angiography. Patients with moderate pretest probability and negative ultrasound should have a repeat test in 1 week or undergo pulmonary angiography.[76]

Patients who have a high probability for PE go directly to ventilation-perfusion scanning as with the other group. For those with a nondiagnostic lung scan, ultrasound is carried out unless negative pulmonary angiography is indicated or the patient undergoes serial ultrasound. As an alternative, patients with nondiagnostic lung scan and a high clinical probability may go directly to spiral CT or pulmonary angiography.

These algorithms are modified for patients with prior PE or DVT, and D-dimer is not recommended for patients in whom it can be predicted that the test will be positive. The future role of spiral CT and MRA will undoubtedly be modified as further studies are carried out and may replace ventilation-perfusion scanning and pulmonary angiography in many patients suspected of having PE.

ANTICOAGULANT THERAPY FOR VENOUS THROMBOEMBOLISM

Anticoagulant drugs (heparin, low-molecular-weight heparin, and warfarin) are the mainstay of the management of venous thromboembolism.[76] As mentioned previously the treatment for DVT and/or PE is the same at the present time. Numerous new antithrombotic agents are under intensive investigation. The anti-Xa inhibitor fondaparinux (Arixtra, Sanofi-Synthelabo, New York, NY) or the antithrombin agent ximelagatran (Xanta, Astra Zeneca LP, Wilmington, DE) will be coming on the market in the near future and will modify the current approach to treatment of VTE.

Objectives of treatment in patients with VTE are to prevent death from PE, recurrent VTE, and post-thrombotic syndrome.

The use of graduated compression stockings has been shown to significantly decrease the incidence of the post-thrombotic syndrome. Furthermore, the incidence of the post-thrombotic syndrome is decreasing in recent years, suggesting that the more efficient treatment of VTE and the prevention of recurrent DVT are having a positive impact on this complication.

UNFRACTIONATED HEPARIN THERAPY

The anticoagulant activity of unfractionated heparin depends on a unique pentasaccharide that binds to antithrombin III (AT III) and potentiates the inhibition of thrombin and activated factor X (Xa) by AT III.[77-79] Approximately one third of all heparin molecules contain the unique pentasaccharide sequence, regardless of whether they are low- or high-molecular-weight fractions.[77-79] It is the pentasaccharide sequence that confers the molecular high affinity for AT III.[77-79] In addition, heparin catalyzes the inactivation of thrombin by another plasma cofactor (cofactor II), which acts independently of AT III.[79]

Heparin has a number of other effects. These include the release of tissue factor pathway inhibitor; binding to numerous plasma and platelet proteins, endothelial cells, and leukocytes[77]; suppression of platelet function; and an increase in vascular permeability.[79] The anticoagulant response to a standard dose of heparin varies widely between patients. This makes it necessary to monitor the anticoagulant response of heparin using either the activated partial thromboplastin time (aPTT) or heparin levels and to titrate the dose to the individual patient.[79]

The accepted anticoagulant therapy for VTE is a combination of continuous intravenous heparin and oral warfarin. The length of the initial intravenous heparin therapy has been reduced to 5 days, thus shortening the hospital stay and leading to significant savings.[80-81] The simultaneous use of initial heparin and warfarin has become clinical practice for all patients with VTE who are medically stable. Exceptions include patients who require immediate medical or surgical intervention, such as in thrombolysis or insertion of a vena cava filter, or patients at very high risk of bleeding. Heparin is continued until the International Normalized Ratio (INR) has been within the therapeutic range (2 to 3) for 2 consecutive days.[82]

It has been established from experimental studies and clinical trials that efficacy of heparin therapy depends on achieving a critical therapeutic level of heparin within the first 24 hours of treatment.[81,83,84] Data from three consecutive double-blind clinical trials indicate that failure to achieve the therapeutic aPTT threshold by 24 hours was associated with a 23.3% subsequent recurrent venous thromboembolism rate, compared with a rate of 4% to 6% for the patient group who were therapeutic at 24 hours.[83,84] The recurrences occurred throughout the 3-month follow-up period and could not be attributed to inadequate oral anticoagulant therapy.[83] The critical therapeutic level of heparin, as measured by the aPTT, is 1.5 times the mean of the control value or the upper limit of the normal aPTT range.[81,83] This corresponds to a heparin blood level of 0.2 to 0.4 U/mL by the protamine sulfate titration assay and 0.35 to 0.70 by the anti–factor Xa assay.

However, there is wide variability in the aPTT and heparin blood levels with different reagents and even with different batches of the same reagent. It is therefore vital for each laboratory to establish the minimal therapeutic level of heparin, as measured by the aPTT, that will provide a heparin blood level of at least 0.35 U/mL by the anti–factor Xa assay for each batch of thromboplastin reagent being used, particularly if the reagent is provided by a different manufacturer.[79]

Although there is a strong correlation between subtherapeutic aPTT values and recurrent thromboembolism, the relationship between supratherapeutic aPTT and bleeding (aPTT ratio 2.5 or more) is less definite.[83] Indeed, bleeding during heparin therapy is more closely related to underlying clinical risk factors than to aPTT elevation above the therapeutic range.[83] Recent studies confirm that weight and age older than 65 are independent risk factors for bleeding on heparin therapy.

Numerous audits of heparin therapy indicate that administration of intravenous heparin is fraught with difficulty and that the clinical practice of using an ad hoc approach to heparin dose titration frequently results in inadequate therapy. The use of a prescriptive approach or protocol for administering intravenous heparin therapy has been evaluated in two prospective studies in patients with venous thromboembolism.[83,85,86]

In one clinical trial for the treatment of DVT, patients were given either intravenous heparin alone followed by warfarin or intravenous heparin and simultaneous warfarin.[81] The heparin nomogram is summarized in Tables 79-2 and 79-3. Only 1% to 2% of the patients were undertreated for more than 24 hours in the heparin group and in the heparin and warfarin group, respectively. Recurrent VTE (objectively documented) occurred infrequently in both groups (7%), at rates similar to those previously reported. These findings demonstrated that subtherapy was avoided in most patients and that the heparin protocol resulted in effective delivery of heparin therapy in both groups.

In the other clinical trial, a weight-based heparin dosage nomogram was compared with a standard-care nomogram (Table 79-4).[85] Patients on the weight-adjusted heparin nomogram received a starting dose of 80 U/kg as a bolus and 18 U/kg/h as an infusion. The heparin dose was adjusted to maintain an aPTT of 1.5 to 2.3 times control. In the weight-adjusted group, 89% of patients achieved the therapeutic

TABLE 79–2. HEPARIN PROTOCOL

1. Administer initial intravenous heparin bolus: 5000 U.
2. Administer continuous intravenous heparin infusion: commence at 42 mL/h of 20,000 U (1680 U/h) in 500 mL of two thirds dextrose and one third saline (a 24-hour heparin dose of 40,320 U), except in the following patients, in whom heparin infusion is begun at a rate of 31 mL/h (1240 U/h, a 24-hour dose of 29,760 U):
   a. Patients who have undergone surgery within the previous 2 weeks
   b. Patients with a previous history of peptic ulcer disease or gastrointestinal or genitourinary bleeding
   c. Patients with recent stroke (i.e., thrombotic stroke within 2 weeks previously)
   d. Patients with a platelet count less than 150/L.
   e. Patients with miscellaneous reasons for a high risk of bleeding (e.g., hepatic failure, renal failure, or vitamin K deficiency)
3. Adjust heparin dose by use of the aPTT. The aPTT test is performed in all patients as follows:
   a. At 4 to 6 hours after commencing heparin, the heparin dose is then adjusted.
   b. At 4 to 6 hours after the first dosage adjustment
   c. Then as indicated by the nomogram for the first 24 hours of therapy
   d. Thereafter once daily, unless the patient is subtherapeutic,* in which case the aPTT test is repeated 4 to 6 hours after the heparin dose is increased.

*Subtherapeutic = aPTT less than 1.5 times the mean normal control value for the thromboplastin reagent being used.
aPTT, activated partial thromboplastin time.

TABLE 79–3. INTRAVENOUS HEPARIN DOSE TITRATION NOMOGRAM ACCORDING TO THE aPTT

aPTT (sec)	Rate Change (mL/h)	Dose Change (IU/24 h)*	Additional Action
≤45	+ 6	+ 5760	Repeated aPTT† in 4 to 6 hours
46-54	+ 3	+ 2880	Repeated aPTT in 4 to 6 hours
55-85	0	0	None‡
86-110	− 3	− 2880	Stop heparin sodium treatment for 1 hour; repeat aPTT 4 to 6 hours after restarting heparin treatment.
>110	− 6	− 5760	Stop heparin treatment for 1 hour; repeat aPTT 4 to 6 hours after restarting heparin treatment

*Heparin sodium concentration 20,000 IU in 500 mL = 40 IU/mL.
†With the use of Actin-FS thromboplastin reagent (Dade, Mississauga, Ontario, Canada)
‡During the first 24 hours, repeat aPTT in 4 to 6 hours. Thereafter, the aPTT will be determined once daily, unless subtherapeutic.
aPTT, activated partial thromboplastin time.
Adapted from Hull RD, Raksob GE, Rosenbloom DR, et al: Optimal therapeutic level of heparin therapy in patients with venous thrombosis. Arch Intern Med 1992;152:1589, with permission.

range within 24 hours compared with 75% in the standard-care group. The risk of recurrent VTE was more frequent in the standard-care group, supporting the previous observation that subtherapeutic heparin during the initial 24 hours is associated with a higher incidence of recurrences. This study included patients with unstable angina and arterial thromboembolism in addition to VTE, which suggests that the principles applied to a heparin nomogram for the treatment of VTE may be generalizable to other clinical conditions. Continued use of the weight-based nomogram has been similarly effective.

Complications of Heparin Therapy

The main adverse effects of heparin therapy include bleeding, thrombocytopenia, and osteoporosis. Patients at particular risk are those who have had recent surgery or trauma or who have other clinical factors that predispose to bleeding on heparin, such as peptic ulcer, occult malignancy, liver disease, hemostatic defects, weight, age older than 65 years, and female gender.[79]

The management of bleeding on heparin will depend on the location and severity of bleeding, the risk of recurrent VTE, and the aPTT. Heparin should be discontinued temporarily or permanently. Patients with recent VTE may be candidates for insertion of an inferior vena cava filter. If urgent reversal of heparin effect is required, protamine sulfate can be administered.[79]

Heparin-induced thrombocytopenia is a well-recognized complication of heparin therapy, usually occurring within 5 to 10 days after heparin treatment has started.[87-90] Approximately 1% to 2% of patients receiving unfractionated heparin will experience a fall in platelet count to less than the normal range or a 50% fall in the platelet count within the normal range. In the majority of cases, this mild to moderate thrombocytopenia appears to be a direct effect of heparin on platelets and is of no consequence. However, 0.1% to 0.2% of patients receiving heparin develop an immune thrombocytopenia mediated by IgG antibody directed against a complex of platelet factor 4 and heparin.[87]

The development of thrombocytopenia may be accompanied by arterial thrombosis or DVT, which may lead to serious consequences such as death or limb amputation.[90] The diagnosis of heparin-induced thrombocytopenia, with or without thrombosis, must be made on clinical grounds, because the assays with the highest sensitivity and specificity are not readily available and have a slow turnaround time.

When the diagnosis of heparin-induced thrombocytopenia is made, heparin in all forms must be stopped immediately. In those patients requiring ongoing anticoagulation, several alternatives exist.[88-90] The agents most extensively used recently include the heparinoid danaparoid,[88] hirudin,[89] and, most recently, the specific antithrombin argatroban.[90] Danaparoid is available for limited use on compassionate grounds, and hirudin and argatroban have been approved for use in the United States and Canada. Warfarin may be used but should not be started until one of the other agents has been used for 3 or 4 days to suppress thrombin generation. Insertion of an inferior vena cava filter is seldom indicated.

Osteoporosis has been reported in patients receiving unfractionated heparin in dosages of 20,000 U/day (or more) for more than 6 months. Demineralization can progress to the fracture of vertebral bodies or long bones, and the defect may not be entirely reversible.[79]

TABLE 79–4. WEIGHT-BASED NOMOGRAM FOR INITIAL INTRAVENOUS HEPARIN THERAPY*

aPTT	Dose (IU/kg)
Initial dose	80 bolus, then 18/h
aPTT <35 sec (<1.2×)	80 bolus, then 4/h
aPTT 35-45 sec (1.2-1.5×)	40 bolus, then 2/h
aPTT 46-70 sec (1.5-2.3×)	No change
aPTT 71-90 sec (2.3-3.0×)	Decrease infusion rate by 2/h
aPTT > 90 sec (>3.0×)	Hold infusion 1 h, then decrease infusion rate by 3/h

*Figures in parentheses show comparison with control.
aPTT, activated partial thromboplastin time.
Adapted from Raschke RA, Reilly BM, Guidry JR, et al: The weight-based heparin dosing nomogram compared with a "standard care" nomogram. Ann Intern Med 1993;119:874, with permission.

LOW-MOLECULAR-WEIGHT HEPARIN (LMWH)

Heparin currently in use clinically is polydispersed unmodified heparin, with a mean molecular weight ranging from 10 to 16 kDa. In recent years, low-molecular-weight derivatives of commercial heparin have been prepared that have a mean molecular weight of 4 to 5 kDa.[91,92]

The LMWHs commercially available are made by different processes (such as nitrous acid, alkaline, or enzymatic

depolymerization), and they differ chemically and pharmacokinetically.[91,92] The clinical significance of these differences, however, is unclear, and there have been very few studies comparing different LMWHs with respect to clinical outcomes.[92] The doses of the different LMWHs have been established empirically and are not necessarily interchangeable. Therefore, at this time, the effectiveness and safety of each of the LMWHs must be tested separately.[92]

The LMWHs differ from unfractionated heparin in numerous ways. Of particular importance are the following: increased bioavailability (>90% after subcutaneous injection), prolonged half-life and predictable clearance enabling once- or twice-daily injection, and predictable antithrombotic response based on body weight, permitting treatment without laboratory monitoring.[79,91,92] Other possible advantages are their ability to inactivate platelet-bound factor Xa, resistance to inhibition by platelet factor 4, and their decreased effect on platelet function and vascular permeability (possibly accounting for less hemorrhagic effects at comparable antithrombotic doses).

There has been a hope that the LMWHs will have fewer serious complications such as bleeding[91,92] and heparin-induced thrombocytopenia[87] when compared with unfractionated heparin. Evidence is accumulating that these complications are indeed less serious and less frequent with the use of LMWH. LMWH has been approved for the prevention and treatment of VTE in pregnancy. These drugs do not cross the placenta, and small case series suggest they may be both effective and safe. The LMWHs all cross react with unfractionated heparin, and they can therefore not be used as alternative therapy in patients who develop heparin-induced thrombocytopenia. The heparinoid danaparoid possesses a 10% to 20% cross-reactivity with heparin, and it can be safely used in patients who have no cross-reactivity.

Several different LMWHs are available for the prevention and treatment of VTE in various countries. Four LMWHs are approved for clinical use in Canada and three LMWHs have been approved for use in the United States.

In a number of early clinical trials (some of which were dose finding), LMWH given by subcutaneous or intravenous injection was compared with continuous intravenous unfractionated heparin, with repeat venography at day 7 to 10 being the primary endpoint. These studies demonstrated that LMWH was at least as effective as unfractionated heparin in preventing extension or increasing resolution of thrombi on repeat venography.

Subcutaneous unmonitored LMWH has been compared with continuous intravenous heparin in a number of clinical trials for the treatment of proximal DVT using long-term follow-up as an outcome measure.[18,94-99,101-103] These studies have shown that LMWH is at least as effective and safe as unfractionated heparin in the treatment of proximal DVT. Pooling of the most methodologically sound studies indicates a significant advantage for LMWH in the reduction of major bleeding and mortality.[98] More recent studies have indicated that LMWH used predominantly out of hospital was as effective and safe as intravenous unfractionated heparin given in hospital (Table 79-5).[101-103] Two clinical trials showed that LMWH was as effective as intravenous heparin in the treatment of patients presenting with PE.[100,104] Economic analysis of treatment with LMWH versus intravenous heparin demonstrated that LMWH was cost effective for treatment in hospital as well as out of hospital.[105] As these agents become more widely available for treatment, they have replaced intravenous unfractionated heparin in the initial management of patients with VTE.

Long-term LMWH has been compared with warfarin therapy in patients presenting with proximal DVT. Although these studies differ in design and doses of LMWH, they do indicate that LMWH is a useful alternative to warfarin therapy, particularly in patients who have recurrence of VTE while on therapeutic doses of warfarin (e.g., in the cancer population).[106,107]

COUMARIN THERAPY

Pharmacokinetics and Pharmacodynamics of Warfarin

There are two distinct chemical groups of oral anticoagulants: the 4-hydroxycoumarin derivatives (e.g., warfarin sodium) and the indane-1,3-dione derivatives (e.g., phenindione).[108] The coumarin derivatives are the oral anticoagulants of choice because they are associated with fewer nonhemorrhagic side effects than are the indanedione derivatives. In North America the most commonly used agent is coumarin (Coumadin, Bristol-Myers Squibb), but in recent years various generic forms of warfarin sodium have been introduced.

Warfarin is a racemic mixture of stereoisomers (R and S forms). Warfarin is highly water soluble and is highly bioavailable.[109] Peak absorption occurs around 90 minutes, and the half-life is between 36 and 42 hours. Warfarin is highly protein bound (primarily albumin), and only the non–protein-bound material is biologically active. Any drug or chemical that is also bound to albumin may displace warfarin from its protein binding sites and thereby increase the biologically active material.[109] Warfarin is metabolized in the liver by the p450 (CYP2C9) system of enzymes. Interference with the CYP2C9 enzymes by various drugs or a mutation in the gene coding for one of the common CYP2C9 enzymes can markedly interfere with the metabolism of warfarin.[110]

TABLE 79-5. PREDOMINANTLY OUTPATIENT TREATMENT OF PROXIMAL DEEP VEIN THROMBOSIS WITH LOW-MOLECULAR-WEIGHT HEPARIN VS. INPATIENT TREATMENT WITH INTRAVENOUS HEPARIN

Study	Treatment	Recurrent DVT	Major Bleeding
Koopman et al[101]	Nadroparin vs. heparin	14/202 (6.9%) 17/198 (8.6%)	1/202 (0.5%) 4/198 (2.0%)
Levine et al[102]	Enoxaparin vs. heparin	13/247 (5.3%) 17/253 (6.7%)	5/247 (2.0%) 3/253 (1.2%)
Columbus study[103]	Reviparin vs. heparin	27/510 (5.3%) 24/511 (4.9%)	16/510 (3.1%) 12/511 (2.3%)

The anticoagulant effect of warfarin is mediated by the inhibition of the vitamin K–dependent gamma-carboxylation of coagulation factors II, VII, IX, and X.[108,109] This results in the synthesis of immunologically detectable but biologically inactive forms of these coagulation proteins. Warfarin also inhibits the vitamin K–dependent gamma-carboxylation of proteins C and S[110] and protein Z.[111] Protein C circulates as a proenzyme that is activated on endothelial cells by the thrombin/thrombomodulin complex to form activated protein C. Activated protein C in the presence of protein S inhibits activated factor VIII and activated factor V activity.[112] Therefore, vitamin K antagonists such as warfarin create a biochemical paradox by producing an anticoagulant effect due to the inhibition of procoagulants (factors II, VII, IX, and X) and a potentially thrombogenic effect by impairing the synthesis of naturally occurring inhibitors of coagulation (proteins C and S).[112] Heparin or LMWH and warfarin treatment should overlap by 4 to 5 days when warfarin treatment is initiated in patients with thrombotic disease. The role of protein Z in the coagulation process is less definite.

The anticoagulant effect of warfarin is delayed until the normal clotting factors are cleared from the circulation, and the peak effect does not occur until 36 to 72 hours after drug administration.[113] During the first few days of warfarin therapy, the prothrombin time (PT) reflects mainly the depression of factor VII, which has a half-life of 5 to 7 hours. Equilibrium levels of factors II, IX, and X are not reached until about 1 week after the initiation of therapy. The use of small initial daily doses (e.g., 5 mg) is the preferred approach for initiating warfarin treatment.[114] The dose-response relationship to warfarin therapy varies widely between individuals and, therefore, the dose must be carefully monitored to prevent overdosing or underdosing.

A number of factors influence the anticoagulant response of warfarin in individual patients; these include inaccuracies in laboratory testing and noncompliance of patients, but more importantly reflect the influence of dietary changes or the influence of drugs that interfere with the metabolism of warfarin. The availability of vitamin K can be influenced by dramatic changes in dietary intake or by drugs such as antibiotics, which interfere with the synthesis of vitamin K in the gastrointestinal tract. A wide variety of drugs may interact with warfarin. However, a critical appraisal of the literature reporting such interactions indicates that the evidence substantiating many of the claims is limited.[115] The interactions of drugs and food with warfarin are reviewed in detail in a recent publication.[8] Aspirin is particularly problematic because it interferes with platelet function and displaces warfarin from its protein binding, thus augmenting its biologic activities. Also, as with the nonsteroidal anti-inflammatory drugs (NSAIDs) it may cause gastric erosions, thus creating a site for bleeding. Nonetheless, in certain patients the use of aspirin and warfarin is indicated to improve efficacy even though bleeding may be somewhat increased. It is important that patients be warned against taking any new drugs without the knowledge of their attending physician, and it is prudent to monitor the INR more frequently when any drug (including natural compounds) is added or withdrawn from the regimen of the patient being treated with an oral anticoagulant.

Laboratory Monitoring and Therapeutic Range

The laboratory test most commonly used to measure the effects of warfarin is the one-stage prothrombin time. The PT is sensitive to reduced activity of factors II, VII, and X but is insensitive to reduced activity of factor IX. Confusion about the appropriate therapeutic range has occurred because the different tissue thromboplastins used for measuring the PT vary considerably in sensitivity to the vitamin K–dependent clotting factors and in response to warfarin.[116,117]

To promote standardization of the PT for monitoring oral anticoagulant therapy, the World Health Organization (WHO) developed an international reference thromboplastin from human brain tissue and recommended that the PT ratio be expressed as the International Normalized Ratio.[109] The INR is the PT ratio obtained by testing a given sample using the WHO reference thromboplastin. For practical clinical purposes, the INR for a given plasma sample is equivalent to the PT ratio obtained using a standardized human brain thromboplastin known as the Manchester Comparative Reagent, which has been widely used in the United Kingdom.[109] In recent years thromboplastins with a high sensitivity have been commonly used. In fact, many centers have been using the recombinant tissue factor that has an International Sensitivity Index (ISI) value of 0.9 to 1.0, giving an INR equivalent to the PT ratio.

Warfarin is administered in an initial dose of 5 mg/day for the first 2 days, and the daily dose is then adjusted according to the INR. Heparin or LMWH therapy is discontinued on the fifth day after initiation of warfarin therapy, provided the INR is prolonged into the recommended therapeutic range (INR 2.0 to 3.0) for at least 2 consecutive days.[109] Frequent INR determinations are required initially to establish therapeutic anticoagulation.

Once the anticoagulant effect and patient's warfarin dose requirements are stable, the INR should be monitored every 1 to 3 weeks throughout the course of warfarin therapy. However, if there are factors that may produce an unpredictable response to warfarin (e.g., concomitant drug therapy),[109,114] the INR should be monitored more frequently to minimize the risk of complications due to poor anticoagulant control.

ADVERSE EFFECTS OF ORAL ANTICOAGULANTS

Bleeding

The major side effect of oral anticoagulant therapy is bleeding.[118] A number of risk factors have been identified which predispose to bleeding on oral anticoagulants.[119-121] The most important factor influencing bleeding risk is the intensity of the INR.[119-122] Other factors include a history of bleeding, previous history of stroke or myocardial infarction, hypertension, renal failure, diabetes, and a decreased hematocrit.[121] Efforts have been made to quantify the bleeding risk according to these underlying clinical factors.[121] Introduction of a multicomponent intervention combining patient education and alternative approaches to the maintenance of the INR resulted in a reduced frequency of major bleeding in the patients in this group.[120] Furthermore, patients in the intervention group were within the therapeutic INR a significantly greater amount of time than were patients in the standard care group.[120] In a retrospective cohort study of patients with an INR greater than 6.0, it was shown that a prolonged delay in the return of the INR to the therapeutic range was seen in patients who had an INR over 4.0 after two doses of warfarin were withheld; patients with an extreme elevation of the INR[121]; and older age patients, particularly

those with decompensated congestive heart failure and active cancer. Numerous randomized clinical trials have demonstrated that clinically important bleeding is lower when the targeted INR is 2.0 to 3.0 and that bleeding increases exponentially when the INR increases above 4.5 or 5.0.[117,122,123] There is a strong negative relationship between the percentage of time that patients are within the targeted INR and both bleeding and recurrent thrombosis.

Oral anticoagulant therapy in elderly patients presents further problems.[124,125] Many of these patients require long-term anticoagulants because of their underlying clinical conditions that increase with age, while at the same time they are more likely to have underlying causes for bleeding, including the development of cancer, intestinal polyps, renal failure, and stroke and they are more prone to having frequent falls. The daily requirements for warfarin to maintain the therapeutic INR also decrease with age, presumably owing to decreased clearance of the drug.[126] Therefore, before initiating oral anticoagulant treatment in elderly patients, the risk/benefit ratio of treatment must be considered. If they are placed on oral anticoagulant therapy, careful attention to the INR is required.

Patients with cancer are more likely to bleed on oral anticoagulant treatment.[127] Compared with patients on oral anticoagulants who do not have cancer, patients with cancer have a higher incidence of both major and minor bleeding and anticoagulant withdrawal is more frequently due to bleeding. Patients with cancer have a higher thrombotic complication rate and a higher bleeding rate regardless of the INR, whereas bleeding in noncancer patients was seen only when the INR was greater than 4.5. Safer and more effective anticoagulant therapy is required for the treatment of VTE in patients with cancer.[127]

Management of Overanticoagulation

The approach to the patient with an elevated INR depends on the degree of elevation of the INR and the clinical circumstances.[114] Options available to the physician include temporary discontinuation of warfarin treatment, administration of vitamin K, or administration of blood products such as fresh frozen plasma or prothrombin concentrate to replace the vitamin K-dependent clotting factors. If the increase is mild and the patient is not bleeding, no specific treatment is necessary other than reduction in the warfarin dose. The INR can be expected to decrease during the next 24 hours with this approach. With more marked increase of the INR in patients who are not bleeding, treatment with small doses of vitamin K_1 (e.g., 1 mg), given either orally or by subcutaneous injection, could be considered.[114,128] With very marked increase of the INR, particularly in a patient who is either actively bleeding or at risk for bleeding, the coagulation defect should be corrected. Vitamin K can be given by the intravenous or subcutaneous route or by the oral route. Where possible the oral route is preferred.[128] If ongoing anticoagulation with warfarin is planned, then repeated small doses of vitamin K should be given so that there is no problem with warfarin resistance.[128,129]

Reported side effects of vitamin K include flushing, dizziness, tachycardia, hypotension, dyspnea, and sweating.[130] Intravenous administration of vitamin K_1 should be performed with caution to avoid inducing an anaphylactoid reaction. The risk of anaphylactoid reaction can be reduced by slow administration of vitamin K_1. In most patients, intravenous administration of vitamin K_1 produces a demonstrable effect on the INR within 6 to 8 hours and corrects the increased INR within 12 to 24 hours. Because the half-life of vitamin K_1 is less than that of warfarin sodium, a repeat course of vitamin K_1 may be necessary. If bleeding is very severe and life threatening, vitamin K therapy can be supplemented with concentrates of factors II, VII, IX, and X.

When bleeding occurs in a patient on oral anticoagulants it is important to consider the site of bleeding. Bleeding from the upper gastrointestinal tract is commonly seen in patients on oral anticoagulants, and the concomitant use of other medications is often an association. When the bleeding is controlled, it is important to carry out the necessary investigations to identify bleeding lesions in the gastrointestinal or genitourinary tract, which are often unsuspected.[114,131] The various protocols for the perioperative management of patients receiving oral anticoagulants were recently reviewed.[132]

CLINICAL USES OF ORAL ANTICOAGULANTS

Long-Term Treatment of VTE

Patients with established DVT or PE require long-term anticoagulant therapy to prevent recurrent disease.[82,133] Warfarin therapy is highly effective and is preferred in most patients. Adjusted dose subcutaneous heparin or LMWH are the treatments of choice where long-term oral anticoagulants are contraindicated, such as in pregnancy,[133] and for the long-term treatment of patients in whom oral anticoagulant therapy proves to be very difficult to control.[106] In patients with proximal DVT, long-term therapy with warfarin reduces the frequency of objectively documented recurrent VTE from 47% to 2%. The use of a less intense warfarin regimen (INR 2 to 3) markedly reduces the risk of bleeding from 20% to 4%, without loss of effectiveness in comparison with more intense warfarin.[117] With the improved safety of oral anticoagulant therapy using a less intense warfarin regimen, there has been renewed interest in evaluating the long-term treatment of thrombotic disorders.

OPTIMAL DURATION OF ORAL ANTICOAGULANTS AFTER A FIRST EPISODE OF VENOUS THROMBOEMBOLISM

It has been recommended that all patients with a first episode of VTE receive warfarin therapy for at least 3 to 6 months. Attempts to decrease the treatment to 4 weeks[134,135] or 6 weeks[136] resulted in higher rates of recurrent VTE in comparison with either 12 or 24 weeks of treatment (11% to 18% recurrent VTE in the following 1 to 2 years). Most of the recurrent thromboembolic events occurred in the 6 to 8 weeks immediately after anticoagulant treatment was stopped, and the incidence was higher in patients with continuing risk factors, such as cancer and immobilization.[136] Treatment with oral anticoagulants for 6 months reduced the incidence of recurrent thromboembolic events, but there was a cumulative incidence of recurrent events at 2 years (11%) and an ongoing risk of recurrent VTE of 5% to 6% per year.[136] In patients with a first episode of idiopathic VTE treated with intravenous heparin followed by warfarin for 3 months, continuation of warfarin for 24 months led to a significant reduction in the incidence of recurrent DVT when compared with placebo.[137] In a further recent trial comparing 3 months with 12 months of oral anticoagulant therapy

after the occurrence of a first episode of idiopathic proximal DVT it was shown that patients treated with 3 months had a higher incidence of recurrence of VTE during the subsequent 12 months compared with those patients who were continued on anticoagulants for 12 months.[138] However, the cumulative hazard of recurrent VTE at 36 months was the same in both groups. The incidence of recurrence after discontinuation of treatment was 5.1% per patient-year in patients in whom oral anticoagulant therapy was discontinued after 3 months and 5.0% per patient-year in patients who received an additional 9 months of oral anticoagulant therapy. The recurrence occurred in the initially unaffected leg more than half the time. This suggests that the recurrences were related to a hypercoagulable state and the duration of anticoagulant therapy did not influence the ultimate recurrence rate.

VTE should be considered a chronic disease, with a continued risk of VTE often associated with minor provocation.[139] The continued risk of recurrent thromboembolism even with 12 months' treatment after a first episode of DVT has encouraged the development of clinical trials evaluating the effectiveness of long-term anticoagulant treatment beyond 6 months. In a recent trial, patients with documented proximal DVT with or without the diagnosis of thrombophilia who had received adequate anticoagulation were randomized to received Coumadin with a targeted INR of 1.5 to 2 compared with an identical placebo. This study showed that the lower intensity warfarin significantly decreased the incidence of recurrent VTE in follow-up with no added risk for major bleeding.[140] However, in a study reported in abstract form, warfarin with a targeted INR of 1.5 to 2 was compared with warfarin with a targeted INR of 2 to 3 in a similar patient population. This study indicated that the usual INR of 2 to 3 resulted in a significantly lower incidence of recurrent VTE with no added risk for bleeding.[141] Therefore, at this time there is no justification for the use of the lesser intensive warfarin program.

OPTIMAL DURATION OF ORAL ANTICOAGULANT TREATMENT IN PATIENTS WITH RECURRENT VTE

In a multicenter clinical trial, Schulman and associates randomized patients with a first recurrent episode of VTE to receive either 6 months or continued oral anticoagulants indefinitely, with a targeted INR of 2.0 to 2.85.[142] The analysis was reported at 4 years. In the patients receiving anticoagulants for 6 months, recurrent VTE occurred in 20.7%, compared with 2.6% of patients on the indefinite treatment ($P < .001$). However, the rates of major bleeding were 2.7% in the 6-month group compared with 8.6% in the indefinite group. In the indefinite group, two of the major hemorrhages were fatal, whereas there were no fatal hemorrhages in the 6-month group. This study showed that extending the duration of oral anticoagulants for approximately 4 years resulted in a significant decrease in the incidence of recurrent VTE, but with a higher incidence of major bleeding. Without a mortality difference, the risk of hemorrhage versus the benefit of decreased recurrent thromboembolism with the use of extended warfarin treatment remains uncertain and will require further clinical trials.

From the sixth American College of Chest Physicians Consensus Conference on Anti-thrombotic Therapy the following recommendations are made.[82] Oral anticoagulant therapy should be continued for at least 3 months to prolong the PT to a targeted INR of 2.5 (range: 2.0 to 3.0). Patients with reversible or time-limited risk factors can be treated for 3 to 6 months. Patients with a first episode of idiopathic VTE should be treated for at least 6 months. It should be noted that these recommendations antedated the results of the Agnelli study.[138] Patients with recurrent VTE or a continuing risk factor such as cancer, antithrombin deficiency, or the antiphospholipid syndrome, should be treated indefinitely. Patients with activated protein C resistance (factor V Leiden) should probably receive indefinite treatment if they have recurrent disease, are homozygous for the gene, or have multiple thrombophilic conditions. Accumulated evidence indicates that symptomatic isolated calf vein thrombosis should be treated with anticoagulants for at least 3 months.[82]

THROMBOLYTIC THERAPY

Several studies have demonstrated that the mortality from PE can be decreased by heparin. Treatment with intravenous heparin and oral anticoagulants reduces the mortality rate to less than 5%, and this may be further reduced with the use of LMWH. In the PIOPED trial,[41] only 10 of 399 (2.5%) patients who had angiographically confirmed PE died. However, patients who present with acute massive PE and hypotension have a mortality rate of approximately 20%. For such patients, the appropriate use of thrombolytic agents has a role.

Several trials have compared thrombolytic drugs with heparin.[143-148] Outcome measures for accelerated thrombolysis included quantitative measures on repeat pulmonary angiograms, quantitative scores on repeat pulmonary perfusion scans, and measures of pulmonary vascular resistance. Although all studies demonstrated superiority of thrombolysis (and in particular with tissue plasminogen activator) in radiographic and hemodynamic abnormalities within the first 24 hours, this advantage was short lived.[143] Repeat perfusion scans at 5 to 7 days revealed no significant difference between the patients treated with thrombolytic agents or with heparin. However, at 1 year, those receiving thrombolytic therapy had both high CO diffusion capacity and lung blood capillary volume compared with patients receiving heparin. Follow-up of 23 patients at 7 years showed that patients who had been treated with thrombolytic therapy had lower pulmonary artery pressure and pulmonary vascular resistance. There have been two recent systematic reviews comparing thrombolytic therapy to heparin treatments.[147,148] In one study the composite endpoint of death and recurrent PE was lower with the use of thrombolytic agents but the risk of major bleeding was higher.[147,148] Both of these studies and an accompanying editorial indicated that until the proper randomized clinical trials have been carried out, thrombolytic therapy should only be used for patients with massive PE complicated by shock.[147-149]

Two thrombolytic agents have been approved by the Food and Drug Administration (FDA) for the treatment of acute PE. The dosage schedules are as follows:

- Streptokinase 250,000 units over 30 minutes, followed by 100,000 U/h for 24 hours
- Recombinant tissue plasminogen activator (rt-PA), 100 mg, administered over 2 hours

Anticoagulation with heparin or LMWH is usually begun when the aPTT is less than two times the control.

INFERIOR VENA CAVAL INTERRUPTION

Early approaches to inferior vena caval interruption included ligation or plication using external clips. Both procedures were accompanied by an operative mortality rate of 12% to 14%, a recurrent pulmonary emboli rate of 4% to 6%, and an occlusion rate of 67% to 69%. These complications gave rise to the development of catheter-inserted intraluminal filters. An ideal filter is one that is easily and safely placed percutaneously, is biocompatible and mechanically stable, is able to trap emboli without causing occlusion of the vena cava, which does not require anticoagulation, and is not ferromagnetic (i.e., does not cause artifacts on MRI). Although there is as yet no ideal filter, several types are available. These include the Greenfield stainless-steel filter, titanium Greenfield filter, bird's nest filter, Vena Tech filter, and Simon-Nitinol filter. In experienced hands, these devices can be quickly and safely inserted under fluoroscopic control. One filter (e.g., Antheor TU 50-125, Medi-Tech, Boston Scientific Corp.) can be inserted temporarily in conjunction with thrombolytic therapy and then removed. The follow-up data available show that the Greenfield filter has had the best performance record and any future comparative studies should use this filter as the standard.[150]

The main indications for caval filters are contraindications to anticoagulants, recurrent PE despite adequate anticoagulation, and prophylactic placement in high-risk patients. In the last category are patients with cor pulmonale or a previous history of PE who are placed in high-risk situations such as acetabular fracture or patients who have cancer. More controversial indications for the prophylactic insertion of a filter include emergency surgery occurring within the first 4 weeks of beginning anticoagulant therapy after thrombolytic therapy.[150]

In the past, the detection of a free-floating thrombus by ultrasound examination has been considered as indication for either thrombectomy or insertion of an inferior vena cava filter.[151] An important study compared the clinical outcomes of patients who had either the presence or absence of a free-floating thrombus in a proximal leg vein.[152] There was no difference in the incidence of PE or death between the two groups. The authors conclude that the routine insertion of inferior vena cava filters in patients with free-floating thrombi cannot be supported.[152] This is in keeping with an earlier observation that free-floating thrombi become attached to the vein wall rather than embolizing. In a further study, patients with proximal DVT were randomized to receive an inferior vena cava filter or anticoagulant treatment alone.[153] All patients were treated with heparin, followed by oral anticoagulant therapy for 3 months. At 10 days, there was a significant difference in the incidence of PE but no difference in mortality. Extended follow-up at 1 to 2 years showed a nonsignificant increase in the incidence of PE in the control group but a higher incidence of recurrent DVT in the vena cava filter group and no difference in mortality.[153]

CONCLUSION

Over the past 20 years a large number of trials have been carried out on the diagnosis, prevention, and treatment of VTE. Clinical practice has dramatically changed in response. A number of studies are underway to explore new approaches to diagnosis and treatment. These include the use of pretest clinical probabilities and the D-dimer, the role of spiral CT, and trials to determine the optimal management using LMWH and newer anticoagulants such as pentasaccharide and specific antithrombin agents. Longer duration of anticoagulant therapy with LMWH or warfarin is aimed at decreasing recurrent DVT and PE and decreasing the incidence of the post-thrombotic syndrome. The role of thrombolytic therapy in patients with submassive or massive PE remains controversial, and further randomized clinical trials are needed.

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Chapter 80
OTHER EMBOLIC SYNDROMES

Claus-Martin Muth • Erik S. Shank

KEY POINTS

GAS EMBOLISM

1. Any venous gas embolism may become an arterial embolism through intracardiac or extracardiac right-to-left shunting. Arterial gas embolus must be entertained early to rapidly initiate hyperbaric therapy.
2. Treatment of venous gas embolism is prevention of further air entry and cardiopulmonary support with emphasis on reestablishing stable hemodynamics. For arterial gas embolism, the definitive therapy is hyperbaric oxygen therapy.

FAT EMBOLISM SYNDROME

3. This syndrome presents as acute respiratory collapse. It is a diagnosis that should be entertained early in orthopedic surgeries and trauma to the long bones. It remains a diagnosis of exclusion.

AMNIOTIC FLUID EMBOLUS

4. This is managed initially with aggressive cardiopulmonary support. In the postresuscitation period it is vital to follow the coagulation profile and be prepared to treat disseminated intravascular coagulation (DIC).
5. It may strike any woman in the peripartum period. Risk factors often cited for amniotic fluid embolus such as tumultuous labor or multiparity in an older woman have not been demonstrated in recent reviews. It is a syndrome of peripartum cardiovascular collapse and coagulopathy.

The presentation, pathophysiology, and treatment of embolic disease other than thromboembolic processes are discussed in this chapter. Included are emboli associated with iatrogenic complications of medical diagnostic and therapeutic manipulations as well as sequelae from skeletal trauma and pregnancy.

AIR EMBOLISM

Air embolism, the entry of gas into vascular structures, is a largely iatrogenic clinical entity responsible for serious morbidity, and even mortality, in many varied medical specialties (Table 80-1).[1] Furthermore, it is one of the most serious problems in diving medicine.[2] The medical use of varied gases has created numerous other gas embolisms, including carbon dioxide, nitrous oxide, and nitrogen emboli.

There are two broad categories of gas embolism, venous and arterial, depending on the mechanism of gas entry and where the emboli ultimately lodge.

VENOUS GAS EMBOLISM

A venous gas embolism occurs by the entry of gas into the systemic venous system.[3] This gas is then transported to the lungs via the pulmonary arteries, causing interference in gas exchange, arrhythmias, pulmonary hypertension, right ventricular strain, and finally cardiac failure. Predispositions that allow the entry of gas into the venous system include incision of noncollapsed veins and the presence of subatmospheric pressure in these vessels. These conditions occur when the surgical field is above the level of the heart (for instance, during neurosurgical operations performed in the sitting position).[4] Other potential pathways include entry of air into central venous and hemodialysis catheters[1] and entry into the veins of the myometrium in the peripartum period.[1,5]

Pathophysiology

The most common scenario is insidious, where there is a continuous entry of small gas bubbles into the venous system. With rapid entry, or larger volumes of gas, increasing strain on the right ventricle follows because of the migration of the emboli to the pulmonary circulation. The pulmonary arterial pressure increases, while the increased resistance to right ventricle outflow causes diminished pulmonary venous return. This is reflected in decreased left ventricular preload, resulting in diminished cardiac output and, ultimately, systemic cardiovascular collapse.[6] Quite often tachyarrhythmias develop, but bradycardias are possible as well. When large quantities of gas/air (over 50 mL) are injected abruptly, acute cor pulmonale and/or asystole can occur.[3] These alterations of lung vessel resistance and ventilation-perfusion mismatch in the lung cause intrapulmonary right-to-left shunt with increased alveolar deadspace, leading to arterial hypoxia and hypercapnia.

Diagnosis

To diagnose venous gas embolism, clinical findings should be assessed. The so-called mill-wheel murmur is relatively typical and can be auscultated by a precordial or esophageal stethoscope. A capnometric decrease of end-tidal carbon

TABLE 80–1. MEDICAL SPECIALTIES WITH DOCUMENTED CASES OF GAS EMBOLISM

Specialty	Mechanism of Gas Embolism
All medical specialties	Inadvertent entry of air through peripheral intravenous circuits
All surgical specialties	Intraoperative use of hydrogen peroxide generating arterial and venous oxygen emboli
Anesthesiology	Entry of air through disconnected intravascular catheters, inadvertent infusion of air through intravascular catheters
Cardiac Surgery	Entry of air into extracorporeal bypass pump circuit, incomplete removal of air from heart post cardioplegic arrest, carbon dioxide–assisted harvesting of peripheral veins
Cardiology	Entry of air through intravascular catheters during angiographic studies and procedures
Critical Care/Pulmonology	Entry of air through disconnected intravascular catheters, pulmonary barotrauma, rupture of intra-aortic balloon pumps, entry of air in extracorporeal membrane oxygenator (ECMO) circuit
Diving Medicine and Hyperbaric Medicine	Pulmonary barotrauma, paradoxical embolism after decompression injury, entry of gas through disconnected intravascular catheters
Endoscopic/Laparoscopic Surgery	Entry of gas into veins or arteries during insufflation of body cavities
Gastroenterology	Entry of gas into veins during upper and lower endoscopies and endoscopic retrograde pancreatography (ERCP)
Neonatology/Pediatrics	Pulmonary barotrauma in treatment of infants with premature lungs
Nephrology	Inadvertent entry of air through hemodialysis catheter and circuit on hemodialysis machine
Neurosurgery	Entry of air through incised veins and calvarial bone especially during sitting craniotomies
Obstetrics/Gynecology	Cesarean sections, gas insufflation into veins during endoscopic surgery, intravaginal/intrauterine gas insufflation during pregnancy
Otolaryngology	Laser (Nd:YAG) surgery on the larynx and trachea/bronchi
Orthopedics	Gas insufflation into veins during arthroscopy, total hip arthroplasty, prone spine surgery
Radiology	Injected air/gas as contrast agent, inadvertent injection of air during angiographic studies
Thoracic Surgery	Entry of air into pulmonary vasculature during lung biopsies and video-assisted thoracoscopy (VATS), chest trauma (penetrating and blunt), lung transplants
Urology	Transurethral prostatectomy (TURP), radical prostatectomy
Vascular Surgery	Entry of air during carotid endarterectomies

dioxide suggests a change in the relation of ventilation and perfusion by the obstruction of the pulmonary arteries.[7] Precordial Doppler ultrasonography is a sensitive and practical monitor to detect intracardiac air and is often utilized in neurosurgical procedures[1,8] in the sitting position and in other procedures with a high risk for gas embolism. An even more sensitive and definitive monitor for detecting intracardiac gas is transesophageal echocardiography; however, this technique requires significant training in application and interpretation to be effective.[1,9]

Treatment (Table 80-2)

When a venous gas embolism is suggested, further entry of gas must be avoided. Catecholamine therapy and cardiopulmonary resuscitation should be initiated for cardiovascular collapse. Adequate oxygenation is often only possible with a significant increase in the oxygen concentration of the inspired gas (i.e., 100% oxygen). Supplemental oxygen also reduces the size of the gas embolism by increasing the gradient for nitrogen egress from the bubble.[10] Rapid volume resuscitation is recommended to elevate venous pressure, thus decreasing the continued entry of gas into the venous circulation. Some authors recommend attempting to evacuate air from the right ventricle by a central venous catheter (multi-orifice catheters may be more effective than a single lumen) or a pulmonary arterial catheter.[11] Hyperbaric oxygen therapy is not a first-line treatment but may be a useful adjunct in severe cases. It should certainly be considered if there are neurologic findings. If central nervous system symptoms are present, a paradoxical embolism should be presumed.

PARADOXICAL EMBOLISM

A paradoxical embolism arises when air/gas entrained in the venous circulation manages to enter the systemic arterial circulation causing symptoms of end-artery obstruction. There are a number of mechanisms by which this can occur. One of these is the passage of gas across a patent foramen ovale to the systemic circulation. A patent foramen ovale is detectable in about 30% of the population and makes right-to-left shunting of gas bubbles possible.[12] Elevated pulmonary arterial pressure due to a venous gas embolism may be reflected

TABLE 80–2. TREATMENT OF GAS EMBOLISM

	Venous Gas Embolism	Arterial Gas Embolism
Prevent Further Gas Entry	Increase venous pressure (e.g., Valsalva, IV fluids) Identify and disable entryway for gas	Identify and disable entryway for gas
Definitive Therapy	Supportive	Hyperbaric oxygen therapy as soon as patient stable for transfer to hyperbaric oxygen facility
Supportive Therapy	Oxygen, intravascular volume expansion, catecholamines	Oxygen, intravascular volume expansion, catecholamines
Positioning	Supine	Supine
Evacuation of Embolized Gas	Aspiration of multi-lumen central venous catheter; patient in left lateral decubitus position	Hyperbaric oxygen
Adjunctive Therapy	Hyperbaric oxygen	Lidocaine, antiepileptics

in elevated right atrial pressures predisposing to bubble transport across a patent foramen. In addition, the decrease in left atrial pressure caused by controlled ventilation and use of positive end-expiratory pressure may create a pressure gradient across the patent foramen ovale favoring passage of gas into the systemic circulation.[1]

In other situations, venous gas may enter the arterial circulation by overwhelming the filter capacity of the lungs normally in place to prevent arterial gas emboli. Clinical cases are documented in which a fatal cerebral arterial gas embolism developed, caused by a large venous gas embolism, although no intracardiac defects or shunt mechanisms could be demonstrated.[13] The filtration threshold of the pulmonary circulation for gas emboli can be affected by various anesthetic agents. In particular, volatile anesthetics have been shown to reduce the threshold for spillover of venous bubbles into systemic arteries in experimental studies.[14]

Treatment

Therapy of paradoxical embolism is identical to that of a primary arterial gas embolism (see Table 80-2). It should be stressed that every venous gas embolism has the potential to evolve into an arterial gas embolism.

ARTERIAL GAS EMBOLISM

Arterial gas embolism occurs by the entry of gas into the pulmonary veins or directly into the arteries of the systemic circulation. Mechanisms include the overexpansion of the lung through decompression barotraumas in diving, pulmonary barotraumas in the ventilatory therapy for critical care patients, and paradoxical embolism. Additionally, all cardiac surgical operations with extracorporal bypass are a potential mechanism for these events.[1] The entry of even small amounts of gas into the arterial system leads to a flow of gas bubbles into functional end arteries and occlusion of these vessels. Although possible in all arteries, the embolic obstruction of the coronary arteries or the nutritive arteries of the brain, termed a *cerebral arterial gas embolism*, are especially critical and can be fatal owing to the vulnerability of these organs to short periods of hypoxia.

Pathophysiology

Entry of gas into the aorta causes distribution of gas bubbles into nearly all organs. Small emboli in the vessels of the skeletal muscles or viscera are well tolerated, although organ dysfunctions such as rhabdomyolysis and/or renal insufficiency may occur as well.[15] Embolization to the cerebral or coronary circulation may result in severe morbidity or death.

Embolization into the coronary arteries can induce electrocardiographic changes typical of ischemia and infarction with dysrhythmias, myocardial depression, cardiac failure, and cardiac arrest. Circulatory responses may also be seen with embolization to the cerebral vessels.[16] Cerebral arterial gas embolization typically involves migration of gas to small arteries of the brain. The emboli generate pathology by two broad mechanisms: reduced perfusion distal to the obstruction and an inflammatory response to the bubble.[1]

Clinical Features

The signs and symptoms associated with cerebral arterial gas embolism can develop suddenly. The clinical presentation is determined by the absolute quantity of gas and the brain areas affected. Thus, a comparatively mild clinical picture with minor motor weakness, headache, or moderately marked confusion may be present. Conversely, complete disorientation, hemiparesis, convulsions, loss of consciousness, and coma may present. Additionally, asymmetry of pupils, hemianopsia, and impairment of respiratory and circulatory centers (bradypnea, Cheyne-Stokes breathing, cardiac arrhythmias, and circulatory failure) are all well-known complications. After surgeries with risks for the development of gas embolism, a delayed recovery from general anesthesia or a transitional stage of impaired consciousness can be a clue to a cerebral arterial gas embolism. The diagnosis in these cases is not easy because anesthesia complications such as central anticholinergic syndrome, residual anesthetic, or muscle relaxant can mimic a mild cerebral arterial gas embolism.

Diagnosis

The most important criterion is the patient's history, because the clinical suspicion of embolism is based on the initial neurologic symptoms and the direct temporal relation with an invasive medical therapy. The greatest risks for venous or arterial gas embolism are present in craniotomies performed in the sitting position, cesarean sections, hip replacements, and cardiac surgery using cardiopulmonary bypass. All these procedures have in common an incised vascular bed and a hydrostatic gradient favoring the intravascular entry of gas.

Differentiating a cerebral arterial gas embolism from a cerebral infarct or an intracerebral hemorrhage can sometimes be made using computed tomography (CT). However, pathologic changes are sometimes very subtle and not well visualized on CT, and the diagnosis of cerebral arterial gas embolism must be entertained early. Magnetic resonance imaging of the cerebrum can sometimes show local increase of water density concentrated in the injured tissue. But this method is not completely reliable and may fail when only mild symptomatology is present. Another nonspecific finding, but described in a number of cases, is hemoconcentration with increased hematocrit, possibly the direct consequence of the extravascular shift of fluid into the injured tissues.[17]

Treatment

Protection and maintenance of vital functions is the primary goal. If warranted, cardiopulmonary resuscitation must be performed, because not only venous but also primary arterial gas embolism may lead to serious impairment of the cardiovascular system. For somnolent or comatose patients, endotracheal intubation should be performed to maintain adequate oxygenation and ventilation. Additionally, oxygen should be administered in as high a concentration as possible.[1,18] This is important not only to treat hypoxia and hypoxemia but also for the elimination of the gas in the bubbles through a diffusion gradient favoring egress of gas from the bubble.

The current therapeutic recommendation is to maintain a flat supine position for these patients, because neither head-down positions nor an elevated head position provides any detectable cardiovascular benefits and may aggravate the cerebral insult.

Cerebral gas embolism may be associated with the development of generalized seizures that may resist management by benzodiazepines. In these cases it is advised to suppress the seizure activity with barbiturates. It must be stressed, however, that with sufficient doses of barbiturates, respiratory drive is depressed and the patient's ventilation must be supported.

The definite treatment of arterial gas embolism is hyperbaric oxygen therapy (HBO-T),[19,20] with best results reported when performed as early as possible. HBO-T involves the placement of the patient in an environment pressurized above sea level pressure while breathing 100% oxygen. This therapy causes a mechanical diminution of the gas bubble by both raising the ambient pressure and creating systemic hyperoxia. Hyperoxia produces a diffusion gradient for oxygen into the gas bubble, as well as for egress of nitrogen (or other gas) from the bubble. Hyperoxia also enables significantly larger quantities of oxygen to be dissolved in the plasma and also increases the diffusion distance of oxygen in tissues. The improved oxygen-carrying capacity and delivery is important to offset the embolic insult to the microvasculature.

Hyperbaric oxygen has other postulated benefits. These include anti-edema effects and reducing blood vessel permeability while supporting the integrity of the blood-brain barrier.[21] In addition, there are experimental studies indicating that hyperbaric oxygen diminishes the adherent properties of leukocytes to the damaged endothelium.[22]

The aforementioned benefits suggest that all patients with the clinical symptomatology of arterial gas embolism should receive treatment with hyperbaric oxygen. Although immediate institution of such therapy demonstrates the best response, treatment in a hyperbaric chamber is still indicated after a longer period of time and may result in amelioration of the patient's condition. Treatment of arterial gas emboli with hyperbaric oxygen is the first-line therapy of choice. Thus, once the patient is stabilized from a cardiopulmonary standpoint, transfer to a hyperbaric oxygen facility should be accomplished without delay.

Further Therapeutic Measures

As a consequence of a gas embolism, hemoconcentration may occur, resulting in increased blood viscosity and further impairing the already compromised microcirculation. One important maneuver to optimize the microcirculation is therefore to achieve euvolemia. In animal studies it has been demonstrated that a moderate hemodilution to a hematocrit of 30% leads to a reduction of the neurologic damage.[23] It is therefore acceptable to decrease the hematocrit within certain limits. The use of crystalloid solutions may exacerbate cerebral edema; thus, colloid solutions should be favored.

Placement of a central venous catheter is strongly recommended to properly assess central venous pressure (CVP). CVP should be kept around 12 mm Hg. As a further monitor of normovolemia, the urine output should be monitored by Foley catheter.

There is some evidence that heparin may be of use in the treatment of gas embolism.[24] Studies have shown that the clinical course of arterial gas embolism is less severe if the patient has been treated with heparin before the embolic event. The mechanism seems to be not only anticoagulative but also that heparin has an inhibitory effect on thromboinflammatory processes. Arguing against heparinization is the risk of hemorrhage into the infarcted tissue. At present, the use of heparin for the acute therapy of cerebral arterial gas embolism is not yet recommended.

The use of corticosteroids remains controversial. Some authors recommend the use of corticosteroids for arterial gas embolism to combat vasogenic brain edema, which results from a gas embolization in the cerebral arteries. Cerebral gas embolism initially induces a rapidly developing cytotoxic brain edema with diminished extracellular spaces and enlarged intracellular areas. This form of edema does not, in general, respond to corticosteroids. Other authors report the use of steroids aggravating ischemic injury post vessel occlusion.[25] Thus, because corticosteroids appear to be without benefit in cytotoxic edema and potentially may aggravate neuronal ischemic injury, they are not indicated in arterial gas embolism.

Although still experimental, there are suggestions that lidocaine may be beneficial.[26,27] In animals receiving prophylactic doses of lidocaine, the depressant effects of gas embolism on somatosensory evoked potentials and elevations in intracranial pressure could both be reduced. In a clinical trial, cerebral protection during cardiac operations was demonstrated.[27] Therefore, a strong argument can be made for the administration of lidocaine in therapeutic concentrations after severe arterial gas embolism.

FAT EMBOLISM SYNDROME

Fat embolism syndrome (FES) is a clinical entity first described over 150 years ago by Bergmann.[28] It is very important to differentiate FES, a complex with potentially catastrophic cardiopulmonary and cerebral dysfunction, from fat embolization, a far more common and often subclinical entity.[29]

FES is most frequently seen status post lower extremity and pelvic trauma, intramedullary nailing of long-bone fractures, hip arthroplasty, and knee arthroplasty.[30] However, FES has also been described in association with diverse diseases, such as sickle cell disease, acute pancreatitis, and diabetes mellitus and with liposuction procedures, burns, decompression sickness, and total parenteral nutrition infusion.[31-33] In a retrospective review of patients with fractures of the long bones from trauma, the incidence of FES was 0.9%.[34]

FES always involves pulmonary compromise. The presentation may range from subclinical shunting to fulminant pulmonary failure. In response to the lodging of fat particles in the pulmonary vasculature, the patient may present with right-sided heart failure, cardiovascular collapse, or severe hypoxia. Frequently there is cerebral involvement. Cerebral symptomatology may be due to paradoxical fat embolization to the central nervous system and/or a response to the severe hypoxia associated with this syndrome.

Intramedullary orthopedic surgeries are the most common iatrogenic cause of FES. In hip and knee arthroplasties, the manipulation of the femoral components can generate intramedullary pressures exceeding 800 mm Hg. Cementing the prosthesis has been implicated in raising the intramedullary pressure even further.[35] However, this may not be as straightforward as previously thought. One study has suggested that there is no additional risk of FES associated with cementing the prosthesis.[36]

The pathophysiology of FES is complex and probably has both a mechanical component as well as a secondary biochemical process. In the initial phase, fat and marrow are displaced from the bones, enter the venous system, and travel through the heart to enter the lungs. There the emboli may cause shunting, severe hypoxemia, and right ventricular dysfunction. Analogous to gas emboli, the fat may travel, paradoxically, to other organs via the systemic circulation either by transpulmonary passage or through an intracardiac shunt, most commonly through a patent foramen ovale. The secondary phase may involve inflammatory mediators

responsible for the interstitial edema or acute respiratory distress syndrome that may ensue. Additionally, bone marrow contains thromboplastin that may activate coagulation cascades. These mechanisms may be responsible for the delayed petechial rash seen 24 to 48 hours after the initial event in approximately 50% of patients with FES.

The diagnosis of FES remains one of exclusion. A number of authors have suggested clinical criteria for diagnosing FES. The most notable are Gurd's,[37] Schonfeld's,[38] and Lindeque's.[39] All include acute respiratory collapse as a major criterion. Schonfeld and Gurd both stress the presence of petechiae in their criteria for FES. Petechiae, as mentioned earlier, are not a consistent sign of FES and present relatively late in the process. Laboratory tests that may help in making the diagnosis include arterial blood gases (hypoxia), electrocardiogram (right-sided heart strain), chest radiograph (diffuse bilateral infiltrates and opacities), magnetic resonance imaging (for signs of cerebral FES), and CT.[40] Bronchoalveolar lavage (BAL) may help confirm the diagnosis by demonstrating fat droplets in alveolar macrophages, although the sensitivity and specificity of this test are unclear.[41,42] Intraoperative transesophageal echocardiography (TEE) will demonstrate multiple echogenicities in the right heart chambers in the presence of fat embolization. It may also show paradoxical echogenic particles in the left heart chambers should a patent foramen ovale or other means for right-to-left intracardiac shunting be present.[43] A pulmonary arterial catheter may show elevations in right-sided heart pressures.[44] Urinalysis may show lipuria.[45]

Treatment of FES remains supportive. There are no specific drug regimens recommended for FES. Cardiovascular therapy including maintaining adequate preload and positive inotropy is necessary to preserve cardiac output. The severe hypoxemia associated with FES must be aggressively treated, usually with 100% oxygen via an endotracheal tube. Even with ideal pulmonary care, lung function may further deteriorate with a clinical picture resembling acute respiratory distress syndrome. Prophylactic corticosteroid therapy may minimize the incidence of FES,[46] but other therapeutic regimens used after the development of FES, including heparinization, dextran, and parenteral ethanol, cannot be recommended.

AMNIOTIC FLUID EMBOLISM

Amniotic fluid embolism is an entity first described by Meyer[47] in 1926 and involves the introduction of amniotic fluid containing fetal elements into the maternal circulation. In 1941, it was further characterized by two pathologists, Steiner and Lushbaugh, who reported the histologic findings in 42 women who died during the third trimester of pregnancy.[48] Nine of the women had squamous cells and eosinophilic material possibly of fetal origin. The pathologists suggested that this was a syndrome associated with tumultuous labor in multiparous older women. This group became the basis for the "classic" amniotic fluid embolism (AFE).

Estimates for the incidence of amniotic fluid embolism vary from 1 in 8000 to 1 in 80,000 pregnancies. It is currently the most common cause of peripartum deaths.[49] Clark and colleagues, reviewing the national registry of AFE, suggested the descriptive terminology "syndrome of acute peripartum cardiovascular collapse and coagulopathy" to describe AFE. They determined, in contrast to previously accepted notions, that no demographic variables, including maternal age, parity, race, or route of delivery of the infant, predicted elevated risk of AFE.[49] In 73% of the patients there were fetal elements in the pulmonary vasculature of the mothers. Interestingly, the syndrome was not associated more with vasopressin-induced labor, nor was cesarean section an apparent risk factor. The authors did note a strong temporal association to placement of intrauterine monitoring devices or artificial rupture of membranes and presentation of AFE symptoms. A significant association was made between AFE and male sex of the fetus.

Amniotic fluid embolism may present initially as seizures or seizure-like states or as cardiopulmonary symptoms.[50] These may include acute dyspnea, hypotension, fetal distress, pulmonary edema, or cardiac arrest. Cardiac events are relatively evenly distributed between pulseless electrical activity, severe bradycardias, ventricular tachycardias, and asystole.

Patients who survive the initial insult usually proceed to a consumption coagulopathy. This is associated with fibrinogen depletion (less than 100 mg/dL), increased fibrin split products, elevation of prothrombin and activated partial thromboplastin times, as well as decreased platelet levels.[51] In some cases, coagulopathy may be the presenting sign of an AFE.[51]

Amniotic fluid embolism appears due to an exposure of the maternal circulation to fetal products. However, unlike other embolic diseases discussed in this chapter, exposure to fetal products usually does not generate the AFE syndrome. In fact, it has been demonstrated that amniotic fluid infusion into the maternal circulation is generally innocuous.[52] This is fortunate because the outcome, over 50 years since the syndrome was described, remains dismal. Fewer than 15% of women who are stricken with AFE survive neurologically intact.

Even with ideal care, AFE remains a disease with an extremely poor outcome. In spite of rapid and aggressive resuscitation, neurologic sequelae are common in the survivors. That AFE should present often as seizures or a seizure-like state is relatively surprising. It may be due to profound hypoxia as well as hypotensive insults to the central nervous system.

Clark and colleagues[49] have suggested that AFE may share similar mechanisms to septic shock and other anaphylactoid responses. The premise is that fetal components in the amniotic fluid initiate a complex inflammatory cascade with resultant cardiopulmonary collapse. Nishio and colleagues presented data that support this hypothesis in a patient with presumed fatal AFE and elevation of serum mast cell tryptase levels indicating recent mast cell degranulation (a common denominator of anaphylactoid reactions).[53] The coagulopathy may be due to the activation of clotting cascades by amniotic fluid containing platelet factor III, factor X–like properties, as well as functionally active tissue factor.[54] Tissue factor when combined with maternal factor VII will activate the extrinsic coagulation pathway.[51]

The diagnosis of AFE is one mostly of exclusion. It should be entertained in any pregnant woman who experiences acute cardiovascular collapse or coagulopathy. It has been described in women undergoing first-trimester therapeutic abortions as well as during the peripartum period. There is no definitive diagnostic test for AFE. Demonstrating fetal matter in the pulmonary vasculature on autopsy supports the diagnosis but is nonspecific.[55] Fetal elements were found in only 73% of patients who died of presumed AFE. Aspirating from a wedged pulmonary artery catheter or sampling mixed venous blood for fetal elements may also help

support the diagnosis,[56] although in one study only 50% of patients being resuscitated for presumed AFE had fetal elements aspirated by a wedged pulmonary artery catheter.

Treatment of AFE is largely supportive. Initial cardiopulmonary resuscitation should be performed with left lateral displacement to maintain uterine perfusion and venous return. Management should be directed toward maintaining oxygenation, usually with 100% oxygen through an endotracheal tube. Additional cardiovascular support should be initiated rapidly with volume and pressor support. If the fetus has not yet been delivered, this should be accomplished by emergent cesarean section.[57] An arterial line and pulmonary catheter may help guide therapy.[55] Epinephrine may be the first-line agent of choice, as it is in other anaphylactoid reactions. Corticosteroids may be helpful, but therapeutic heparinization to minimize consumption coagulopathies remains controversial.[55]

It is vital to aggressively follow the coagulation profile and treat the disseminated intravascular coagulation (DIC) that frequently ensues once the initial cardiovascular collapse has been addressed. The mortality from DIC may be as great as 75%, in spite of optimal therapy.[51] Treatment is usually with blood components, including red blood cells followed by platelets, fresh frozen plasma, and cryoprecipitate.[58]

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Chapter 81
PULMONARY HYPERTENSION

David B. Badesch • Lewis J. Rubin

KEY POINTS

1. **The evaluation of patients with pulmonary artery hypertension (PAH) is directed at the detection of underlying contributing factors and associated conditions,** such as left-sided cardiac dysfunction, underlying congenital heart disease, pulmonary thromboembolic disease, collagen vascular disease, parenchymal lung disease, obstructive sleep apnea, liver disease, amphetamine or appetite suppressant use, intravenous drug abuse, or human immunodeficiency virus (HIV) infection.
2. **Patients with severe PAH are particularly prone to vasovagal events,** and when these occur they can lead to severe consequences, including syncope, cardiopulmonary arrest, and death.
3. **Hypoxemia and hypercarbia are both pulmonary vasoconstrictors** and can contribute to the worsening of pulmonary hypertension.
4. **The induction of anesthesia and intubation for surgical procedures can be a particularly high-risk time for patients with PAH,** as they are at risk for vagal events, hypoxemia, hypercarbia, and shifts in intrathoracic pressure with associated changes in cardiac filling pressures.

Pulmonary hypertension is defined as a pulmonary artery mean pressure (PAPm) of 25 mm Hg or greater and may be precapillary or postcapillary in etiology. Postcapillary causes include processes affecting the left side of the heart (e.g., left ventricular systolic or diastolic dysfunction, mitral stenosis or regurgitation, aortic valvular disease) or, more rarely, the pulmonary veins (pulmonary veno-occlusive disease). Management of postcapillary pulmonary hypertension typically involves treating the underlying left-sided cardiac process. Medications used to treat precapillary pulmonary hypertension are often not only ineffective for postcapillary pulmonary hypertension but may, in fact, be harmful, potentially leading to the development of pulmonary edema.

Precapillary pulmonary hypertension, or pulmonary arterial hypertension (PAH), can be idiopathic (IPAH—previously known as primary pulmonary hypertension [PPH]) or may occur in association with a variety of underlying disease processes such as collagen vascular disease, portal hypertension, congenital systemic to pulmonary shunts, drug or toxin exposure, or HIV infection.[1] IPAH/PPH is principally a disease of young women, but it can affect all age groups and both sexes. A genetic predisposition may underlie a substantial proportion of these cases.[2-8]

Initial therapy may be directed at an underlying cause or contributing factor, such as using continuous positive airway pressure (CPAP) and supplemental oxygen for PAH associated with obstructive sleep apnea. Following the identification and treatment of underlying associated disorders and contributing factors, specific therapy for PAH should be considered. IPAH/PPH carried a very poor prognosis (median survival approximately 2.8 years from the date of diagnosis) through the mid-1980s. Subsequently, a number of therapeutic options have been developed, and three have been approved by the U.S. Food and Drug Administration (FDA): epoprostenol, treprostinil, and bosentan. Other agents that are being studied for PAH include sitaxsenten, ambrisentan, sildenafil, and inhaled iloprost.

DIAGNOSIS

SYMPTOMS, SIGNS, AND CLINICAL HISTORY

Because of the insidious onset of symptoms, PAH is often advanced at the time of diagnosis. Dyspnea on exertion is a common presenting symptom, but it is sometimes attributed to deconditioning or other cardiorespiratory ailment. Chest pain, mimicking angina pectoris, may occur. Patients with advanced disease may present with syncope or signs and symptoms of right-sided heart failure, including lower extremity edema, jugular venous distention, and ascites.

The clinical history should focus initially on the exclusion of underlying causes of pulmonary hypertension. Important clues to an underlying condition might include a previous history of a heart murmur, deep venous thrombosis or pulmonary embolism, Raynaud's phenomenon, arthritis, arthralgias, rash, heavy alcohol consumption, hepatitis, heavy snoring, daytime hypersomnolence, morning headache, and morbid obesity. A careful family history should be taken. Medication exposures, particularly to appetite suppressants and amphetamines, should be noted. Cocaine is a powerful vasoconstrictor and may contribute to the development of pulmonary hypertension. Intravenous drug abuse has been associated with the development of PAH.

PHYSICAL EXAMINATION

Signs of PAH may not become apparent until late in the disease. Findings such as an accentuated second heart sound, a systolic murmur over the left sternal border, jugular venous distention, peripheral edema, and/or ascites might suggest the presence of pulmonary hypertension and right

ventricular dysfunction. Associated systemic diseases, such as collagen vascular disease or liver disease, may also become apparent during routine examination.

LABORATORY EVALUATION

Laboratory evaluation can provide important information in detecting associated disorders and contributing factors. A collagen vascular screen, including antinuclear antibodies, rheumatoid factor, and erythrocyte sedimentation rate, is often helpful in detecting autoimmune disease, although some patients with IPAH/PPH will have a low titer positive antinuclear antibody test.[9] The scleroderma spectrum of disease, particularly limited scleroderma or the CREST syndrome, has been associated with an increased risk for the development of PAH.[10,11] Liver function tests (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase) may be elevated in patients with right ventricular failure and passive hepatic congestion but may also be associated with underlying liver disease. Liver disease with portal hypertension has been associated with the development of pulmonary hypertension. Thyroid disease may occur with increased frequency in patients with IPAH/PPH and should be excluded with thyroid function testing.[12] HIV testing and hepatitis serologic studies should be considered in patients at risk. Routine laboratory studies such as the complete blood cell count, complete metabolic panel, prothrombin time, and partial thromboplastin time are recommended during the initial evaluation and as indicated to monitor the patient's long-term clinical status.

ECHOCARDIOGRAPHY

Doppler echocardiography is useful in estimating the severity of pulmonary hypertension and detecting left-sided heart disease. Findings may include enlargement of the right ventricle, flattening of the interventricular septum, and compression of the left ventricle. Bubble contrast echocardiography may detect a right-to-left shunt, but exclusion of a left-to-right intracardiac shunt may require cardiac catheterization with an oximetry series. Echocardiography may be a useful noninvasive means of long-term follow-up,[13] although not all patients have suitable echocardiographic windows.

RADIOGRAPHIC EVALUATION AND EXCLUSION OF THROMBOEMBOLIC DISEASE

Chest radiography may reveal enlargement of the central pulmonary vessels and evidence of right ventricular enlargement. Evidence of parenchymal lung disease may be apparent. When parenchymal lung disease is suspected, pulmonary function testing and high-resolution computed tomography (CT) of the chest may be indicated. Ventilation-perfusion lung-scanning should be performed in an attempt to exclude chronic-recurrent pulmonary thromboembolic disease, which is among the most preventable and treatable causes of pulmonary hypertension. Diffuse mottled perfusion can be seen in IPAH/PPH, whereas larger segmental and subsegmental mismatched defects are suggestive of chronic recurrent pulmonary thromboembolic disease. Intermediate results on ventilation-perfusion lung scanning may require pulmonary arteriography to obtain a definitive diagnosis. Although contrast medium–enhanced CT has been popularized recently for the diagnosis of acute pulmonary thromboembolic disease, there is limited experience with this technique in chronic thromboembolic disease. Accordingly, we recommend caution at present in using contrast-enhanced CT to exclude chronic recurrent thromboembolic disease.

PULMONARY FUNCTION TESTING

Pulmonary function testing is indicated to detect underlying parenchymal lung disease. The diffusing capacity is often reduced in pulmonary vascular disease, consistent with impaired gas exchange. Oximetry testing of patients at rest, with exertion, and nocturnally, is useful in detecting hypoxemia and the need for supplemental oxygen.

RIGHT-SIDED HEART CATHETERIZATION AND VASOREACTIVITY TESTING

Right-sided heart catheterization remains an important part of the evaluation. Left-sided heart dysfunction and intracardiac shunts can be excluded, the degree of pulmonary hypertension can be accurately quantified, and the cardiac output can be measured. Pulmonary vascular resistance can then be calculated. Acute pulmonary vasoreactivity can be assessed using a short-acting agent such as prostacyclin (epoprostenol), inhaled nitric oxide, or intravenous adenosine.[14,15] The European Society of Cardiology consensus definition of a positive acute vasodilator response in an IPAH/PPH patient is a fall of PAPm of at least 10 mm Hg to less than or equal to 40 mm Hg, with an increased or unchanged cardiac output. The primary objective of acute vasodilator testing in patients with IPAH/PPH is to identify patients who might be effectively treated with oral calcium channel blockers. The acute response to a short-acting agent, such as prostacyclin, has been shown to be predictive of the response to calcium channel blocker.[14] Unstable patients or those in severe right-sided heart failure, who would not be candidates for treatment with calcium channel blockers, need not undergo vasodilator testing.

TREATMENT

GENERAL CARE

Warfarin, Oxygen, Diuretics, Digoxin, and Vaccination

Improved survival has been reported with oral anticoagulation in IPAH/PPH.[16,17] The target International Normalized Ratio in these patients is 1.5 to 2.5. Anticoagulation of patients with PAH occurring in association with other underlying processes, such as scleroderma or congenital heart disease, is controversial. Generally, patients with PAH treated with chronic intravenous epoprostenol are anticoagulated in the absence of contraindications, owing in part to the additional risk of catheter-associated thrombosis.

Hypoxemia is a pulmonary vasoconstrictor and can contribute to the development or progression of PAH. It is generally considered important to maintain oxygen saturations at greater than 90% at all times. Supplemental oxygen use is more controversial in patients with Eisenmenger physiology but may decrease the need for phlebotomy and potentially reduce the occurrence of neurologic dysfunction and complications.

Diuretics are indicated in patients with evidence of right ventricular failure and volume overload (i.e., peripheral edema and/or ascites). Careful dietary restriction of sodium and fluid intake is important in the management of patients with PAH with right-sided heart failure. Rapid and excessive diuresis may produce systemic hypotension, renal insufficiency, and syncope. Serum electrolytes and measures of renal function should be followed closely in patients receiving diuretic therapy.

Although not extensively studied in PAH, digitalis is sometimes utilized in refractory right ventricular failure or atrial dysrhythmias. Drug levels should be followed closely, particularly in patients with impaired renal function.

Because of the potentially devastating effects of respiratory infections in PAH, immunization against influenza and pneumococcal pneumonia is recommended.

Calcium Channel Blockers

Patients with IPAH/PPH who respond to vasodilators and calcium channel blockers[16] generally have improved survival. Unfortunately, this tends to represent a relatively small proportion of patients, comprising fewer than 20% of IPAH/PPH patients and even fewer patients with other causes of PAH.

Prostanoids

Prostacyclin, a metabolite of arachidonic acid produced primarily in vascular endothelium, is a potent systemic and pulmonary vasodilator that also has antiplatelet aggregatory effects. A relative deficiency of prostacyclin may contribute to the pathogenesis of PAH.[18]

Epoprostenol

In a 12-week, prospective, multicenter, randomized, controlled, open-label trial, continuously intravenously infused epoprostenol plus conventional therapy (oral vasodilators and anticoagulation) improved exercise capacity and hemodynamics compared with conventional therapy alone.[19] Eight patients died during the study, all of whom had received conventional therapy. Serious complications included four episodes of catheter-related sepsis and one thrombotic event.

A similar multicenter, randomized, controlled, open-label study of chronic intravenous epoprostenol showed improvement in exercise capacity and hemodynamics in patients with PAH occurring in association with the scleroderma spectrum of disease.[20] Four patients in the epoprostenol group and five in the conventional therapy group died.

Epoprostenol therapy is complicated by the need for continuous intravenous infusion. The drug is unstable at room temperature and is generally best kept cold before and during infusion. It has a very short half-life in the bloodstream (<6 minutes), is unstable at acidic pH, and cannot be taken orally. Because of the short half-life, the risk of rebound worsening with abrupt/inadvertent interruption of the infusion, and its effects on peripheral veins, it should be administered through an indwelling central venous catheter. Common side effects of epoprostenol therapy include headache, flushing, jaw pain with initial mastication, diarrhea, nausea, a blotchy erythematous rash, and musculoskeletal aches and pain (predominantly involving the legs and feet). These tend to be dose dependent and often respond to a cautious reduction in dose. Severe side effects can occur with overdosage of the drug. Acutely, overdosage can lead to systemic hypotension. Chronic overdosage can lead to the development of a hyperdynamic state and high output cardiac failure.[21] Abrupt or inadvertent interruption of the epoprostenol infusion should be avoided, because this may lead to a rebound worsening of pulmonary hypertension with symptomatic deterioration and even death. Other complications of chronic intravenous therapy with epoprostenol include line-related infections (which can range from small exit site reactions to tunnel infections and cellulitis to bacteremic infections with sepsis), catheter-associated venous thrombosis, systemic hypotension, thrombocytopenia, and ascites.

The beneficial effects of epoprostenol therapy appear to be sustained for years in many patients with IPAH/PPH. Barst and coworkers[22] reported long-term benefit in a small group of patients from several centers involved in the earliest clinical usage of epoprostenol. Shapiro and colleagues[23] and McLaughlin and associates[24] have described sustained benefit in larger numbers of patients. McLaughlin and associates have reported long-term epoprostenol therapy in 162 patients with IPAH/PPH followed for a mean of 36.3 months.[25] Observed survival with epoprostenol therapy at 1, 2, and 3 years was 87.8%, 76.3%, and 62.8% and was significantly greater than the expected survival of 58.9%, 46.3%, and 35.4% based on historical data.

Treprostinil

Treprostinil, a prostacyclin analog with a half-life of 3 hours, is stable at room temperature. An international, placebo-controlled, randomized trial demonstrated that treprostinil improved exercise tolerance, although the 16-meter median difference between treatment groups in 6-minute walk distance was relatively modest.[26] Treprostinil also improved hemodynamic parameters. Common side effects included headache, diarrhea, nausea, rash, and jaw pain. Side effects related to the infusion site were common (85% of patients complained of infusion site pain and 83% had erythema or induration at the infusion site).

Inhaled Iloprost

Iloprost is a chemically stable prostacyclin analog, with a serum half-life of 20 to 25 minutes.[27] In IPAH/PPH, acute inhalation of iloprost resulted in a more potent pulmonary vasodilator effect than acute nitric oxide inhalation.[28,29] In uncontrolled and controlled studies of iloprost for various forms of PAH,[30-32] inhaled iloprost at a total daily dose of 30 to 200 μg divided in 6 to 12 inhalations improved functional class, exercise capacity, and pulmonary hemodynamics for periods up to 1 year of follow-up. The treatment was generally well tolerated except for mild coughing, minor headache, and jaw pain in some patients. The most important drawback of inhaled iloprost is the relatively short duration of action, requiring the use of 6 to 9 inhalations a day.

Beraprost

Beraprost sodium is an orally active prostacyclin analog[33] that is absorbed rapidly in fasting conditions. It has been evaluated in peripheral vascular disorders such as intermittent claudication,[34] Raynaud's phenomenon, and digital necrosis in systemic sclerosis,[35] with variable results. Although several small open uncontrolled studies reported beneficial hemodynamic effects with beraprost in patients with IPAH/PPH,[33,36,37] two randomized, double-blind, placebo-controlled trials have shown only modest improvement and suggest that beneficial effects of beraprost may diminish with time.[38,39]

Endothelin Receptor Antagonists

Endothelin-1 is a vasoconstrictor and a smooth muscle mitogen that may contribute to the pathogenesis of PAH.[40] Endothelin-1 expression, production, and concentration in plasma[41,42] and lung tissue[43] are elevated in patients with PAH, and these levels are correlated with disease severity.[43]

Bosentan

Bosentan is a dual endothelin receptor blocker that has been shown to improve pulmonary hemodynamics and exercise tolerance and delay the time to clinical worsening in PAH patients falling into NYHA Classes III and IV.[44,45] The most frequent and potentially serious side effect with bosentan is dose-dependent abnormal hepatic function (as indicated by elevated levels of alanine aminotransferase and/or aspartate aminotransferase). Because of the risk of potential hepatoxicity, the FDA requires that liver function tests be performed at least monthly in patients receiving this drug. Bosentan may also be associated with the development of anemia, which is typically mild: hemoglobin/hematocrit should be checked regularly.

Phosphodiesterase Inhibitors

Phosphodiesterases (PDEs) are enzymes that hydrolyze the cyclic nucleotides, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), and limit their intracellular signaling. Drugs that selectively inhibit cGMP-specific PDEs (or type 5, PDE5 inhibitors) augment the pulmonary vascular response to endogenous or inhaled nitric oxide in models of pulmonary hypertension.[46-52] PDE5 is strongly expressed in the lung, and *PDE5* gene expression and activity are increased in chronic pulmonary hypertension.[53,54]

Dipyridamole

Early studies demonstrated that dipyridamole can lower pulmonary vascular resistance (PVR), attenuate hypoxic pulmonary vasoconstriction, decrease pulmonary hypertension, and, at least in some cases, augment or prolong the effects of inhaled nitric oxide in children with pulmonary hypertension.[51,55] Some patients who failed to respond to inhaled nitric oxide responded to the combination of inhaled nitric oxide plus dipyridamole.[51]

Sildenafil

Sildenafil is a potent specific PDE5 inhibitor that is approved for erectile dysfunction. Recent reports have shown that sildenafil blocks acute hypoxic pulmonary vasoconstriction in healthy adult volunteers[56] and acutely reduces PAPm in patients with PAH.[57] In comparison with inhaled nitric oxide, sildenafil produced similar reductions in PAPm; but unlike nitric oxide, sildenafil also had apparent systemic hemodynamic effects.[57,58] When combined with inhaled nitric oxide, sildenafil appears to augment and prolong the effects of inhaled nitric oxide.[57,58] As observed with dipyridamole, sildenafil appears to prevent rebound pulmonary vasoconstriction after acute withdrawal of inhaled nitric oxide.[59] Several nonrandomized, single-center studies suggest promise in PAH with chronic sildenafil.[60-63] Appropriately designed randomized clinical trials are needed and are in progress. Sildenafil treatment in animal models with experimental lung injury reduced PAP, but gas exchange worsened owing to impaired ventilation-perfusion mismatch.[64,65] Accordingly, caution is advised when using sildenafil to treat pulmonary hypertension in patients with severe lung disease.

Nitric Oxide

Nitric oxide contributes to maintenance of normal vascular function and structure. It is particularly important in normal adaptation of the lung circulation at birth, and impaired nitric oxide production may contribute to the development of neonatal pulmonary hypertension.[66,67] L-Arginine is the sole substrate for nitric oxide synthase and thus is essential for nitric oxide production.

Inhaled Nitric Oxide

Inhaled nitric oxide has been shown to have potent and selective pulmonary vasodilator effects during brief treatment of adults with IPAH/PPH.[28] It is a potent pulmonary vasodilator in newborns with pulmonary hypertension (PPHN), children with congenital heart disease, and patients with postoperative pulmonary hypertension, acute respiratory distress syndrome, or undergoing lung transplantation.[68] It is of substantial benefit in PPHN, decreasing the need for support with extracorporeal membrane oxygenation (ECMO).[69,70] Although inhaled nitric oxide has been used in diverse clinical settings, especially in intensive care medicine, FDA approval for this therapy is limited to newborns with hypoxemic respiratory failure at this time.

In chronic PAH, the use of inhaled nitric oxide has been primarily for acute testing of pulmonary vasoreactivity during cardiac catheterization (see earlier) or for acute stabilization of patients during deterioration. Pulsed delivery of inhaled NO has been shown to lower PVR in some patients,[71] and experience with the use of chronic inhaled nitric oxide therapy in children and adults with PAH has been described[72] but is quite limited. Work is needed to determine whether chronic inhaled nitric oxide in the ambulatory setting is safe, acceptable, feasible, and effective.

LUNG TRANSPLANTATION

Lung transplantation for PAH is generally reserved for patients whose condition is failing despite the best available medical therapy. Whereas lung transplantation is challenging in general, it is even more so in the group of patients with PAH.[73] Worldwide, overall survival is approximately 77% at 1 year and 44% at 5 years.[74] Survival in PAH patients undergoing lung transplantation is 66% to 75% at 1 year (one center has reported 1- and 5-year actuarial survival of 75% and 57%, respectively).[75] The higher early mortality in PAH patients may be related to higher anesthetic and operative risks, the need for cardiopulmonary bypass,[76] and the increased occurrence of postoperative reperfusion pulmonary edema in patients with PAH undergoing single lung transplantation. In this situation, reperfusion pulmonary edema may be aggravated by the increased blood flow to the newly engrafted lung. In addition, ventilation-perfusion mismatching can be particularly severe.[77] Most centers therefore seem to prefer bilateral lung transplantation for patients with PAH.[78] The timing of transplantation in PAH is challenging. It is probably most useful in patients showing clear evidence of deterioration, such as decline in functional capacity and the development of right-sided heart failure, despite maximal medical therapy.

SPECIAL SITUATIONS IN THE ICU

DEEP VENOUS THROMBOSIS PROPHYLAXIS

Patients with PAH are likely at increased risk for the occurrence of deep venous thrombosis (DVT) and are certainly at increased risk for poor outcomes as a consequence of the development of DVT. Patients with PAH are prone to a more sedentary lifestyle and to chronic venous congestion of the lower extremities owing to increased right-sided cardiac filing pressures. Hospitalization in the ICU, often with discontinuation of anticoagulation in anticipation of invasive procedures, likely places these patients at even higher risk for DVT. For these reasons, meticulous attention must be paid to DVT prophylaxis.

PROCEDURES AND SURGERY

Procedures and surgery in patients with PAH can be associated with substantially increased operative and perioperative risks, and appropriate precautions should be undertaken to optimize outcomes. As always, careful consideration should be given to whether an invasive procedure is absolutely necessary.

Vasovagal Events

Patients with severe PAH are particularly prone to vasovagal events, which can lead to severe consequences, including syncope, cardiopulmonary arrest, and death. Pain, nausea, vomiting, or even a bowel movement can lead to a vasovagal event in patients with severe PAH. Cardiac output may be particularly dependent on heart rate in this situation, and the bradycardia and systemic vasodilatation that accompany a vasovagal event can therefore result in an abrupt decrease in systemic arterial pressure. Patients should therefore have close monitoring of their heart rate during invasive procedures, with ready availability of atropine or a similar agent.

Avoidance of Hypoxemia and Hypercarbia

Hypoxemia and hypercarbia are both pulmonary vasoconstrictors and can contribute to the worsening of pulmonary hypertension. Oversedation can lead to ventilatory insufficiency and precipitate clinical deterioration. Caution should be utilized in laparoscopic procedures in which carbon dioxide is used for abdominal insufflation, because absorption can lead to hypercarbia. The induction of anesthesia and intubation for surgical procedures can be a particularly high-risk time for patients with PAH, because they are at risk for vagal events, hypoxemia, hypercarbia, and shifts in intrathoracic pressure with associated changes in cardiac filling pressures.

PREGNANCY

The hemodynamic changes in pregnancy are substantial, and volume shifts occur immediately post partum, with cardiac filling pressures increasing as a result of decompression of the vena cava and the return of uterine blood into the systemic circulation. The changes induced by pregnancy impose a significant hemodynamic stress in women with IPAH/PPH, leading to an estimated 30% to 50% mortality rate.[79,80] A meta-analysis of the outcome of pulmonary vascular disease and pregnancy reported a maternal mortality rate of 36% in Eisenmenger's syndrome, 30% in IPAH/PPH, and 56% in secondary pulmonary hypertension.[80] Because of high maternal and fetal morbidity and mortality rates, most experts recommend effective contraception and early fetal termination in the event of pregnancy.[81] There have been case reports of successful treatment of pregnant IPAH/PPH patients with chronic intravenous epoprostenol,[82-85] inhaled nitric oxide,[86-88] and oral calcium channel blockers.[89] In general, management includes early hospitalization for monitoring, supportive therapy with cautious fluid management, supplemental oxygen, diuretics, and dobutamine, as needed. The use of a pulmonary artery catheter for close hemodynamic monitoring and for titration of vasodilator and cardiotonic therapy has been recommended. Recommendations regarding mode of delivery remain controversial.

PORTOPULMONARY HYPERTENSION

Patients with chronic liver disease have an increased prevalence of pulmonary vascular disease.[90,91] Two forms of pulmonary vascular disease can complicate chronic liver disease: the hepatopulmonary syndrome and portopulmonary hypertension. Both tend to occur in patients with chronic, late-stage liver disease, and each may increase the risk associated with liver transplantation.

Hypoxemia and intrapulmonary shunting characterize the hepatopulmonary syndrome. Shunting may be manifest echocardiographically by the late appearance (after three to five cardiac cycles) of bubble contrast in the left side of the heart. Treatment is generally supportive, with supplemental oxygen. The syndrome may improve in some patients after liver transplantation. Severe hepatopulmonary syndrome may increase the risk associated with undergoing liver transplantation.

Portopulmonary hypertension occurs in patients with chronic, late-stage liver disease and/or portal hypertension.[92-98] Portopulmonary hypertension often differs hemodynamically from IPAH/PPH, and these differences may affect the approach to therapy. Patients with portopulmonary hypertension have lower pulmonary arterial diastolic and mean pressures, higher cardiac outputs, and lower pulmonary and systemic resistances.[92] Later-stage patients may develop hemodynamic findings more similar to those of patients with IPAH/PPH, and this group may have a poorer prognosis and be at higher risk with attempted liver transplantation. It is occasionally possible to make a borderline candidate for liver transplantation an acceptable one through aggressive treatment of the PAH. Supplemental oxygen should be used as needed to maintain saturations greater than or equal to 91% at times. Diuretic therapy should be utilized to control volume overload, edema, and ascites. Anticoagulant therapy has not been carefully studied in this population and should probably be avoided in patients with significant coagulopathy due to impaired hepatic synthetic capability and in patients at increased risk of bleeding due to gastroesophageal varices. There have been a number of case reports and small case series describing the use of intravenous epoprostenol for treatment of portopulmonary hypertension.[99-103] Interestingly, some patients may demonstrate improvement in their pulmonary hypertension after liver transplantation.[104] Other patients may develop worsening of their pulmonary hypertension well after transplantation. It may be possible to wean an occasional patient off epoprostenol after liver transplantation. This should probably be done very gradually, under

close observation. The development of increasing dyspnea, fluid retention, or fatigue should prompt reevaluation and reinstitution of epoprostenol if necessary. Because of its potential for hepatoxicity, most experts would likely recommend avoiding the oral endothelin antagonist bosentan in this population.

ANNOTATED REFERENCES

Barst RJ, et al: A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. N Engl J Med 1996;334:296-302.

This prospective, multicenter, randomized, and controlled trial showed that chronic therapy with intravenous epoprostenol improved exercise capacity, cardiopulmonary hemodynamics, and survival in patients with IPAH/PPH.

Fuster V, et al: Primary pulmonary hypertension: Natural history and the importance of thrombosis. Circulation 1984;70:580-587.

This early study suggested that anticoagulation with warfarin improved survival in patients with IPAH/PPH.

Lane KB, et al: Heterozygous germline mutations in *BMPR2*, encoding a TGF-beta receptor, cause familial primary pulmonary hypertension. The International PPH Consortium. Nat Genet 2000;26:81-84; and Deng Z, et al: Familial primary pulmonary hypertension (gene *PPH1*) is caused by mutations in the bone morphogenetic protein receptor-II gene. Am J Hum Genet 2000;67:737-744.

These seminal papers report that mutations in the BMPR2 gene, encoding a TGF-beta receptor, cause familial IPAH/PPH. This important discovery may provide critical insight into the mechanisms underlying the development of IPAH/PPH and ultimately lead to better-targeted and more effective therapy.

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This study showed that a subset of patients with IPAH/PPH demonstrate vasoreactivity and will respond to chronic therapy with oral calcium channel blockers. It also supported the concept that anticoagulation with warfarin may improve survival in IPAH/PPH.

Rubin LJ, et al: Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896-903.

This international, prospective, multicenter, randomized, placebo-controlled, double-blind trial showed that endothelin receptor blockade with bosentan improved exercise capacity in patients with IPAH/PPH and PAH occurring in association with collagen vascular disease.

Chapter 82

PLEURAL DISEASE IN THE INTENSIVE CARE UNIT

John T. Huggins • Dov Weissberg • Steven A. Sahn

KEY POINTS

1. Ultrasonography is an emerging diagnostic tool in the management of pleural complications in the ICU. Pleural ultrasound has a sensitivity of 84%, a specificity of 100%, and 94% accuracy in detecting a pleural effusion. **Use of ultrasonography during thoracentesis increased the rate of accurate site location in 26% of cases and prevented the possibility of accidental organ puncture in 10% of cases.**
2. Approximately 50% of patients develop small unilateral or bilateral pleural effusions 24 to 48 hours after abdominal surgery. These effusions generally resolve spontaneously and do not require diagnostic thoracentesis. Loculation and persistent fever may mandate a diagnostic thoracentesis to exclude infection.
3. **Congestive heart failure (CHF) is the most common cause of all transudative pleural effusions.** Increase in pulmonary venous pressure is the mechanism responsible for pleural fluid formation in CHF. Therapy for CHF-related pleural effusions consists of decreasing preload and afterload and improving cardiac output.
4. **Pleural effusions are commonly observed with pancreatitis.** The pathogenesis of pleural fluid formation in acute pancreatitis involves the transdiaphragmatic passage of amylase-rich fluid as well as increased capillary permeability mediated by the release of inflammatory cytokines. In acute pancreatitis, the pleural effusion is small to moderate and on the left side in 60%. Chronic pancreatic effusions result from pancreatic duct disruption and fistula formation into the pleural space. These are large to massive, unilateral, left-sided effusions that recur rapidly after therapeutic thoracentesis. Fifty percent will resolve spontaneously, whereas the other half require surgery.
5. **Small left-sided pleural effusions after coronary artery bypass surgery (CABG) are universally present in the immediate postoperative course.** Some patients after CABG may develop a moderate to large hemorrhagic pleural effusion associated with internal mammary artery harvesting. Infrequently, a trapped lung can develop months after CABG.
6. **Esophageal rupture carries a significant morbidity and mortality risk and requires a timely diagnosis** so that appropriate therapy can be instituted. Disruption of the mediastinal pleura in effect will create an anaerobic empyema. The presence of food particles and squamous epithelial cells on cytologic examination confirms the diagnosis of esophageal rupture. **When surgical closure is performed in the first 24 hours, survival exceeds 90%.**
7. **Hemothorax can be differentiated from a bloody pleural effusion by arbitrarily defining hemothorax with a hematocrit or red blood cell count that is 50% or more of the peripheral blood hematocrit or red blood cell count.** The treatment of a hemothorax involves volume expansion, correction of coagulopathy, and pleural space drainage with a large-bore chest tube. Guidelines for surgical management of a hemothorax include initial drainage exceeding 1500 mL, continued bleeding of more than 200 mL/h for 2 to 4 hours, or ongoing hemodynamic instability despite aggressive volume resuscitation.
8. **Pleural effusions occur in approximately 6% of patients with cirrhosis and clinical ascites.** Hepatic hydrothorax presents as a right-sided pleural effusion in 85% of patients. An important complication of a hepatic hydrothorax is the development of spontaneous bacterial empyema (SBE). The clinical criterion for the diagnosis of SBE is similar to that established for spontaneous bacterial peritonitis (SBP); however, it is important to exclude pneumonia before making the diagnosis of SBE. Antibiotic therapy alone is sufficient for treatment of SBE.
9. **Approximately 50% of patients with pulmonary embolism develop a pleural effusion.** Pleural fluid formation is the result of ischemia leading to increased pleural capillary permeability, pulmonary infarction, or atelectasis. With pulmonary infarction, more than 80% will have a hemorrhagic exudative pleural effusion. The presence of a bloody pleural effusion is not a contraindication to full dose anticoagulation.
10. **Postcardiac injury syndrome (PCIS) is characterized by fever, pleuropericarditis, and pulmonary**

infiltrates within days to weeks after traumatic insult to the pericardium or myocardium. The incidence of PCIS after myocardial infarction is 4% and is up to 30% after cardiac surgery. The detection of antimyocardial antibodies in the pleural fluid can assist in discriminating PCIS-related pleural effusion from other exudates.

11. **The radiographic sign of pneumothorax in the supine patient differs from an erect view in which the visceral pleural line is visualized.** In the supine patient, pneumothorax gas migrates along the anterior surface of the lung, requiring careful inspection of the base, lateral chest wall, and juxtacardiac areas.
12. **The detection of a pneumothorax in a patient receiving positive-pressure ventilation mandates placement of a chest tube to prevent the development of a tension pneumothorax.** A tension pneumothorax usually presents as an acute cardiopulmonary emergency, beginning with respiratory distress; and if unrecognized and untreated, it can lead to cardiovascular collapse and death.

Pleural disease as a primary reason for admission to the ICU is relatively uncommon. These instances include unilateral or bilateral large pleural effusions causing respiratory failure, hemothorax requiring intensive monitoring for rate of bleeding and hemodynamic status, empyema with associated sepsis, and secondary spontaneous pneumothorax causing respiratory insufficiency and tension physiology. Pleural complications of diseases and procedures performed in the ICU are common and may even be overlooked in the critically ill patient; they are often overshadowed by the major presenting illness that is the reason for admission to the ICU.

The detection of pleural effusion or pneumothorax in the critically ill patient is often a subtle finding on clinical examination and even on chest radiography. A pleural effusion may not be seen on the supine chest radiograph because a diffuse alveolar infiltrate may silhouette the posterior layering of pleural fluid; the effusion may be misinterpreted by the physician as an underexposed film or attributed to objects outside the chest. Pneumothorax may not be detected in the supine patient because pleural air is situated anteriorly and will not produce the diagnostic visceral pleural line seen on upright radiographs. When a pneumothorax develops in the setting of positive-pressure ventilation, it can be a life-threatening event, and appropriate action should be taken without delay to prevent a tension pneumothorax.

RADIOLOGIC SIGNS OF PLEURAL EFFUSION

STANDARD CHEST RADIOGRAPH

In the normal pleural space, air and fluid distribute according to gravitational effects. Air accumulates in the apex and superior portion of the lung, whereas fluid accumulates between the inferior margin of the lung and the diaphragm on erect radiographs. In the critically ill patient, radiographs are often taken in the supine or semi-erect positions, thereby changing the radiographic appearance of free pleural fluid and air.

In the supine position, the radiolucency of the lung base is equal to or greater than that of the lung apex owing to the anteroposterior diameter of the lung apex being greater than the lung base. Furthermore, lateral displacement of breast and pectoral tissue in the supine patient generates increased radiolucency. A pleural effusion is suspected on supine radiographs when there is an increased homogeneous density over the lower lung fields compared with the upper lung fields. This radiographic appearance can be mimicked by patient rotation, absent pectoral muscle, previous lobectomy or mastectomy, scoliosis, hypoplastic pulmonary artery, and pleural or chest wall mass.[1]

On an erect chest radiograph 175 to 525 mL of pleural fluid will produce blunting of the costophrenic angle.[2] This quantity of pleural fluid can be detected on a supine chest radiograph as a homogeneous density over the lower lung zone. An inability to visualize the hemidiaphragm and apical capping is likely to be seen in pleural effusions of at least 500 mL.[3] The major radiographic finding of a pleural effusion on supine radiographs is an increased homogeneous density in the lower lung zone; until the effusion is large, this density does not obliterate the normal bronchovascular markings, demonstrate air bronchograms, or produce hilar or mediastinal displacement (Fig. 82-1). Obtaining an erect or lateral decubitus radiograph may be helpful to confirm the presence of a suspected pleural effusion seen on a supine chest radiograph (Table 82-1).

A common and often problematic diagnostic dilemma is the differentiation of an empyema from a lung abscess. Radiographic clues that are helpful in making this differentiation include the following[4]:

- Bronchovascular markings are displaced by an empyema and obliterated by a lung abscess.
- An empyema crosses major lobar boundaries, whereas a lung abscess conforms to segmental or lobar boundaries.
- An empyema forms an obtuse angle and a lung abscess forms an acute angle with the chest wall.

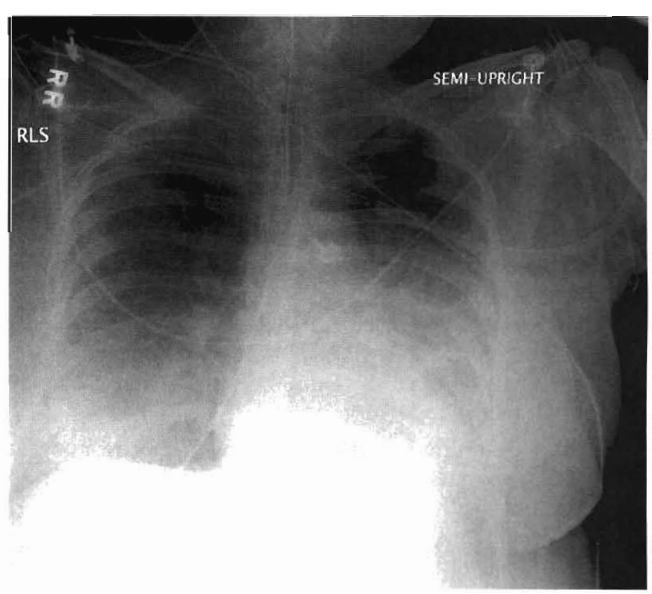

FIGURE 82–1. A semi-upright anteroposterior chest radiograph shows bilateral alveolar infiltrates and pleural fluid veiling consistent with pleural effusions.

TABLE 82–1. RADIOGRAPHIC SIGNS OF PLEURAL EFFUSION AND PNEUMOTHORAX IN THE SUPINE PATIENT

Pleural Effusion	Pneumothorax
<500 mL fluid (small)	Hyperlucency in anteromedial and subpulmonic recesses (64%)
Homogeneous density over lower lung zone	Visualization of visceral pleural line (rare)
Veil appearance to lung	Deep sulcus sign
Lung markings not obliterated	*Tension pneumothorax*
Air bronchograms absent	Increased volume of hemithorax
500 to 1000 mL fluid (moderate)	Depression of hemidiaphragm
Silhouetting of diaphragm	Widening of intercostal spaces
Apical capping	Contralateral tracheal deviation
1000 to 3000 mL fluid (large)	
Silhouetting of diaphragm	
(±) Contralateral mediastinal shift	
>3000 mL fluid (massive)	
Opacification of the hemithorax	
Contralateral mediastinal shift	

- A lung abscess has a spherical shape and equal length of the air-fluid level in both frontal and lateral views, whereas the air-fluid level of an empyema is longer in one of the two projections.
- The air-fluid level of an empyema extends to the periphery of the lung.
- The edge of a lung abscess tends to be indistinct from the surrounding lung, whereas the edge of an empyema is sharply defined.

Because of concomitant parenchymal lung disease in the critically ill patient, the identification of a pleural effusion can be problematic. Therefore, the utilization of more sensitive diagnostic modalities—ultrasonography and computed tomography (CT)—can confirm the presence of a pleural effusion.

COMPUTED TOMOGRAPHY

CT is helpful in assessing the pleural process in the critically ill patient and has several advantages over a standard chest radiograph. CT provides better resolution of both parenchymal abnormalities and evaluation of the cardiomediastinal structures and distinguishes pleural from parenchymal abnormalities.[1] On CT, free-flowing pleural fluid produces a sickle-shaped opacity in the most dependent portion of the thorax.[5] Loculated pleural fluid collections are seen as lenticular or round opacities in a fixed position. CT may also be helpful in the diagnosis and management of loculated pleural collections.[6,7] A reliable CT sign for an empyema is the "split pleura" sign.[6] After the administration of intravenous contrast medium, both the parietal and visceral pleura will be thickened and will demonstrate contrast medium enhancement around the fluid collection. The extrapleural fat between the empyema and the chest wall may be increased.[6-9] The "split pleura" sign is seen in up to 68% of patients presenting with an empyema and is usually identified during the organizing late phase.[7]

ULTRASONOGRAPHY

Pleural-based opacities on chest radiographs are often diagnostically problematic. If the opacity is free flowing on decubitus films, one can be certain of the presence of a pleural effusion. However, in the absence of mobility, the differential diagnosis includes a loculated pleural effusion, consolidated lung, pleural thickening, atelectasis, or consolidated lung. Real-time ultrasonography is a sensitive tool in distinguishing these diagnostic possibilities.

The advantages of chest sonography compared with CT are decreased time consumption, less expense, and greater convenience; for example, chest sonography allows critically ill patients to be evaluated at bedside rather than being transported to the CT scanner. The disadvantages of chest sonography include strong dependence on the operator expertise; inhibition of air artifact in the evaluation of thoracic structures being studied; inferior evaluation of the lung parenchyma compared with CT; and restricted field of view owing to the bony structures of the thoracic cage.[10]

Pleural ultrasound in the detection of pleural effusion has a sensitivity of 84%, a specificity of 100%, and 94% accuracy.[11] The diagnosis of pleural fluid on sonography can be made with certainty when any dynamic sign during respiration is visualized, such as change in shape of the collection, flapping movements of the edge of the lung, undulating movements of fibrinous strands, or swirling motion of debris within a hypoechoic space.

The value of chest ultrasonography to clinical examination for diagnostic thoracentesis has been studied: it prevented the possibility of accidental organ puncture in 10% of cases and increased the rate of accurate site location in 26% of cases. These findings were independent of physician experience in performing the physical examination.[12] It is clear that ultrasonography is an emerging diagnostic tool that can increase patient safety during invasive procedures, such as thoracentesis, and can positively affect patient management and outcome.[10]

PLEURAL EFFUSIONS

Refer to Table 82-2 for a list of the pleural effusions commonly seen in the ICU. Table 82-3 lists the differential diagnosis of pleural effusions in the ICU.

ABDOMINAL SURGERY

Approximately 50% of patients develop small unilateral or bilateral pleural effusions 24 to 48 hours after

TABLE 82–2. LIST OF COMMON CAUSES OF PLEURAL EFFUSIONS IN THE ICU

Medical ICU	Surgical ICU
Atelectasis	Atelectasis
Congestive heart failure	Congestive heart failure
Pneumonia	Duropleural fistula
Hypoalbuminemia	Pneumonia
Pancreatitis	Pancreatitis
ARDS	Hypoalbuminemia
Pulmonary embolism	Coronary artery bypass surgery
Hepatic hydrothorax	ARDS
Esophageal sclerotherapy	Pulmonary embolism
Postmyocardial infarction	Esophageal rupture
Iatrogenic	Hemothorax
	Chylothorax
	Abdominal surgery
	Iatrogenic

TABLE 82–3. DIFFERENTIAL DIAGNOSIS OF PLEURAL EFFUSIONS IN THE ICU

	Clinical Features	Chest Radiograph	Pleural Fluid Analysis	Diagnosis	Comments
Transudates					
CHF	Usual signs and symptoms plus I > O, weight gain, worsening $(P_A\text{-}a)O_2$, $\downarrow C_{ST}$	Bilateral effusions, R > L, cardiomegaly, extravascular lung water	Serous, nucleated cells < 1000/μL, lymphocytes, mesothelial cells, pH 7.45-7.55	Presumptive	Associated with ↑ PCWP, acute diuresis may result in an exudate
Atelectasis	Asymptomatic or dyspnea, worsening $(P_A\text{-}a)O_2$	Small unilateral or bilateral effusions, volume loss	Serous, nucleated cells < 1000/μL, lymphocytes, mesothelial cells, pH 7.45-7.55	Presumptive	Common after upper abdominal surgery, also with PE, mucus plug
Hepatic hydrothorax	Stigmata of liver disease, clinical ascites, asymptomatic or dyspnea, worsening $(P_A\text{-}a)O_2$, poor response to low-flow O_2	Unilateral R or bilateral effusions, small to massive, normal heart size, no other CXR abnormalities	Serous-serosanguineous nucleated cells < 1000/μL, lymphocytes, mesothelial cells, pH 7.40-7.55	Presumptive PF protein and LDH similar to ascitic fluid	6% of patients with clinical ascites, fluid movement from abdomen to chest via diaphragm defect
Hypo-albuminemia	Asymptomatic or dyspnea, anasarca	Small to moderate bilateral effusions, normal heart size, no other CXR abnormalities	Serous, nucleated cells < 1000/μL, lymphocytes, mesothelial cells, pH 7.45-7.55	Presumptive	Serous albumin < 1.5 g/dL, never have isolate pleural effusion
Iatrogenic: extravascular migration of central venous catheter	Chest pain, dyspnea	Abnormal position of catheter, widening of mediastinum, small to large unilateral effusion	Serous-hemorrhagic, may contain PMNs, chemistries similar to infusate, PF/S glucose > 1.0	Presumptive	Highest incidence with L external jugular vein placement, aspiration or retrograde flow of blood confirms intravascular placement
Exudates					
Para-pneumonic effusions: uncomplicated	Fever, chest pain, ↑WBC, purulent sputum	New alveolar infiltrate, moderate to large ipsilateral free-flowing effusion	Turbid, PMNs, glucose > 60 mg/dL, LDH < 700 IU/L, pH ≥ 7.30	Presumptive	Effusion resolves without sequelae on antibiotics only
Para-pneumonic effusion: complicated	Fever, chest pain, ↑WBC, purulent sputum	New alveolar infiltrate, moderate to large ipsilateral effusion with or without loculation	Pus, positive bacteriology, pH < 7.10, glucose < 40 mg/dL, LDH > 1000 IU/L	Based on PFA, positive bacteriology, aspiration of pus, loculation	Putrid odor, anaerobic empyema, requires pleural space drainage for resolution
Pancreatitis	Acute abdominal pain, nausea, vomiting, fever	Small, unilateral, L effusion (60%), atelectasis	Turbid, nucleated cells 10,000-50,000 /μL PMNs, pH 7.30-7.35, PF/S amylase > 1.0	PF/S amylase > 1.0 or > upper limits of normal for serum	Effusion resolves as pancreatitis resolves without need for pleural space drainage
Pulmonary embolism	Acute dyspnea, tachypnea, chest pain, ↑ $(PA\text{-}a)O_2$	Unilateral, small to moderate effusion, peripheral infiltrate atelectasis	Serous-bloody nucleated cells 100-50,000/μL, PMNs or lymphocytes	Presumptive	20% transudates, effusion present on admission, reaches maximum by 72 h
Postcardiac injury syndrome	Chest pain, pericardial rub, fever, dyspnea 3 days to 3 wk after cardiac injury, ↑ WBC, ↑ ESR	L or bilateral small to moderate effusion, L lower lobe infiltrates	Serosanguineous-bloody, nucleated cells 500-39,000/μL, PMNs or lymphocytes, pH > 7.30	Presumptive	Effusion resolves in 1-3 wk, may require steroids
Esophageal sclerotherapy	Chest pain after sclerotherapy with large sclerosant volume, effusion appears by 48-72 h	Small, unilateral or bilateral effusion	Serous-sanguineous, nucleated cells 100-38,000/μL, PMNs or mononuclear, pH > 7.30	Presumptive	Requires no specific therapy, resolves over days to weeks
ARDS	Depends on cause	Bilateral alveolar infiltrates tend to mask small bilateral effusions	Serous-serosanguineous, PMNs	Presumptive	Requires no specific therapy, effusions resolve as ARDS resolves
Spontaneous esophageal rupture	Severe retching or vomiting followed by thoraco-abdominal pain, fever, subcutaneous air	Subcutaneous/mediastinal air; L pneumothorax, followed by L effusion	Early: serous, pH > 7.30; later: turbid-purulent effusion, PMNs, pH approaches 6.00, ↑ amylase	Pleural fluid pH < 7.00, with ↑ salivary amylase and positive bacteriology	With early diagnosis prognosis good with primary closure and drainage

TABLE 82–3. DIFFERENTIAL DIAGNOSIS OF PLEURAL EFFUSIONS IN THE ICU—CONT'D

	Clinical Features	Chest Radiograph	Pleural Fluid Analysis	Diagnosis	Comments
Hemothorax	After blunt and penetrating chest trauma, invasive procedures, malignancy, anticoagulation	Small to massive unilateral effusion, other abnormalities depending on cause of hemothorax	Gross blood, PF/blood Hct > 50%	PF/blood Hct > 50%	Often not appreciated on initial radiograph in setting of trauma; should be drained with chest tube
Coronary artery bypass graft	Asymptomatic, dyspnea	Small to moderate L effusion without parenchymal infiltrates, L lower lobe atelectasis, elevation of L hemidiaphragm	Hemorrhagic PF/blood Hct 5%, nucleated cells < 10,000/μL, pH > 7.40	Presumptive	May require weeks for resolution, rarely results in trapped lung
Abdominal surgery	Asymptomatic 48-72 h after upper abdominal surgery	Small bilateral effusions, atelectasis	Serous nucleated cells < 10,000/μL, pH usually > 7.40	Presumptive	Larger L effusions following splenectomy Most commonly found with atelectasis and diaphragmatic irritation, resolves spontaneously
Chylothorax (traumatic)	Asymptomatic or dyspnea after Intrathoracic surgery, especially coarctation and esophagectomy	Small to massive L, R, or bilateral effusion	Milky, fluid, nucleated cells < 7,000/μL almost all lymphocytes, pH 7.40-7.80, ↑ triglycerides	Triglycerides > 110 mg/dL chylomicrons on lipoprotein electrophoresis	Defect in thoracic duct frequently closes spontaneously with tube drainage, minimizing chyle formation

ARDS, acute respiratory distress syndrome; CXR, chest radiograph; ESR, erythrocyte sedimentation rate; I, input; L, left; LDH, lactate dehydrogenase; O, output; PCWP, pulmonary capillary wedge pressure; PF, pleural fluid; PFA, pleural fluid acidosis; PF/S, pleural fluid/serum; PMN, polymorphonuclear leukocyte; R, right; WBC, white blood cell.

Adapted from Sahn SA: Pleural disease in the critically ill patient. In Irwin RS, Cerra FB, Rippe JM (eds): Intensive Care Medicine, 4th ed. Philadelphia, Lippincott-Raven, 1999, pp 714-715.

abdominal surgery.[13-15] The incidence is higher with upper abdominal surgery, preexisting ascites, and concomitant atelectasis.[14] Large, left-sided pleural effusions can occur after splenectomy.[14] The effusions are exudative with normal glucose levels, pH greater than 7.40, and less than 10,000 nucleated cells/μL.[14] These pleural effusions generally resolve spontaneously and do not require diagnostic thoracentesis. Loculation and persistent fever may mandate a diagnostic thoracentesis to exclude the presence of an empyema.

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

The presence of pleural effusions in the setting of ARDS has not been well appreciated. In a retrospective study of 25 patients with ARDS, 36% were found to have pleural effusions.[16] All patients had extensive alveolar pulmonary edema and endotracheal fluid that was compatible with increased permeability pulmonary edema. Several experimental models of increased permeability pulmonary edema have been shown to produce pleural effusions.[17-19] Based on these animal models, it appears that the pleura acts as a reservoir for excess lung water in both increased capillary permeability and hydrostatic pulmonary edema. Pleural effusions in the setting of ARDS are clinically underdiagnosed because they are often masked by diffuse alveolar infiltrates. Experimentally, the effusion is serous to serosanguineous, with a predominance of neutrophils.[19] The effusions diminish as ARDS resolves and require no specific therapy.

ATELECTASIS

Atelectasis is a common cause of small pleural effusions in comatose, immobile patients in the ICU.[20] Other causes of atelectasis include abdominal surgery, bronchial obstruction from a mucus plug, malignancy, and foreign body. The mechanism by which atelectasis causes pleural fluid formation is related to decreased pleural pressure. With alveolar collapse, the lung and chest wall separate, creating local areas of decreased pleural pressure. A hydrostatic gradient is created, favoring the movement of fluid, presumably from the parietal pleural surface into the pleural space. The fluid accumulates until equilibrium is established between the parietal pleura, the interstitial space, and the intrapleural environment.[21]

Pleural fluid from atelectasis is a serous transudate; glucose concentration is equivalent to serum with a low number of mononuclear cells and a pH range from 7.45 to 7.55. Once the atelectasis resolves, the pleural fluid dissipates over several days.

CHYLOTHORAX

A chylothorax is defined by the accumulation of chyle in the pleural space. The three major mechanisms of chylothorax formation include disruption of the thoracic duct, extravasation from pleural lymphatics, or transdiaphragmatic flow from chylous ascites.[22,23] Lymphoma is the most common cause of chylothorax, accounting for 37% of chylothoraces in a series of 191 patients.[24] In this series, the second leading

cause of chylothorax was trauma, accounting for 25%. Most of the traumatic chylothoraces were related to surgical procedures. The incidence of chylothorax after cardiothoracic surgery is reported to be 0.36% to 0.42%,[25,26] and after lower neck surgery it is 1.9%.[27] Postoperative chylothorax has been described after virtually every cardiothoracic procedure as well as neck surgery. The highest incidence (4%) of chylothorax has been associated with esophagectomy.[28] Nonsurgical trauma, including blunt or penetrating injuries, can lead to the formation of a chylous pleural effusion. Obstruction of the superior vena cava or left subclavian vein thrombosis from a central venous catheter can produce a chylothorax.[29] Esophageal varices, when treated by sclerotherapy, and translumbar aortography have been reported as rare causes of iatrogenic chylothorax.[30,31]

The patient may be asymptomatic if the effusion is small or dyspneic with a larger effusion. The pleural fluid is usually milky; however, it may be serous, serosanguineous, or even bloody.[32] The pleural fluid typically has less than 7000 nucleated cells/μL and greater than 80% lymphocytes. The pH is alkaline (7.40 to 7.80), and the triglyceride concentration in the pleural fluid exceeds that in serum.[21] Pleural triglyceride levels greater than 110 mg/dL virtually diagnose a chylothorax, whereas triglyceride levels less than 50 mg/dL are usually not chylous. If the pleural fluid triglyceride level is in the intermediate range (50 to 110 mg/dL), then a lipoprotein electrophoresis should be performed to evaluate for the presence of chylomicrons. The presence of chylomicrons establishes that the fluid is a chylothorax.[32]

Up to 2 to 3 L of chyle is produced daily. Severe nutritional depletion and immunodeficiency can result if the losses through the chest tube drainage are not addressed in a timely fashion. The optimal management of a chylothorax remains controversial. The underlying cause, volume, duration of the chylothorax, and the patient's underlying comorbid and nutritional state are important factors in determining the optimal management. Resolution of a chylothorax occurs in the majority of patients with a traumatic chylothorax in 10 to 14 days when managed by a nonsurgical approach, including chest tube drainage, bowel rest, and total parenteral nutrition.[33-35] If the chylothorax fails to resolve with conservative measures, there are several surgical options that can be effective in controlling the chylous leak. These options include pleuroperitoneal shunt, chemical pleurodesis, parietal pleurectomy, percutaneous transabdominal embolization of the thoracic duct, and thoracic duct ligation/repair.[24,36,37]

CONGESTIVE HEART FAILURE

CHF is the most common cause of all transudative pleural effusions; and in one study, it was the leading cause of pleural effusions seen in a medical ICU.[38] The mechanism by which pleural effusions form in CHF is attributed to an increase in pulmonary venous pressure.[39] In a study of 37 patients admitted for CHF, the mean pulmonary capillary wedge pressure was higher in those with pleural effusions compared with those without, 24.1 versus 17.2 mm Hg, respectively.[39] Isolated increases in systemic venous pressure and right atrial pressure are not associated with pleural effusions. Therefore, patients with chronic obstructive pulmonary disease (COPD) and cor pulmonale rarely develop pleural effusions in the absence of left ventricular dysfunction or other causes of transudates or exudates.

For virtually all patients presenting with pleural effusions secondary to CHF, signs and symptoms related to CHF will be present. The chest radiograph will typically demonstrate cardiomegaly with the presence of bilateral, small to moderate-sized pleural effusions. The right-sided pleural effusion is slightly greater than the left. Pulmonary edema is usually present in a perihilar distribution.

Pleural effusions from CHF are transudates with less than 1000 nucleated cells/μL. In up to 38% of patients receiving diuretics, the pleural effusion may develop classic exudative characteristics.[40,41] In the afebrile patient with clinical signs and symptoms of CHF, cardiomegaly, and bilateral pleural effusions (right > left), the diagnosis is secure and observation is warranted. However, in patients who present with fever, pleuritic chest pain, a unilateral effusion, effusions of disparate size, and a larger left-sided effusion, pleural fluid analysis to exclude other causes of the effusion is recommended.

Therapy for CHF-related pleural effusions consists of decreasing preload with diuretics, improving cardiac output with inotropes, and decreasing afterload with optimal blood pressure control. The pleural effusions resolve within days to a few weeks after resolution of the pulmonary edema.

CORONARY ARTERY BYPASS SURGERY

Immediately after CABG, a small left-sided (presumably transudative) pleural effusion is universally present and is associated with left hemidiaphragm elevation and left lower lobe atelectasis. Some patients after CABG may develop moderate to large hemorrhagic pleural effusions.[42] These effusions are associated with internal mammary artery harvesting.[43]

The pleural fluid is an exudate with a low nucleated cell count, glucose level similar to serum, and a pH greater than 7.40. Rarely, a loculated hemothorax may form after CABG and lead to a trapped lung that requires decortication.[44] In these patients with persistent, large bloody pleural effusions and pleural fluid/blood hematocrit less than 50%, a single therapeutic thoracentesis is usually curative if trapped lung is excluded.

Finally, patients undergoing CABG may develop a recurrent, neutrophil predominant, presumably immunologic mediated exudate that is secondary to a postcardiac injury (PCIS). Therapy for these patients consists of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids.[42] Postcardiac injury is discussed later in this chapter.

DUROPLEURAL FISTULA

Duropleural fistula (DPF) develops if there is disruption of the dural membrane and parietal pleura either from trauma or during surgery. Of the 33 reports of DPF documented in medical literature since 1959, 23 resulted from blunt or penetrating trauma, 6 followed thoracotomy, 1 case followed rupture of an intrathoracic meningocele, and 3 followed elective spinal surgery.[45-48]

The pleural fluid characteristics of a DPF vary depending on the cause (traumatic or nontraumatic). In a nontraumatic DPF, the pleural fluid is colorless with a low nucleated cell count, glucose values equivalent to serum, total protein (<1.0 g/dL), and LDH values in the transudative range. Previous authors have described both transudates and exudates with traumatic DPF.[47,48] Because concomitant pleural

processes related to trauma (hemothorax) may be present, the diagnosis of DPF by pleural fluid analysis may be obscured.

Beta$_2$-transferrin is accepted as a specific marker for cerebrospinal fluid leaks. The detection of beta$_2$-transferrin in the pleural fluid establishes the diagnosis of DPF.[49] Confirmation with conventional or radionuclide myelograms to demonstrate a fistula between the subarachnoid and pleural space is advocated if surgery is contemplated.

ESOPHAGEAL RUPTURE

Esophageal rupture carries significant morbidity and a mortality risk and requires a timely diagnosis so that appropriate therapy can be instituted. Esophageal rupture most commonly occurs as a complication of endoscopy and can also be associated with nasogastric/orogastric tube placement, Minnesota tubes, and rarely blunt thoracic trauma. Spontaneous esophageal rupture (Boerhaave's syndrome) after severe retching and vomiting occurs rarely and may initially be clinically silent.[50]

The chest radiograph findings vary depending on the interval between the time of perforation and when the radiograph is obtained, the site of perforation, and the integrity of the mediastinal pleura.[51] Pneumothorax is present in 75% (70% on left, 20% on right, and 10% bilateral) of patients.[52] Pleural effusion with or without pneumothorax occurs in 75%, whereas mediastinal emphysema is seen in approximately 50% of cases.[53]

Pleural fluid characteristics depend on the timing and the integrity of the mediastinal pleura. With an intact mediastinal pleura, pleural fluid is a sterile, serous exudate with a predominance of neutrophils, pleural glucose level equivalent to that of serum glucose, and a pH greater than 7.30.[54] Disruption of the mediastinal pleura in effect will create an anaerobic empyema. Amylase of salivary origin will appear in high concentrations in the pleural fluid.[55] The pleural pH rapidly falls and may approach 6.00 owing to seeding of anaerobic bacteria and neutrophil influx.[54,56] The presence of food particles and squamous epithelial cells on cytologic examination confirms and may obviate the need for radiographic confirmation with an esophagogram.

Spontaneous esophageal rupture dictates early operative intervention. If a primary closure is accomplished in the first 24 hours, greater than 90% survival is noted. Survival is reduced if treatment is not begun until after 24 hours. In conjunction with surgical therapy, pleural and mediastinal drainage, antibiotics, and bowel rest should be promptly instituted.

ESOPHAGEAL SCLEROTHERAPY

Sodium morrhuate and absolute alcohol are sclerotherapeutic agents used in the treatment of esophageal varices and are common causes of pleural effusions. The reported incidence of pleural effusions with the use of sodium morrhuate is 40% to 50% and with absolute alcohol 19%.[57] Patients most commonly present with pleuritic chest pain. Pleural effusions associated with sclerotherapeutic agents occur mostly on the right side; however, they may occur on the left or bilaterally, depending on the site of injection. The proposed mechanism for pleural fluid formation after variceal injection with these chemicals involves a transmediastinal spread of inflammation from the esophagus to the mediastinal pleura. Effusions are radiographically evident within 24 hours and spontaneously resolve by 7 days. Empyema is an infrequent complication.

EXTRAVASCULAR MIGRATION OF A CENTRAL VENOUS CATHETER

Insertion of a central venous catheter (CVC) and its extravascular migration can cause a pneumothorax, hemothorax, chylothorax, or transudative pleural effusions.[58-60] Extravascular migration of a CVC occurs in 0.4% to 1.0% of insertions and is more common with left subclavian and internal jugular vein approaches.[59] The proper placement of a CVC on a postprocedure chest radiograph is confirmed when the catheter is parallel to the long axis of the superior vena cava and the tip is positioned at the right tracheobronchial angle.[61]

In the conscious patient, infusion of fluid into an extravascular space, such as the mediastinum, may result in dyspnea and chest pain. Respiratory compromise and cardiac tamponade can occur with rapid and large volume infusions into the mediastinum. The pleural effusion will have similar biochemical properties to the infusate. If a glucose-containing solution is being infused, the pleural fluid to serum glucose ratio is greater than unity.[59] Protein and LDH values are in the transudative range with pleural fluid protein less than 1 g/dL.

If extravascular migration of CVC is suspected, the catheter should be removed immediately. Observation is sufficient if the effusion is small. Thoracentesis should be performed if the effusion is large or causes respiratory distress.

HEMOTHORAX

Hemothorax results most commonly from blunt, penetrating, or iatrogenic thoracic trauma. Spontaneous hemothorax may be a complication of anticoagulation therapy, and coagulopathy, pulmonary embolism with infarction, ruptured aortic aneurysm, and malignancy are rare causes of hemothorax.[62-64]

It is important to differentiate a hemothorax from a bloody, pleural effusion, because the latter can result from only a few drops of blood in a serous fluid collection. An arbitrary definition of a hemothorax is a bloody pleural effusion with a hematocrit or red blood cell count that is 50% or more of the peripheral blood hematocrit or red blood cell count.[65] A hemothorax should be suspected in any patient with a pleural effusion on a chest radiograph after blunt or penetrating trauma.

The treatment of a hemothorax involves volume expansion to correct hypovolemia and pleural space drainage. Pleural drainage is best accomplished with the placement of a chest tube (28 to 36 Fr. for adults). Pleural space drainage achieves the following goals in the treatment of hemothorax: (1) it allows the clinician to monitor the rate of bleeding; (2) it allows for apposition of the parietal and visceral pleurae, potentially tamponading the site of bleeding; and (3) it will decrease the risk of empyema and subsequent fibrothorax.[63,64]

The guidelines for surgical management of a hemothorax include hemodynamic instability despite aggressive resuscitation, initial drainage exceeding 1500 mL, continued bleeding of more than 200 mL/h for 2 to 4 hours, and a retained

blood clot exceeding more than one third of the pleural space.[64] Likely sources of bleeding include intercostal vessels, major pulmonary vessels, great vessels, and the heart. The chest tube should never be clamped, because it will not provide a tamponade effect and can worsen gas exchange and hemodynamics.[66]

HEPATIC HYDROTHORAX

Pleural effusions occur in approximately 6% of patients with cirrhosis of the liver and clinical ascites.[67,68] The effusions result from movement of ascitic fluid through congenital or acquired diaphragmatic defects.[67] A patient with a hepatic hydrothorax usually has the classic stigmata of cirrhosis and clinically apparent ascites. Rarely, an hepatic hydrothorax may exist without clinically apparent ascites, implying the presence of a large diaphragmatic defect.

The chest radiograph usually demonstrates a normal cardiac silhouette and a right-sided pleural effusion in 85% of patients, which can vary from small to massive; effusions are less commonly isolated to the left pleural space (13%) or are found bilaterally (2%).[69] The right hemidiaphragm is more likely to have embryologic or acquired defects.[70] The pleural fluid is a serous transudate with a low nucleated cell count, a predominance of mononuclear cells, a pH greater than 7.40, a glucose level similar to the serum glucose level, and an amylase value less than the serum amylase level. If the diagnosis remains unclear, injection of a radionuclide into the ascitic fluid and detection of the radioisotope in the pleural space confirms the diagnosis.

A reported complication of a hepatic hydrothorax is SBE. SBE is comparable to spontaneous bacterial peritonitis (SBP), which can occur in patients who have hepatic hydrothorax with or without ascites.[71,72] *Spontaneous bacterial pleuritis* is a better descriptive term for this clinical entity. Nevertheless, the criteria for diagnosis of SBE are similar to that of SBP and include a positive pleural fluid culture or total neutrophil count exceeding 500 cells/μL; pleural effusion with a serum to pleural fluid albumin gradient greater than 1.1 is also seen with the absence of radiographic infiltrates. The formation of SBE is a result of either bacterial translocation from infected ascitic fluid or hematogenous spread. SBE can occur even in the absence of SBP.[72] Antibiotic therapy is sufficient for treatment of SBE. Chest tube drainage is not recommended unless an empyema is identified.

Treatment of hepatic hydrothorax is similar to the treatment of ascites and involves sodium restriction, diuretics, and paracentesis.[69,74] The management of hepatic hydrothorax is problematic and often does not respond to medical therapy. If the patient is acutely dyspneic and hypoxemic, therapeutic thoracentesis may be done as a temporizing measure. Chest tube drainage is contraindicated because it may lead to pleural space infection, lymphocyte depletion, and renal failure. Attempts to seal the pleural space with chemical pleurodesis are usually unsuccessful owing to rapid movement of ascitic fluid into the pleural space. Transjugular intrahepatic portosystemic shunt (TIPS) and video-assisted thoracoscopic surgery (VATS) to patch the diaphragmatic defect, followed by pleural abrasion procedure, have been used successfully to treat refractory cases of hepatic hydrothorax but are associated with significant morbidity and mortality.[74-76] Currently, the only definitive treatment of refractory hepatic hydrothorax associated with end-stage cirrhosis remains liver transplantation.

HYPOALBUMINEMIA

Most patients admitted to the medical ICU have underlying chronic illness and associated hypoalbuminemia. The true incidence of hypoalbuminemia-related pleural effusions remains unknown. When serum albumin levels are less than 1.8 g/dL, pleural effusions may be observed.[77] Because the pleural space has an effective lymphatic drainage system, it tends to be the final reservoir for extravascular fluid to collect in those with low oncotic pressure. Therefore, it is unusual to see an isolated pleural effusion due to hypoalbuminemia in a patient without anasarca. The chest radiograph usually shows small bilateral effusions. The cardiac silhouette is normal in size. The pleural fluid is a serous transudate with less than 1000 nucleated cells/μL, with glucose levels equivalent to serum. Diagnosis is presumptive when other causes of transudative effusions are excluded. Correction of hypoalbuminemia either by maximizing nutrition or by preventing protein loss results in resolution of the effusions.

PANCREATITIS

Pleural effusions are commonly observed with pancreatitis due to the close proximity of the pancreas to the diaphragm. There are striking differences between pleural effusions in acute versus chronic pancreatitis. In acute pancreatitis, the incidence of pleural effusions ranges from 3% to 17%,[78,79] whereas the incidence of pleural effusions due to chronic pancreatitis is unknown. The pathogenesis of pleural fluid formation in acute pancreatitis involves the transdiaphragmatic passage of amylase-rich fluid as well as increased capillary permeability due to inflammatory mediators. In chronic pancreatitis, the effusions are associated with pancreatic duct disruption with fistula formation and movement of fluid into the pleural space. In acute pancreatitis, the pleural effusions are small to moderate and are found on the left side in 60%; the effusions may be isolated to the right side in 30% or occur bilaterally in 10%.[80] Chronic pancreatic effusions are large to massive unilateral left effusions that recur rapidly after thoracentesis. Pleural fluid in acute pancreatitis is turbid to hemorrhagic; nucleated cell counts approach 50,000 cells/μL, with a predominance of neutrophils, pH ranges from 7.30 to 7.35, glucose level is similar to serum, and the pleural fluid to serum amylase ratio is greater than 1. A normal pleural fluid amylase may be seen in the acute presentation.[21] The pleural effusions in chronic pancreatitis tend to be serous or hemorrhagic exudates, with amylase levels exceeding 100,000 IU/L.

No specific therapy is necessary for pleural effusions associated with acute pancreatitis. The pleural effusions tend to resolve in 2 to 3 weeks after resolution of the pancreatic inflammation. Some studies suggest that there is an increased mortality in those who develop pleural effusions in acute pancreatitis.[81] The management of chronic pancreatitis-induced pleural effusions is more problematic. Conservative strategies consisting of bowel rest and pleural drainage are successful in only 50%, whereas the remainder will require surgical intervention or somatostatin.

PARAPNEUMONIC EFFUSIONS AND EMPYEMA

Parapneumonic effusions occur as a complication of pneumonia. Although most patients with community-acquired pneumonia do not develop pleural effusions, up to 60% of patients hospitalized for community-acquired pneumonia have radiographic evidence of pleural effusions.[82-85] Most of these effusions are uncomplicated and resolve with appropriate antibiotic therapy. However, in 5% to 10% of patients, these effusions follow a complicated course and will need pleural drainage for complete recovery. The end stage of a parapneumonic effusion is an empyema, which, by definition, is frank pus.

The pleural fluid protein, nucleated cell count, and percentage of neutrophils are not helpful in differentiating a complicated from an uncomplicated parapneumonic effusion. When the effusion is free flowing on a lateral decubitus chest radiograph or ultrasound and has a lactate dehydrogenase (LDH) level less than 1000 IU/L, a glucose level greater than 60 mg/dL, and a pH greater than 7.20, the patient has a high likelihood of pleural fluid resolution with antibiotics alone (uncomplicated parapneumonic effusion). If frank pus is aspirated during the thoracentesis, the diagnosis of empyema is established and pleural drainage is mandated. Most authorities would advocate pleural drainage if the Gram stain or culture is positive, regardless of the fluid biochemical properties. Most clinicians would also recommend drainage if the pH is less than 7.20, the LDH is greater than 1000 IU/L, the glucose level is less than 40 mg/dL, and the effusion occupies more than one third of a hemothorax or shows radiographic evidence of loculation. All of the above findings define the effusion as complicated. A recent meta-analysis examined the diagnostic utility of pleural fluid pH, LDH, and glucose in identifying patients who require pleural drainage. This report concluded that pleural fluid pH had a higher diagnostic accuracy compared with glucose or LDH for identifying the need for drainage.[88] This analysis suggested that a single pH cutoff point is not ideal for all patients with parapneumonic effusions because of the variability of host factors and the nature of the bacterial pathogen. The authors recommended draining fluid with pH less than 7.30 in high-risk patients and less than 7.20 in low-risk patients. A high-risk patient would have one or more of the following: a large or loculated pleural effusion, advanced age, underlying comorbid conditions, or virulent organism (*Staphylococcus aureus, Streptococcus pyogenes,* or gram-negative bacteria). Pleural fluid samples for pH should be handled similarly to blood gas specimens and measured in a blood gas analyzer to ensure accurate results.[82,90]

In nonloculated complicated parapneumonic effusions and empyemas, drainage can be accomplished by chest tube thoracostomy or image-guided percutaneous catheters. No prospective randomized trial exists to guide clinicians concerning the optimal treatment of multiloculated parapneumonic effusions. Nevertheless, potential strategies include image-guided catheters with instillation of fibrinolytic agents[91,92] or VATS.[93,94]

Percutaneous catheters are most effective in patients with nonviscous pleural fluid in the exudative or early fibrinopurulent phase of empyema.[95,96] However, in patients who have progressed to the late fibrinopurulent or organized stage of empyema formation, percutaneous drainage is usually ineffective and slows recovery for this subset of patients. The options for surgical drainage are multiple. VATS is an effective and minimally invasive approach to drain the fibrinopurulent or early empyema stage. Conversion to open thoracotomy is required in 10% to 20% of patients undergoing VATS.[97-101] For some in the late fibrinopurulent and virtually all in the organized stage of empyema formation and who are deemed appropriate surgical candidates, the primary surgical drainage involves an open thoracotomy. Decortication may need to be performed to allow for lung expansions if there is a significant pleural peel.

PULMONARY EMBOLISM

Approximately 50% of patients with pulmonary embolism have a pleural effusion.[102] There are several pathogenic mechanisms by which pleural effusions form in this setting: ischemia and increased pleural capillary permeability, pulmonary infarction, and atelectasis.[102,103] In the setting of pulmonary infarction, more than 80% will have a hemorrhagic pleural effusion. Ipsilateral pleuritic chest pain occurs in most patients with pleural effusions complicating pulmonary embolism.[102] A coexistent pulmonary infiltrate is noted on a chest radiograph in up to 50% who have pulmonary embolism and pleural effusion.

Pleural fluid analysis is quite variable, and both transudative and exudative effusions can be present.[21] In the absence of chest trauma, recent cardiac surgery, asbestos exposure, and malignancy, the presence of a bloody pleural effusion should increase the suspicion of a pulmonary embolism.[104] In two of three patients, the gross appearance of pleural fluid is hemorrhagic. The number of red blood cells exceeding 100,000/μL is seen in less than 20%.[21]

The nucleated cell count ranges from less than 100 in the atelectatic transudate to 50,000 cells/μL in the setting of pulmonary infarction. Neutrophils predominate in the acute phase but are subsequently replaced with lymphocytes. Pleural fluid eosinophilia has also been described. Effusions from pulmonary embolism are apparent in more than 90% of patients on initial presentation, and they reach maximum volume in the first 72 hours.[102] Progression of the pleural effusion after 72 hours despite therapy would mandate evaluation for a recurrent embolism, a hemothorax secondary to anticoagulation, an infected infarct with empyema or parapneumonic fluid collection, or an alternate diagnosis. In the absence of an infiltrate on chest radiograph, effusions normally resolve in 1 week. With the presence of an infiltrate, presumably representing a pulmonary infarction, the resolution time is longer, typically 2 to 3 weeks.

The association of pleural effusion with pulmonary embolism does not alter therapy. The presence of a bloody effusion is not a contraindication to full dose anticoagulation therapy.[105] However, an enlarging pleural effusion on anticoagulation necessitates thoracentesis to exclude hemothorax, because hemothorax has been described as a rare complication of heparin therapy. The development of a hemothorax during therapy requires discontinuation of anticoagulation, drainage of the pleural space, and placement of an inferior vena caval filter.

POSTCARDIAC INJURY SYNDROME/DRESSLER'S SYNDROME

PCIS is characterized by the development of fever, pleuropericarditis, and pulmonary infiltrates in days to weeks

after a traumatic insult to the pericardium or myocardium.[106-108] PCIS has been described after myocardial infarction, cardiac surgery, blunt chest trauma, percutaneous left ventricular puncture, and pacemaker implantation. The incidence of PCIS after myocardial infarction is estimated at 4%[109] and occurs at a greater frequency (up to 30%) after cardiac surgery.[110] The pathogenic mechanism is speculated to be an autoimmune process mediated by the development of antimyocardial antibodies.[111] Pleuropulmonary manifestations are the hallmark of PCIS. The most common presenting symptoms are pleuritic chest pain, fever, pericardial/pleural friction rub, dyspnea, and crackles.[111] Fifty percent of patients will have leukocytosis, and almost all will have an elevated erythrocyte sedimentation rate.[112]

The most common radiographic abnormality is a left-sided or bilateral pleural effusion; a unilateral right pleural effusion is unusual.[112] Pulmonary infiltrates are seen in 75% of patients and are most commonly evident in the left lower lobe. The pleural fluid is a serosanguineous or bloody exudate with a glucose level greater than 60 mg/dL and a pleural fluid pH greater than 7.30. Nucleated cell counts range from 500 to 39,000 cells/μL, with a predominance of neutrophils evident early in the course. The detection of high titer antimyocardial antibodies in the pleural fluid can assist in discriminating PCIS-related pleural effusion from other possible diagnoses, such as a parapneumonic effusion, early post-CABG surgery effusion, or pulmonary embolism.

PCIS is usually a self-limited illness and requires no therapy if symptoms are minimal. PCIS responds to aspirin or other NSAIDs; however, some patients may require systemic corticosteroids for resolution. In those who respond, the pleural effusion resolves in 1 to 3 weeks.

UREMIA

Uremic pleural effusions have been reported in 3% to 5% of patients receiving chronic dialysis.[113] In a study of 100 patients on long-term hemodialysis with pleural effusions, uremic pleurisy was thought to be the cause in 16% of cases.[114] Uremic pleurisy typically presents as fever, cough, dyspnea, chest pain, and pleural friction rub. The chest radiograph usually shows a moderate, unilateral pleural effusion, although massive and bilateral effusions have been reported.[113-115] The pleural fluid is a serosanguineous or bloody exudate, with less than 1500 nucleated cells/μL and a predominance of lymphocytes. Although the pleural fluid creatinine concentration is high, the pleural fluid to serum creatinine ratio is less than unity, in contrast to a urinothorax in which the pleural fluid to serum creatinine ratio is greater than 1 and is a transudate.[21] The effusion generally resolves over several weeks with continued dialysis. A late pleural sequela of uremic pleuritis is the development of a trapped lung.[116,117]

PNEUMOTHORAX

DEFINITIONS AND CLASSIFICATION

Pneumothorax is defined by the presence of air in the pleural space and represents one of several forms of extra-alveolar air. Other examples of extra-alveolar air include pneumomediastinum, pneumopericardium, pneumoperitoneum, pulmonary interstitial emphysema, systemic air embolism, and subcutaneous emphysema.

The classification of pneumothorax is shown in Table 82-4. Spontaneous pneumothorax occurs without an obvious inciting event. Primary spontaneous pneumothorax occurs without clinical evidence of underlying lung disease. Secondary spontaneous pneumothorax occurs as a consequence of clinically manifest lung disease. Traumatic pneumothorax results from penetrating or blunt chest injury. Iatrogenic pneumothorax occurs as a consequence of diagnostic or therapeutic procedures, which may include barotrauma secondary to mechanical ventilation, placement of central venous catheters, thoracentesis, pericardiocentesis, or placement of small-bore feeding tubes. Common causes of pneumothorax in the ICU are listed in Table 82-4.

PATHOPHYSIOLOGY

During normal breathing, airway presence exceeds intrapleural pressure during the entire respiratory cycle.[118] Airway pressures can be increased dramatically during coughing, Valsalva maneuvers, or strenuous exercise; however, pleural pressures rise concomitantly, such that the transpulmonary pressure gradient is changed minimally. With rapid fluctuations in intrathoracic pressures, a large transpulmonary pressure gradient can occur transiently.

TABLE 82–4. CLASSIFICATION AND CAUSES OF PNEUMOTHORAX

Spontaneous
Primary
No clinical lung disease
Secondary
Clinical presence of lung disease
Airway diseases
COPD
Status asthmaticus
Cystic fibrosis
Interstitial lung diseases
Langerhans' cell histiocytosis
Usual interstitial pneumonitis
Stage IV sarcoidosis
Pulmonary Infections
Pneumocystis carinii
Necrotizing pneumonia
Tuberculosis
Lung abscess
Diffuse alveolar damage
ARDS
Iatrogenic
Barotrauma
Mechanical ventilation
Procedure-related
Central venous catheter placement
Thoracentesis
Endotracheal intubation
Tracheostomy
Cardiopulmonary resuscitation
Bronchoscopy
Nasogastric tube placement
Trauma
Blunt chest trauma
Penetrating chest trauma
Rib fractures
Esophageal rupture
Tracheobronchial injuries

This can surface in the setting of positive-pressure ventilation and bronchial obstruction, resulting in air trapping, inducing a large transpulmonary pressure gradient. When the transpulmonary pressure gradient is transiently increased, alveolar rupture can occur; air will enter the interstitial tissue of the lung and will either dissect through the visceral pleural, resulting in pneumothorax, or move toward the hilum, along with the bronchovascular bundle, creating a pneumothorax.[119,120] Mediastinal air may decompress into subcutaneous tissues or the retroperitoneum. With acute increase in mediastinal pressure, air can rupture the mediastinal parietal pleura, yielding a pneumothorax. it is by this mechanism, rather than by direct rupture of subpleural blebs, that a pneumothorax occurs.[119]

In the setting of a pneumothorax, the lung collapses due to its elasticity, and it continues to collapse until either the pleural defect seals or there is equalization between alveolar and pleural pressures. Occasionally, a ball-valve effect occurs at the pleural defect, allowing an excess of air into the pleural space. This results in an accelerated increase in pleural pressure, producing a tension pneumothorax. Tension pneumothorax compresses the mediastinal structures, causing a decrease in venous return, cardiac output, and, at times, hemodynamic collapse.[121,122]

Patients with primary spontaneous pneumothorax have a decreased vital capacity and an increased alveolar-arterial (A-a) gradient. The development of hypoxemia and increased A-a gradient is due to an intrapulmonary shunt and decreased ventilation-perfusion matching in the atelectatic lung.[123,124] The uninvolved lung can maintain the necessary alveolar ventilation to prevent hypercapnia. In contrast, patients with secondary spontaneous pneumothorax commonly develop hypercapnia in addition to hypoxemia.[125,126]

Because of the potential severity for gas exchange abnormality in secondary spontaneous pneumothorax, it is not uncommon to have these patients admitted to the ICU.

RADIOGRAPHIC EVALUATION

The radiographic signs of pneumothorax in the supine patient differ from an erect view in which the classic visceral pleural line is seen. In the supine patient, pneumothorax gas migrates along the anterior surface of the lung; therefore, careful inspection of the base, lateral chest wall, and juxtacardiac areas should be performed.[127] In a study of 88 critically ill patients with 112 pneumothoraces, the anteromedial and subpulmonic recesses were involved in 64% of patients in the supine and semi-erect position.[128] Thirty percent of the pneumothoraces in this study were not initially detected on standard chest radiography, whereas 50% of these patients progressed to tension pneumothorax (see Table 82-1). Therefore, a high clinical suspicion is essential in critically ill patients to avoid catastrophic complications.

Pneumothorax in supine patients can occur in subpulmonic and posteromedial locations (Fig. 82-2).[128] A subpulmonic pneumothorax may be recognized as a basilar hyperlucency.[129,130] Occasionally, a distinct pleural line may be visualized at the base of the lung. A subpulmonic pneumothorax may be present if there is a hyperlucency extending deep into the costophrenic sulcus (deep sulcus sign), depression of the hemidiaphragm, or visualization of a very distinct cardiac border (Fig. 82-3).[131,132]

Radiographic signs of a tension pneumothorax include an increase in the volume of the ipsilateral hemithorax,

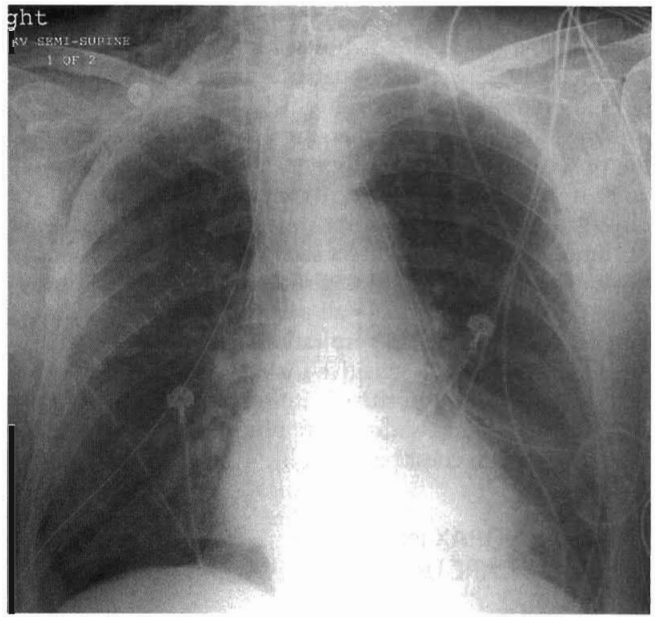

FIGURE 82–2. A semi-upright anteroposterior chest radiograph shows subcutaneous air and a hyperlucency along the right hemidiaphragm consistent with a basilar pneumothorax.

depression of the ipsilateral hemidiaphragm, contralateral displacement of the mediastinum, widening of the intercostal space due to increase in hemithorax volume, and compression of the contralateral lung. In patients with decreased lung compliance, a tension pneumothorax may be present with minimal mediastinal shift and only diaphragmatic depression (see Table 82-3).[133]

If possible, an erect or decubitus radiograph should be obtained to confirm or dismiss the presence of a pneumothorax. In problematic cases, CT or ultrasonography can be diagnostic. CT remains the gold standard for diagnosing pneumothorax, with numerous studies documenting the

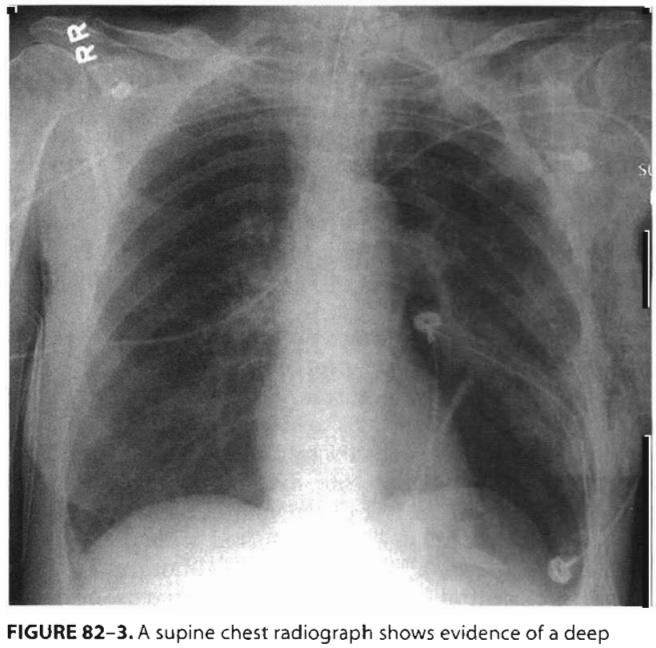

FIGURE 82–3. A supine chest radiograph shows evidence of a deep sulcus sign on the left consistent with the presence of a pneumothorax.

presence of pneumothorax on CT that was not apparent on chest radiography.[134-136] At times, a pneumothorax may be confused with large bulla in patients with COPD, and it may be helpful in making the diagnosis.[137]

Ultrasonography is an emerging diagnostic tool to evaluate the presence of a pneumothorax. Air cannot be visualized with ultrasound; therefore, a pneumothorax cannot be directly observed. On real-time ultrasonography, the absence of "lung sliding" is an indirect sign that establishes the diagnosis of pneumothorax. "Lung sliding" refers to lung movement relative to the chest wall and can be seen as a sliding motion synchronized to respiration. The disappearance of lung sliding was 95% sensitive for detecting a pneumothorax, although false-positive results did occur.[138-140] The specificity of "lung sliding" on ultrasonography is lower than CT or plain chest radiography.

PNEUMOTHORAX IN THE INTENSIVE CARE UNIT

The most common cause of pneumothoraces in ICU patients is barotrauma/volutrauma from mechanical ventilation and invasive procedures. Unlike patients with primary spontaneous pneumothorax, those with secondary spontaneous pneumothorax may be admitted to the ICU because they develop hypoxemic and occasionally hypercapnic respiratory failure. The mechanism of hypoxemia is thought to be a result of the development of anatomic shunts and low ventilation-perfusion defects in the atelectatic lung.[141,142]

In patients with primary spontaneous pneumothorax, the contralateral lung can maintain alveolar ventilation while the hypoxemia is managed with supplemental oxygen. In those who suffer a secondary spontaneous pneumothorax the contralateral lung cannot maintain the necessary ventilation to prevent severe gas exchange abnormalities.[143,144]

IATROGENIC PNEUMOTHORAX

The placement of CVCs is routinely done in the critically ill patient for aggressive volume resuscitation as well as drug and parenteral nutrition administration. The morbidity and mortality associated with CVC use are physician related and are, more importantly, associated with physician experience with placement.[145]

The reported incidence of iatrogenic pneumothorax after invasive procedures ranges from 6% to 52%.[146,147] The wide range in iatrogenic pneumothorax is multifactorial and may reflect institutional variability in the utilization of various invasive techniques, reporting biases, and, primarily, level of training by performing physicians at different medical centers.[148]

The pneumothorax occurrence rate also varies, depending on the type of invasive procedure performed. The estimated pneumothorax occurrence rates for transthoracic lung biopsy are less than 10% to 50% and are 5% to 20% for thoracentesis and less than 1% to 13% for central line placement.[149] The cannulation site for central line placement associated with higher risk of pneumothorax rests with the subclavian vein (13%) when compared with the internal jugular vein (<0.2%).[150,151] Most pneumothoraces occur at the time of central line placement and result from direct lung puncture. Delayed pneumothoraces have been reported; therefore, it is prudent to view a chest radiograph 12 to 24 hours after the procedure. Bilateral pneumothoraces have been reported after unilateral attempts, and death can occur if the diagnosis is delayed.

Cardiopulmonary resuscitation has been noted as a cause of iatrogenic pneumothorax. A pneumothorax may occur in this setting either from rib fractures sustained during resuscitation or from barotrauma as a consequence of bag ventilation.[152,153] Because of these observations, a chest radiograph should be obtained in all patients after successful resuscitation to evaluate for pneumothorax. Furthermore, if a patient becomes difficult to bag ventilate, if subcutaneous emphysema develops, or if electromechanical dissociation is present, the diagnosis of a tension pneumothorax should be suspected. Immediate steps should be undertaken to decompress, because this may be a lifesaving endeavor.

Pneumothorax has been reported after endotracheal intubation. The mechanism of pneumothorax in this setting is due to rupture of the membranous portion of the trachea.[154,155] The incidence of pneumothorax after endotracheal intubation is reported to be approximately 1%.[156] Pneumothorax has also been reported with open or bedside percutaneous dilational tracheostomy. The incidence of pneumothorax after tracheostomy ranges from less than 1% to 4%.[157-159]

Bronchoscopy in critically ill patients may also cause a pneumothorax. The risk is higher when transbronchial biopsies are performed compared with bronchoalveolar lavage (BAL). The degree of risk for pneumothorax in the setting of bronchoscopy for those on positive-pressure ventilation compared with nonventilated patients is unknown. Furthermore, the performance of BAL alone may produce a pneumothorax, and all ventilated patients undergoing BAL should have a chest radiograph to exclude pneumothorax.[160-162]

BAROTRAUMA

Because of the widespread use of mechanical ventilation, pulmonary barotrauma is recognized as a common clinical problem. In the 1970s, mechanical ventilation–related iatrogenic pneumothorax was the leading cause of pneumothoraces in the ICU.[148] Barotrauma is manifested by parenchymal interstitial gas, pneumomediastinum, subcutaneous emphysema, pneumoperitoneum, and pneumothorax.[163-165]

The form most clinically relevant is pneumothorax, occurring in 1% to 15% of all patients on positive-pressure ventilation. In patients with ARDS, pneumothorax may occur in 25% to 87%.[166,167] Important predictors in the development of a pneumothorax include the number of ventilator days, underlying lung disease (ARDS, necrotizing pneumonia, COPD), plateau pressures, and the use of positive end-expiratory pressure (PEEP).[163-165] When a pneumothorax develops in the setting of positive-pressure ventilation, 30% to 97% of patients develop tension pneumothorax.[167-169]

Currently, there is a decline in mechanical ventilation–related pneumothoraces. The decline may be attributed to newer ventilator modes and strategies.[170-171] Limiting the delivered tidal volume, utilizing permissive hypercapnia, and setting PEEP above the lower inflection point on static pressure-volume curves appear to have lowered the incidence of iatrogenic pneumothoraces in ARDS.

When evidence of barotrauma without pneumothorax is observed in a patient requiring mechanical ventilation, immediate attempts should be made to lower the plateau airway pressure. This can be accomplished by decreasing tidal

volumes and allowing for controlled hypoventilation.[172,173] Decreases in inspiratory flow rates and attempts to minimize PEEP should be strongly considered. In situations in which ventilator-patient dyssynchrony is present, neuromuscular blockers and sedatives should be considered.[174] There is no evidence to support the use of prophylactic chest tubes for those with barotrauma without pneumothorax. However, this subgroup of patients should be monitored closely for the development of a tension pneumothorax and provisions made to perform an emergent bedside tube thoracostomy.

TENSION PNEUMOTHORAX

A tension pneumothorax occurs when intrapleural pressure exceeds atmospheric pressure throughout the respiratory cycle. Tension pneumothorax occurs when a one-way valve exists on either the visceral or mediastinal pleura, allowing air to enter the pleural space during inspiration and close during expiration, preventing the egress of air from the pleural space.[175]

A tension pneumothorax usually presents as an acute cardiopulmonary emergency, beginning with respiratory distress; if unrecognized and untreated, it progresses to cardiovascular collapse and subsequent death. Conscious patients with tension pneumothorax appear acutely ill with dyspnea, tachypnea, tachycardia, and cyanosis. The following are evident on physical examination: decreased ipsilateral breath sounds, hyperresonance to percussion, distended neck veins, tracheal deviation to the contralateral side, and hypotension. Hypoxemia may be one of the earlier signs of a tension pneumothorax in the unconscious or critically ill patient. For those on mechanical ventilation, increasing PEEP and plateau air pressures, decreasing static and dynamic lung compliance, and the development of auto-PEEP should alert the clinician of the possibility of a tension pneumothorax. Difficulty in bag ventilation in delivering adequate tidal volumes may be noted. Furthermore, it is paramount to consider a tension pneumothorax in the differential diagnosis of any patient who develops pulseless electrical activity (electromechanical disassociation).

When the clinical signs and symptoms are noted in mechanically ventilated patients, treatment should not be delayed to obtain radiographic confirmation. This point is illustrated in a report of 74 patients who developed mechanical ventilator-associated pneumothoraces. The diagnosis of pneumothorax was made clinically in 45 (61%) patients based on hypotension, hyperresonance, decreased breath sounds, and tachycardia.[176] The mortality rate was 7% in the patients diagnosed clinically. The diagnosis of the remaining 29 patients was delayed between 30 minutes to 8 hours, and 31% mortality secondary to tension pneumothorax was reported. In summary, the diagnosis of a tension pneumothorax is a clinical diagnosis, and radiographic findings of tension pneumothorax, such as contralateral mediastinal shift, tracheal deviation, and ipsilateral diaphragmatic depression, may be absent on chest radiographs.[133,177]

MANAGEMENT OF IATROGENIC AND TENSION PNEUMOTHORAX

Most critically ill patients in the ICU have poor underlying cardiopulmonary reserves and may be unable to tolerate even a minimal pneumothorax. In nonventilated patients who sustain an iatrogenic pneumothorax after placement of a CVC, close observation and supplemental oxygen are recommended in those who have minimal symptoms and a small (<15%) pneumothorax. If a patient is more symptomatic or has a larger pneumothorax (>15%), placement of a small-bore chest tube is recommended.[178,179] In the ACCP consensus statement, the distance between the chest wall and visceral pleural surface can be used in substitution of the percent of lung collapse. Based on these guidelines, observation is done for a pneumothorax of less than 3 cm and pleural drainage is required for 3 cm or greater of lung collapse.

Patients with iatrogenic pneumothoraces on mechanical ventilation, regardless of cause, are highly likely to develop a tension pneumothorax. All patients in this setting require placement of a chest tube; observation should not be considered.

TRAUMATIC PNEUMOTHORAX

Traumatic pneumothoraces can be either closed or open and are usually accompanied by additional injuries, such as pulmonary contusion, fractured ribs, flail chest, and ARDS. Diagnosis of pneumothorax by chest radiography may be difficult in this setting, and these patients may require chest CT. The management follows the same guidelines as for spontaneous pneumothorax, with modifications for concomitant injuries.

PERSISTENT PNEUMOTHORAX

Pneumothorax is defined as persistent when it lasts more than 10 days, while treated uninterruptedly by tube thoracostomy with underwater seal, with or without suction. The most common cause of persistence is bronchopleural fistula[8,27,180,181]; other causes include formation of fibrinous peel over the lung, pleural adhesions, bronchial or pulmonary tear due to trauma, and bronchial obstruction. The possibility of obstruction mandates bronchoscopy to rule out mucus plugs, tumor, or a foreign body. Extraction of the foreign body or aspiration of bronchial secretions will nearly always result in immediate expansion of the lung.[21,182] Other causes of persistence are best sought by inspection of the pleura at thoracoscopy. Thoracoscopy is also indicated for evaluation of patients with recurrent pneumothorax. Approximately 90% of patients with pneumothorax suffer either one or two episodes of pneumothorax on the same side, and only 10% have three or more ipsilateral episodes.[11,183] While those 90% do not usually need further investigation, thoracoscopy is indicated in the 10% who experience multiple recurrences. It enables direct inspection of the entire pleural surface and search for causes of recurrence.

The use of direct thoracoscopy in the management of pneumothorax was first suggested by Anton Sattler in 1937.[28,184] Using an instrument of his own device, he observed pleural changes in patients with pneumothorax, either recurrent or persistent, and suggested immediate treatment according to findings. It has been recommended that thoracoscopy be performed for persistence, or for second ipsilateral recurrence, when pneumothorax occupies at least 20% of the pleural space. If irregularly scattered adhesions are found, they are divided with diathermy, and then 2 g of asbestos-free sterile talc is lightly sprinkled over the entire pleural surface. If subpleural blebs are seen and the lung is fully expansible, the blebs are excised, talc is insufflated,

and the pleural drain is attached to underwater seal with suction. Expansion is thus maintained, while adhesions form, preventing further episodes of recurrence. If there is a tear and the lung does not expand well, all blebs are resected and the tear is stapled. Finding a large emphysematous bulla makes resection mandatory. Presence of pleural fibrosis mandates decortication, either open or thoracoscopic. If no abnormalities are found, talc is insufflated, and a pleural drain is attached to underwater seal with suction.[29,182] ARDS after the use of talc has been reported by Rinaldo and associates.[30,186] This is apparently a dose-related phenomenon, and the amount of talc used per insufflation should be less than 2 g.[31,187]

Of other agents used to obliterate the pleural space, tetracycline, bleomycin, and quinacrine were used most commonly. However, the use of tetracycline results in much pain. Stephenson compared it to injecting scalding water through the pleural tube.[32,188] Therefore, it must be used with the patient under heavy sedation. In addition, the effectiveness of tetracycline is only about 50%, compared with 95% for talc.[33,34,189,190] Bleomycin and quinacrine are systemically absorbed, and both have a potential for systemic toxicity.[31,35-37,187,191-193] Alternatively, obliteration of the pleural cavity can be achieved without the use of any chemical agents, by surgical means only. It includes suture or stapling of air leaks, resection of all blebs and bullae, and either abrasion of the entire pleural surface using dry gauze or a limited apical pleurectomy.[38,194] Both procedures are highly effective and can be performed either through a small, muscle-sparing axillary thoracotomy[39,40,195,196] or with VATS.[41,197] Hemostasis must be meticulous and, at the end of the procedure, a large-bore pleural drain should be placed at the apex of the chest cavity.

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In a study of 88 patients with 112 pneumothoraces, the anteromedial and subpulmonic recesses were involved in 64% of patients in the supine and semi erect positions. Thirty percent of the pneumothoraces were not initially detected on standard chest radiography.

Valentine VG, Raffin TA: The management of chylothorax. Chest 1992; 102:586-591.

In a series of 191 patients with chylothorax, lymphoma was the most common cause, accounting for 37% of cases. The second leading cause of chylothorax was trauma (25% of cases) in this series.

Weissberg D, Refaely Y: Pneumothorax: Experience with 1199 patients. Chest 2000;117:1279-1285.

Summary of experience with nearly 1200 patients with pneumothorax, all managed by one surgeon and his team over 18 years. It brings into account changes in management of pneumothorax that occurred during that time and supplies an algorithm of management.

Chapter 83
COMMUNITY-ACQUIRED PNEUMONIA

Michael S. Niederman

KEY POINTS

1. Community-acquired pneumonia (CAP) is a common illness, but only about 20% of all affected patients are admitted to the hospital and only 10% to 20% of admitted patients require ICU care.
2. Risk factors for CAP becoming severe include smoking, alcohol abuse, serious comorbid medical illnesses, and advanced age. Risk factors for CAP mortality include severe physiologic abnormalities, delays in the initiation of appropriate antibiotic therapy, advanced age, rapid radiographic progression, the development of respiratory failure, and the presence of certain high-risk pathogens.
3. Prognostic scoring systems are useful for predicting CAP mortality but are less accurate for identifying patients who require ICU care. ICU care is needed for patients with respiratory failure, septic shock, multilobar infiltrates, severe hypoxemia (PaO_2/FIO_2 ratio < 250), and systolic blood pressure less than 90 mm Hg. Early recognition of severe CAP may allow the ICU to be used in a fashion that can reduce the mortality of this illness.
4. The failure to localize infection to a single site in the lung, with excessive systemic and pulmonary inflammation, is a common feature in patients with severe forms of CAP.
5. Clinical features of pneumonia cannot help to predict the microbial etiology, especially in older patients with impaired immune response who commonly have less dramatic clinical findings than younger patients with a similar severity of illness.
6. The most common pathogens causing severe CAP include pneumococcus, atypical pathogens (*Legionella* species, *Mycobacterium pneumoniae*, and *Chlamydia pneumoniae*), enteric gram-negatives (including *Pseudomonas aeruginosa*), *Staphylococcus aureus*, and *Haemophilus influenzae*, but infection can also be the result of viral illness (influenza, SARS), bioterrorism (anthrax), and other miscellaneous organisms.
7. Antibiotic-resistant pneumococci are increasingly common and must be considered in the choice of initial antibiotic therapy for severe CAP, but the impact of resistance on the outcomes of patients is uncertain.
8. It is difficult to establish an exact etiologic diagnosis in patients with severe CAP, but diagnostic testing should always include a chest radiograph, oxygenation assessment, blood cultures, and, in selected patients, sputum Gram's stain and culture, bronchoscopic culture, and urinary antigen testing for *Legionella* and pneumococcus.
9. Therapy for severe CAP must be done promptly and empirically, using multiple antibiotics directed against pneumococcus, atypical pathogens, enteric gram-negative organisms, and, in some patients, *P. aeruginosa*. This usually requires the combination of a specific beta-lactam with either a macrolide or a quinolone and sometimes the addition of other agents. Quinolone monotherapy is not recommended for the empirical management of severe CAP.
10. Adjunctive therapies for severe CAP include chest physiotherapy, inhaled bronchodilators, and activated protein C, all used in carefully selected populations.
11. Nonresponse in severe CAP can be recognized as early as 24 to 48 hours and requires consideration of unusual or drug-resistant pathogens, noninfectious diseases that mimic pneumonia, and pneumonia complications.
12. Prevention of pneumonia can be accomplished by focusing on smoking cessation and immunization for pneumococcus and influenza, with consideration of a hospital-based immunization program.

Pneumonia is an infection of the gas exchanging units of the lung that is most commonly caused by bacteria but occasionally caused by viruses, fungi, parasites, and other infectious agents. It is the sixth leading cause of death in the United States and the number one cause of death from infectious diseases.[1] When this infection arises in patients who are residing out of the hospital, it is termed *community-acquired pneumonia* (CAP), although the population included in this definition is expanding. Currently, the "community" includes complex patients such as those who have recently been hospitalized, those in nursing homes, and those with chronic diseases who are commonly managed in such facilities as dialysis centers or nursing homes. This discussion includes pneumonia arising in immune-competent individuals and excludes discussion of patients with HIV

infection or traditional immune suppression (cancer chemotherapy, immune suppressive medications).

INCIDENCE

In 1994, over 5.6 million people were diagnosed with CAP in the United States. The majority, 4.5 million, were treated out of the hospital, yet only a minority of hospitalized patients were cared for in the ICU.[1,2] Although the majority of CAP is managed in the outpatient setting, the morbidity, the mortality, and the overwhelming majority of the cost of treatment is focused on hospitalized patients, particularly those admitted to critical care units. In addition, those with comorbid illness and those of advanced age make up a large proportion of the hospitalized, critically ill population. In particular, the elderly have a higher mortality from CAP than younger patients, generally as a reflection of the fact that they more commonly have comorbid illness.[2]

Although CAP can vary from being a mild to a severe illness, very few hospitalized patients are severely ill enough to require ICU admission.[3-5] Torres specifically examined all ICU admissions over a 4-year period and found that 10% were related to CAP.[4] In that study, CAP patients who required ICU care were admitted directly to the ICU 42% of the time, after admission to another ward 37% of the time, or after transfer from another hospital in 21% of patients.[4] In another study, of 395 patients admitted to the hospital with CAP, only a total of 64 (approximately 15%) were admitted to the ICU.[3] Whereas the proportion of CAP patients admitted to the ICU will vary in relation to the types of patients who develop pneumonia, there still remains no exact definition of which patients have severe pneumonia and require ICU care.

Recently, Kaplan and colleagues evaluated the cost of care for elderly patients with CAP in the United States.[5] Using Medicare data, they evaluated all individuals age 65 or older admitted to nonfederal hospitals in 1997. A total of 623,718 patients were evaluated, with 86% being age 70 or older, and the mean age was 77 years. Underlying illness was present in two thirds, with congestive heart failure, the most common comorbidity, present in 32%. In this population, the use of ICU, mechanical ventilation, or both, was common, with 140,226 patients having complex courses of illness. The overall mortality rate was 10.6% but rose higher with advancing age, nursing home residence, and comorbid illness. The mean length of stay was 7.6 days, with a mean cost of $6949, but costs were greater for patients with complex illness and mechanical ventilation and less for those with simple pneumonia. Costs generally paralleled length of stay but were disproportionately high for those needing mechanical ventilation, where the mean length of stay was 15.7 days and the cost $23,961. Interestingly, there was little extra cost for nonsurvivors compared with survivors, except in the group with complex pneumonia as a whole but not in those requiring mechanical ventilation. The findings not only emphasize the high impact of CAP on costs and outcomes in the United States but also demonstrate the disproportionate increase in costs when patients are treated with mechanical ventilation, thereby raising for discussion the ethics and appropriateness of such care in the very elderly.

RISK FACTORS

In all studies of CAP, patients who are admitted to the hospital or ICU commonly have a number of coexisting illnesses, suggesting that individuals who are chronically ill have an increased risk of developing severe illness (Table 83-1). In one study, the mean age of all CAP patients was 59 years, coexisting illness was present in 46%, whereas 74% had a history of prior cigarette smoking.[6] The most common chronic illnesses in these patients were respiratory disease, cardiovascular disease, and diabetes mellitus, findings that have been echoed in a number of studies.[4,6-8] In studies of severe CAP, serious coexisting illness is present in 46% to 66% of all patients.[4,5,9] The most common respiratory illness in CAP patients is chronic obstructive pulmonary disease (COPD), a finding that applies to those with either mild or severe forms of CAP.[4] Among those with severe CAP, cigarette smoking and alcohol abuse are also quite common, and cigarette smoking has been identified as a risk factor for bacteremic pneumococcal infection.[4,10] Other common illnesses in those with CAP include malignancy, neurologic illness (including seizures), as well as AIDS.[6-8] One recent study identified alcohol abuse as a risk factor, along with the failure to receive antibiotic therapy before hospital admission, a finding suggesting that a delay in therapy may convert milder forms of pneumonia into a more severe illness.[7,11] In addition, genetic differences in the immune response may predispose certain individuals to more severe forms of infection and adverse outcomes and may be reflected by a family history of severe pneumonia or adverse outcomes from infection.

TABLE 83-1. RISK FACTORS FOR DEVELOPING SEVERE COMMUNITY-ACQUIRED PNEUMONIA

Advanced age
Comorbid illness (e.g., chronic respiratory illness, cardiovascular disease, diabetes mellitus, neurologic illness, renal insufficiency, malignancy)
Cigarette smoking
Alcohol abuse
Absence of antibiotic therapy before hospitalization
Failure to contain infection to its initial site of entry
Immune suppression
Genetic polymorphisms in the immune response

PROGNOSTIC FACTORS

In a meta-analysis of 33,148 patients with CAP, the overall mortality rate (OR) was 13.7%, but those admitted to the ICU had a mortality rate of 36.5%, a finding that has been corroborated in a number of other studies.[12] Eleven prognostic factors were significantly associated with mortality:

1. Male sex (OR = 1.3)
2. Pleuritic chest pain (OR = 0.5)
3. Hypothermia (OR = 5.0)
4. Systolic hypotension (OR = 4.8)
5. Tachypnea (OR = 2.9)
6. Diabetes mellitus (OR = 1.3)
7. Neoplastic disease (OR = 2.8)
8. Neurologic disease (OR = 4.6)
9. Bacteremia (OR = 2.8)
10. Leukopenia (OR = 2.5)
11. Multilobar infiltrates (OR = 3.1)

In other studies, the clinical features that predict a poor outcome (Table 83-2)[13] include advanced age (>65 years), preexisting chronic illness of any type, the absence of fever

TABLE 83–2. RISK FACTORS FOR A POOR OUTCOME FROM COMMUNITY-ACQUIRED PNEUMONIA

Patient-Related Factors
Male sex
Absence of pleuritic chest pain
Nonclassic clinical presentation
Neoplastic illness
Neurologic illness
Age >65 years
Family history of severe pneumonia or death from sepsis
Abnormal Physical Findings
Respiratory rate >30 breaths/min on admission
Systolic (<90 mm Hg) or diastolic (<60 mm Hg) hypotension
Tachycardia (>125 beats/min)
High fever (>40°C) or afebrile
Confusion
Laboratory Abnormalities
Blood urea nitrogen >19.6 mg/dL
Leukocytosis or leukopenia
Multilobar radiographic abnormalities
Rapidly progressive radiographic abnormalities during therapy
Bacteremia
Hyponatremia (<130 mmol/L)
Multiple organ failure
Respiratory failure
Hypoalbuminemia
Arterial pH <7.35
Pleural effusion
Pathogen-Related Factors
High-risk organisms
Type III pneumococcus, *Staphylococcus aureus,* gram-negative bacilli (including *Pseudomonas aeruginosa*), aspiration organisms, severe acute respiratory syndrome (SARS)
Possibly high levels of penicillin resistance (minimal inhibitory concentration of at least 4 mg/L) in pneumococcus
Therapy-Related Factors
Delay in initial antibiotic therapy (more than 4 hours)
Initial therapy with inappropriate antibiotic therapy
Failure to have a clinical response to empirical therapy within 72 hours

on admission, respiratory rate greater than 30 breaths/min, diastolic or systolic hypotension, elevated blood urea nitrogen (>19.6 mg/dL), profound leukopenia or leukocytosis, inadequate antibiotic therapy, need for mechanical ventilation, hypoalbuminemia, and the presence of certain "high risk" organisms (type III pneumococcus, *Staphylococcus aureus*, gram-negative bacilli, aspiration organisms, or post-obstructive pneumonia). Other studies have found that when CAP patients have a delay in the initiation of appropriate antibiotic therapy, mortality is increased.[4,9,11,14]

When these findings are viewed together, they suggest some general principles. Mortality is more likely in CAP patients who have severe physiologic derangements, serious underlying illnesses, delay in the initiation of appropriate therapy, and the presence of atypical clinical features. This last factor suggests that an unusual clinical presentation (low fever, nondistinct respiratory symptoms) is associated with mortality, which may be the result of its reflecting an inadequate inflammatory response to infection and because it can also lead to a delay in the recognition of pneumonia and the institution of appropriate therapy.

One approach to evaluating CAP patients is to use a scoring system to define prognosis and predict the risk of death. The investigators in the Pneumonia Outcomes Research Team (PORT) study have developed a mortality prediction rule that classifies all patients into one of five groups (Pneumonia Severity Index [PSI] classes I to V), each with a different risk for death.[15] Patients in classes IV and V have a predicted mortality risk of 8.2% to 9.3% and 27% to 31.1%, respectively, whereas those in classes I and II have a mortality risk of 0.1% to 0.4% and 0.6% to 0.7%, respectively, and those in class III have a risk of death of 0.9% to 2.8%. To use this scoring system, patients have points calculated based on such factors as age, sex, the presence of comorbid medical disease, certain physical findings, and certain laboratory data.[15]

While the PORT scoring system has been shown to be accurate for predicting mortality and prognosis, it is important to realize that it does not directly measure severity of illness, since many points in the scoring system are for comorbid conditions, rather than features of illness. The investigators from the PORT study evaluated the use of ICU by patients with CAP, and the ability of the scoring system to predict need for ICU care. From the original database of the PORT study, 170 patients were admitted to the ICU and compared to 1169 who were managed out of the ICU.[16] Reasons for ICU admission included respiratory failure (57%), hemodynamic monitoring (32%), and shock (16%). While the PORT rule was useful for predicting mortality, there was a poor correlation between the need for ICU admission and the risk of death. In fact, 27% of the ICU patients were in PSI risk classes I to III, and this group, although needing intensive care, had a significantly lower mortality than patients in risk classes IV and V.[16] The findings are quite important for demonstrating that the need for ICU care is not the same as meaning that the patient has a high risk of death. In the American Thoracic Society (ATS) CAP guidelines, these limitations were discussed, including the fact that age and comorbidity are heavily weighted variables for defining mortality risk, tending to move all older patients into high PORT score classes.[1] On the other hand, in a young patient without comorbid illness, the pneumonia must be particularly severe to place the patient in a high mortality risk group, and certain vital sign thresholds must be exceeded to accumulate points toward a poor prognosis. These thresholds are heart rate greater than 125 beats/min, respiratory rate greater than 30 breaths/min, and systolic blood pressure less than 90 mm Hg.

Although prognostic scoring systems can be complex and difficult to apply in clinical practice, the PORT prediction rule has been promoted as a way to avoid overestimating severity of illness, and calculation of the score has been advocated as a way of keeping some patients out of the hospital who have a low risk of death. For the critical care physician, the opposite problem, underestimating severity of illness, is a more serious concern, and the use of the British Thoracic Society (BTS) rule, which is simple and easily applied, may help to avoid this problem. In one study, Farr and colleagues examined 245 patients with CAP and evaluated 42 prognostic factors using a stepwise logistic regression analysis.[13] With this approach, only three factors, the BTS rule, emerged as predictive of mortality in a multivariate analysis: respiratory rate greater than or equal to 30 breaths/min, diastolic blood pressure less than or equal to 60 mm Hg, and a blood urea nitrogen greater than 19.6 mg/dL.[13] If any two of these variables were present, the risk of dying was 9 to 21 times greater

than if fewer than two of these variables were present. Overall, the positive predictive value for mortality of finding two of these abnormalities was 28.6%, while the negative predictive value of two abnormalities being absent was 96.9%. More recently, Neill and colleagues used a modified version of the BTS rule, adding a fourth criterion, confusion, to the other three findings and identified patients as having increased mortality risk if two of four criteria were present.[17] This rule was then applied prospectively and was able to identify, on admission, 19 of the 20 patients (of a group of 255) who died of CAP. Interestingly, of the 19 patients identified as severely ill by this rule, only 12 were identified by the clinicians, at the time of initial assessment, as being seriously ill. In this study, the BTS rule was a valuable way to accurately assess severity of illness, which was a problem for some clinicians who did not adequately evaluate respiratory rate and signs of reduced tissue perfusion. One other advantage to using the BTS rule is that the prognosis of CAP can be accurately determined using relatively simple assessments, all of which are immediately available when first evaluating a patient in the hospital setting.

Another modification of the BTS has been termed *CURB-65*, an acronym for the clinical features used to assess pneumonia severity and prognosis.[18] With this approach, the factors associated with 30-day mortality are each given 1 point, on a 5-point scale, including confusion, blood urea greater than 7 mmol/L, respiratory rate greater than or equal to 30 breaths/min, blood pressure of <90 mm Hg systolic or ≤60 mm Hg diastolic, and age greater than or equal to 65 years. In one study, when the score was 0 to 1, the mortality rate was 0%, whereas mortality was more than 20% for a score of 3 or higher, and those with a score of 2 had a mortality of 8.3%. The use of prediction rules is a particular problem in the elderly. Recently, Lim and associates have shown that the BTS rule does not work as well in the elderly as in younger patients, reflecting the altered clinical presentations of pneumonia in this population. In one study, the rule had a 66% sensitivity and a 73% specificity for predicting mortality in a population that included 48% who were at least 75 years of age.[19,20] Interestingly, although the BTS rule was not optimal in an elderly population and did not work as well as it did in other populations, it had a higher sensitivity for predicting mortality than the Prognostic Scoring Index (PSI), derived from the PORT study.[15,19]

PATHOGENESIS

Pneumonia results when host defenses are overwhelmed by an infectious pathogen. This may occur because the patient has an inadequate immune response, often as the result of underlying comorbid illness (congestive heart failure, diabetes, renal failure, COPD, malnutrition), because of anatomic abnormalities (endobronchial obstruction, bronchiectasis), as a result of acute illness-associated immune dysfunction (as can occur with certain viral infections) or because of therapy-induced dysfunction of the immune system (corticosteroids). Pneumonia can also occur in patients who have an adequate immune system if the host defense system is overwhelmed by a large inoculum of microorganisms or if the patient encounters a particularly virulent organism to which he or she has no preexisting immunity or to which the patient has an inability to form an adequate acute immune response.[21,22]

Most pneumonias result from microaspiration, but patients can also aspirate large volumes of bacteria if they have impaired neurologic protection of the upper airway (stroke, seizure) or if they have intestinal illnesses that predispose to vomiting. Other routes of entry include inhalation, which applies primarily to viruses, *Legionella pneumophila,* and *Mycobacterium tuberculosis;* hematogenous dissemination from extrapulmonary sites of infection (right-sided endocarditis); and direct extension from contiguous sites of infection (such as liver abscess).

With this paradigm in mind, it is easy to understand why previously healthy individuals develop infection with virulent pathogens such as viruses *L. pneumophila, Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Streptococcus pneumoniae.* On the other hand, chronically ill patients can be infected by these organisms, as well as by organisms that commonly colonize patients, but only cause infection when immune responses are inadequate. These organisms include enteric gram-negative bacteria (e.g., *Escherichia coli, Klebsiella pneumoniae, P. aeruginosa, Acinetobacter spp.*) and fungi.

Recent studies have evaluated the normal lung immune response to infection and have shown that in most patients with unilateral CAP the inflammatory response is limited to the site of infection, not spilling over to the uninvolved lung or the systemic circulation.[21] In patients with localized pneumonia, tumor necrosis factor (TNF), interleukin (IL)-6, and IL-8 levels were increased in the pneumonic lung and generally not increased in the uninvolved lung or in the serum.[23,24] In patients with severe pneumonia, the immune response is characterized by a "spillover" of the immune response into the systemic circulation, reflected by increases in serum levels of TNF and IL-6.[25] It remains uncertain why localization does not occur in all individuals and why some patients develop diffuse lung injury (e.g., acute respiratory distress syndrome [ARDS]) or systemic sepsis as a consequence of pneumonia. These complications may result from an inability to develop a brisk lung immune response, as a consequence of either specific bacterial virulence factors, inadequate or delayed therapy, or genetic polymorphisms in the immune response. In fact, one study suggested that if bacteria persisted in the lung in spite of therapy, then inflammation in the form of IL-1β was persistent, and at a high level, presumably being driven by the ongoing presence of the organisms.[26]

CLINICAL FEATURES

SYMPTOMS AND PHYSICAL FINDINGS

Patients with CAP and an intact immune system generally have respiratory symptoms such as cough, sputum production, and dyspnea, along with fever and other complaints. Cough is the most common finding and is present in up to 80% of all patients but is less common in those who are elderly, those with serious comorbidity, or patients coming from nursing homes.[27,28] The elderly generally have fewer respiratory symptoms than a younger population, and, as mentioned, the absence of clear-cut respiratory symptoms and an afebrile status have themselves been predictors of an increased risk of death.[29] Pleuritic chest pain is also common in patients with CAP, and in one study its absence was also identified as a poor prognostic finding.[30]

In the elderly patient, pneumonia can have a nonrespiratory presentation with symptoms of confusion, falling, failure to thrive, altered functional capacity, or deterioration in a

preexisting medical illness, such as congestive heart failure.[27-31] In one study, delirium or acute confusion were significantly more frequent in the elderly patients with pneumonia than in age-matched controls who did not have pneumonia.[31] In that study there was no association between the type of isolated microorganisms and the clinical presentation of CAP, except for pleuritic chest pain, which was more common in pneumonia caused by bacterial pathogens such as *S. pneumoniae*. Approximately 16% of elderly patients with pneumonia were considered well nourished, compared with 47% of controls, with kwashiorkor-like malnutrition being the predominant type of nutritional defect and the one associated with delirium on initial presentation. Several other studies have examined the clinical presentation of pneumonia in the elderly and found that a nursing home elderly population had a substantially higher mortality rate than other individuals with CAP (32% vs. 14%).[28] These findings may be a reflection of the fact that those from the nursing home had a higher frequency of comorbid illness and dementia. In another study, Metlay and coworkers studied 1812 patients of all ages and found that with advancing age, patients tended to have a longer duration of symptoms such as cough, sputum production, dyspnea, fatigue, anorexia, myalgia, and abdominal pain.[27] In general, overall symptoms were less prominent in those older than age 65 than in those who were younger.

Another study evaluated 1474 patients with CAP of whom 305 were older than age 80 years.[32] The population excluded those in nursing homes and the population of severe immune suppression (neutropenia, AIDS, and transplant). Clinically, the very elderly had less pleuritic chest pain, headache, and myalgias and were more likely to be afebrile and to have altered mental status on admission. Overall mortality was higher in the older patients (15% vs. 6%), as were in-hospital complications and early mortality (within 48 hours). The PSI values, as expected, were higher in the older population, in part because comorbid illness and age itself add to the PSI score, but, still, the mortality rate for patients in PSI class V was 24% in the younger population versus 32% in the elderly.

Physical findings of pneumonia include tachypnea, crackles, rhonchi, and signs of consolidation (egophony, bronchial breath sounds, dullness to percussion). Patients should also be evaluated for signs of pleural effusion. In addition, extrapulmonary findings should be sought to rule out metastatic infection (arthritis, endocarditis, meningitis) or to add to the suspicion of an "atypical" pathogen such as *M. pneumoniae* or *C. pneumoniae*, which can lead to such complications as bullous myringitis, rash, pericarditis, hepatitis, hemolytic anemia, or meningoencephalitis. As already discussed, one of the most important ways to recognize severe CAP early in the course of illness is to carefully count the respiratory rate. In the elderly, an elevation of respiratory rate can be the initial presenting sign of pneumonia, preceding other clinical findings by as much as 1 to 2 days.[33] In fact, in one study, tachypnea was the most common finding in elderly patients with pneumonia, being present in over 60% of all patients and being present more often in the elderly than in younger patients with pneumonia.[27]

RADIOGRAPHIC FEATURES

The entry point into most algorithms for CAP is the presence of a new radiographic infiltrate, but not all patients with this illness will have this finding when first evaluated. Even when the radiograph is negative, if the patient has appropriate symptoms and focal physical findings, pneumonia may still be present. In one study, 47 patients with clinical signs and symptoms of CAP were evaluated with both chest radiography and high-resolution CT of the chest.[34] Eight patients were identified by CT to have pneumonia; they also had a negative chest radiograph, and many patients had more extensive disease on CT than on chest radiography.[34] The findings of this study confirm the need to repeat the chest film after 24 to 48 hours in certain symptomatic patients with an initially negative chest film. Although some studies have suggested that febrile and dehydrated patients can have a normal chest radiograph when first admitted with pneumonia, the idea of hydrating pneumonia is in the realm of "conventional wisdom" and anecdotal reports.[35]

The presence of alveolar densities (lobar or bronchopneumonic) has been associated with a high likelihood of a bacterial etiology, but there is strong evidence that it is extremely difficult to distinguish among specific pathogens by using patterns of radiographic abnormalities.[36] The chest radiograph may have prognostic value in patients with severe pneumonia, with multilobar infiltrates or rapid progression of infiltrates serving as poor prognostic signs, helping to identify patients who require intensive care.[4] Chest radiographs can be supplemented by CT, which can have value in the critically ill patient in situations when a noninfectious process is being considered, or when complications such as pneumothorax, empyema, or abscess are suspected. CT can suggest certain alternative noninfectious diagnoses such as Wegener's granulomatosis, acute eosinophilic pneumonia, and bronchiolitis obliterans with organizing pneumonia.

When a pleural effusion appears on the initial chest radiograph, it is necessary to distinguish an empyema from a simple parapneumonic effusion, which is best done by sampling the pleural fluid. In some studies, the presence of bilateral pleural effusion has been an independent predictor of short-term mortality in CAP.[37] Pneumococcal pneumonia is the infection most commonly complicated by effusion (36% to 57% of patients), but other pathogens causing effusion include *H. influenzae*, *M. pneumoniae*, *Legionella* species, and tuberculosis.[38]

TYPICAL VS. ATYPICAL PNEUMONIA SYNDROMES

In the past, the clinical and radiographic features of CAP have been organized into patterns of either "typical" or "atypical" pneumonia, with the idea being that specific patterns could suggest certain etiologic agents. The typical pneumonia syndrome is characterized by sudden onset of high fever, shaking chills, pleuritic chest pain, lobar consolidation, a toxic-appearing patient, and the production of purulent sputum. Although this pattern has been attributed to pneumococcus and other bacterial pathogens, these organisms do not always lead to such classic symptoms, particularly in the elderly. The atypical pneumonia syndrome, which is characterized by a subacute illness, nonproductive cough, headache, diarrhea, or other systemic complaints, is usually the result of infection with *M. pneumoniae*, *C. pneumoniae*, *Legionella* species, or viruses. However, patients with impaired immune responses may present in this fashion, even with bacterial pneumonia. Thus, the ability to use the

features on clinical presentation to predict the likely etiologic agents is limited and often misleading.[1,36,39-41]

In one study examining the microbial etiology and clinical presentation of CAP, clinical features were no more than 42% accurate in differentiating pneumococcus, *M. pneumoniae*, and other pathogens from one another.[40] In another study of 359 patients with CAP, a comparison of patients with *S. pneumoniae*, *H. influenzae*, *L. pneumophila*, and *C. pneumoniae*, revealed no significant differences in their clinical presentations.[41] The limitations of clinical features in defining the microbial etiology also apply to evaluations of radiographic pattern.[36]

USING CLINICAL FEATURES TO DEFINE SEVERE COMMUNITY-ACQUIRED PNEUMONIA

Although there is no uniformly accepted definition for severe CAP, this term generally refers to any patient who is admitted to the ICU because of CAP. Most of these patients have "respiratory failure," which is defined by the presence of hypoxemia or hypercarbia, and not all such patients require mechanical ventilation. Bacteremia may not specifically correlate with more severe illness, and its presence alone is not always a predictor of a poor outcome, with most episodes of bacteremia being due to pneumococcus. However, in the elderly with pneumococcal pneumonia, bacteremia is present in one fourth of patients with CAP and is often associated with azotemia and multilobe involvement.[42] When an infection, such as pneumonia, is complicated by severe sepsis or septic shock (not just bacteremia), outcome is adversely affected, with increases in mortality, length of stay, and costs for survivors.[43]

In the 1993 ATS guidelines, 10 criteria from the literature were identified to define patients who needed ICU admission, with the presence of any one of these criteria defining severe illness.[3] However, subsequent studies showed that 65% of all admitted CAP patients (not needing ICU care) also had one of these criteria, and thus a more specific definition of the need for ICU admission was required.[3] To better define the need for ICU care in CAP, Ewig and colleagues applied the 10 ATS criteria to 64 patients who were admitted to the ICU and compared the findings to the features present in 331 patients admitted to the hospital but not the ICU.[3] With this approach, a better definition of severe CAP was derived, with a sensitivity of 78%, a specificity of 94%, a positive predictive value of 75%, and a negative predictive value of 95%. This definition required the presence of either two of three "minor criteria" present on admission or one of two "major criteria" present on admission or later in the hospital course. The minor criteria were systolic blood pressure less than 90 mm Hg, PaO_2/FIO_2 ratio less than 250, or multilobar infiltrates. The major criteria were need for mechanical ventilation or septic shock. As discussed earlier, another way to identify patients with more severe illness is to apply the BTS rule in its original or modified version. One study found that the use of the revised ATS criteria had a sensitivity of 70.7% and a specificity of 72.4% for predicting need for ICU admission.[16] The BTS criteria were much less sensitive, with similar specificity, whereas the PORT rule (class IV or V) had similar sensitivity but lower specificity (although this latter rule was very effective at predicting risk of death).

There is some debate about the benefit of ICU care for patients with CAP, but the benefit seems most certain if patients are admitted early in the course of severe illness, thus emphasizing the need for sensitive criteria to define severe illness.[44] The measurement of admission respiratory rate is a simple and reliable assessment, and in one study investigators observed a linear relationship between admission respiratory rate (once it rose >30 breaths/min) and mortality.[45] If patients are put in the ICU when they meet several "minor" criteria, or when they have an elevated respiratory rate, this type of expectant management may have benefits and may keep mortality rates in the 25% to 50% range. This is in marked contrast to the experience of Hook and coworkers, who observed a 76% mortality rate for pneumococcal bacteremia patients admitted to an ICU, leading the investigators to conclude that ICU care could not favorably affect the outcome of this illness.[44] However, in that study, 45 patients were admitted to the ICU and 42 required intubation, a marked contrast to other studies of severe CAP in which approximately 60% of all patients admitted to the ICU were intubated.[3,4] Comparing Hook's data to these experiences, it seems quite likely that if the critical care physician can rapidly identify a CAP patient with a poor prognosis, this can lead to the use of the ICU in an expectant fashion, and this type of early intervention may have a mortality benefit, compared with an approach that reserves ICU care only for patients with far-advanced pneumonia.

ETIOLOGIC PATHOGENS

LIKELY PATHOGENS

Even with extensive diagnostic testing, an etiologic agent is defined in only about half of all patients with CAP, pointing out the limited value of diagnostic testing and the possibility that we do not know all the organisms that can cause CAP.[1,41] In the past 3 decades, a variety of new pathogens for this illness have been identified, including *L. pneumophila*, *C. pneumoniae*, and hantavirus. In addition, antibiotic-resistant variants of common pathogens such as *S. pneumoniae* have become increasingly common. One of the ways that CAP leads to respiratory failure is when it is complicated by ARDS. All of the bacteria and viruses listed here, as well as pneumonia due to aspiration, have been reported to cause ARDS.

The likely pathogens for infection vary depending on patient risk factors for specific pathogens and the presence of certain comorbid illnesses, referred to in guidelines as "modifying factors," but for all patient groups, including those with severe CAP, pneumococcus is the most common pathogen.[1] In fact, in one recent study, this organism was even identified as being common in patients who had no diagnosis established by routine diagnostic testing.[46] In the past several years, the incidence of antibiotic-resistant pneumococci has increased, and up to 40% of these organisms can have reduced sensitivity to penicillin or other antibiotics.[1,47-51] Not every patient is at risk for infection with these organisms, but identified risk factors for drug-resistant *S. pneumoniae* (DRSP) include beta-lactam therapy in the past 3 months, alcoholism, age older than 65 years, immune suppression, multiple medical comorbidities, and contact with a child in day care.[1,51-53] Other common infecting organisms in those with severe CAP include viruses (e.g., influenza, respiratory syncytial virus, and the coronavirus illness of severe acute respiratory syndrome [SARS]), *L. pneumophila*,

M. pneumoniae, M. tuberculosis, and *H. influenzae* (especially in smokers). In the setting of severe pneumonia, patients can be infected with *S. aureus* or enteric gram-negatives and, rarely, anaerobes. In the elderly, and in those with underlying cardiopulmonary disease, enteric gram-negative organisms are often seen.

The frequency of gram-negative CAP is difficult to define, but in one study of 559 hospitalized patients with CAP, 60 patients had gram-negative enteric infections, including 39 with *P. aeruginosa.*[1,54] A definite etiologic diagnosis of bacterial pneumonia was made if one of the following was present: blood cultures were positive, pleural fluid was positive, or bacterial cultures were positive above a diagnostic threshold using bronchoscopic sampling. A presumptive diagnosis was made if there was a predominant organism on a valid sputum culture. Risk factors for gram negative organisms were probable aspiration (OR = 2.3), previous hospital admission within 30 days of admission (OR = 3.5), previous antibiotics within 30 days of admission (OR = 1.9), and presence of pulmonary comorbidity (OR = 2.8). Risk factors for *P. aeruginosa* were pulmonary comorbidity (OR = 5.8) and previous hospitalization (OR = 3.8). Infection with a gram-negative pathogen led to ICU admission and mechanical ventilation more often than infection with other organisms. The mortality rate of CAP due to *P. aeruginosa* was 28%.

Although aspiration has often been considered a risk factor for anaerobic infection, studies of severe CAP in elderly patients with aspiration risk factors suggested that this population is very likely to have gram-negative infection.[55,56] One study evaluated 95 residents of long-term care facilities who had pneumonia requiring ICU admission, in the presence of risk factors for oropharyngeal aspiration, such as swallowing disorders due to neurologic illness, disruption of the gastroesophageal junction, dysphagia, or anatomic abnormalities. Using protected bronchoalveolar lavage (BAL) sampling within 4 hours of admission, a total of 67 pathogens were identified, with enteric gram-negatives in 49%, anaerobes in 16%, and *S. aureus* in 12%. Fifty-five percent of the anaerobes were recovered along with aerobic gram-negative co-infection. The presence of anaerobes did not correlate with oral hygiene but did correlate with functional status, being more common in patients who were totally dependent. Of the seven patients who received inadequate therapy for anaerobes, six recovered, raising a question about whether these organisms really need to be treated. These findings suggest that anaerobes may not really be pathogens but could simply be colonizers in the institutionalized elderly, including those with aspiration risks.[55]

Primary pulmonary infection with atypical pathogens has been reported for patients with severe CAP for many years. In fact, in one ICU in Spain, atypical pathogens were present in almost 25% of all patients but the responsible organism varied over time. *Legionella* was the most common atypical pathogen leading to severe CAP in 14% of patients during one time period, but in the same hospital a decade later, it was seen in only 2%, having been replaced by *Mycoplasma* and *Chlamydia* infection, which were found in 17% of patients compared with only 6% a decade earlier.[11] Several studies have shown that even if bacterial pathogens lead to CAP, they can be accompanied by atypical pathogens, in the form of mixed infection.[57-59] Atypical pathogens can include *C. pneumoniae, M. pneumoniae,* and *L. pneumophila,* and some recent studies have shown that these infections are common in patients of all ages, not just young and healthy individuals; these organisms have even been reported among the elderly in nursing homes.[1,57,60] When mixed infection is present, it may lead to a more complex course and a longer length of stay than if a single pathogen is present, which may explain the increasing number of studies that show a reduction in CAP mortality, including those in the ICU, when initial therapy provides coverage for these organisms, compared with regimens that do not provide coverage for these organisms.[61,62] There may be a particular synergy between *C. pneumoniae* and pneumococcus, with either sequential, or mixed infection with *C. pneumoniae* leading to a more severe course for pneumococcus.[58] The frequency of atypical pathogens can be as high as 60%, in some series, with as many as 40% of all CAP patients having mixed infection.[59] These high incidence numbers have been derived with serologic testing, which is of uncertain accuracy.

Atypical organism pneumonia may not be a constant phenomenon, and the frequency of infection may vary over the course of time and with geography. In fact, one study showed that the benefit of providing empirical therapy directed at atypical pathogens was variable, being more important in some calendar years than in others.[62] The incidence of *Legionella* infection among admitted patients has varied from 1% to 15% or more and is also a reflection of geographic and seasonal variability in infection rates, as well as a reflection of the extent of diagnostic testing.

RISK FACTORS FOR SPECIFIC PATHOGENS

Table 83-3 summarizes the common pathogens causing CAP in hospitalized patients, including those admitted to the ICU. The classification is based on the presence of clinical risk factors for specific pathogens, referred to as "modifying factors." The modifying factors for DRSP are age older than 65 years, beta-lactam therapy within the past 3 months, alcoholism, immune suppressive illness (including therapy with corticosteroids), multiple medical comorbidities, and exposure to a child in day care.[1,52,63] The modifying factors for

TABLE 83–3. COMMON PATHOGENS CAUSING COMMUNITY-ACQUIRED PNEUMONIA

Inpatient, with no cardiopulmonary disease or modifying factors	*Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae,* mixed infection (bacteria plus atypical pathogen), viruses, *Legionella* species, and others (*M. tuberculosis,* endemic fungi, *Pneumocystis carinii*)
Inpatient, with cardiopulmonary disease and/or modifying factors	All of the above, but drug-resistant *S. pneumoniae* (DRSP) and enteric gram-negative organisms are more of a concern.
Severe community-acquired pneumonia, with no risks for *P. aeruginosa*	*S. pneumoniae* (including DRSP), *Legionella* species, *H. influenzae,* enteric gram-negative bacilli, *S. aureus, M. pneumoniae,* respiratory viruses, others (*C. pneumoniae, M. tuberculosis,* endemic fungi)
Severe CAP, with risks for *P. aeruginosa*	All of the pathogens above plus *P. aeruginosa.*

TABLE 83-4. CLINICAL ASSOCIATIONS WITH SPECIFIC PATHOGENS

Condition	Commonly Encountered Pathogens
Alcoholism	*Streptococcus pneumoniae* (including penicillin-resistant), anaerobes, gram-negative bacilli (possibly *Klebsiella pneumoniae*), tuberculosis
Chronic obstructive pulmonary disease/current or former smoker	*S. pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*
Residence in nursing home	*S. pneumoniae,* gram-negative bacilli, *H. influenzae, S. aureus, Chlamydia pneumoniae;* consider *M. tuberculosis.* Consider anaerobes, but less common.
Poor dental hygiene	Anaerobes
Bat exposure	*Histoplasma capsulatum*
Bird exposure	*Chlamydia psittaci, Cryptococcus neoformans, H. capsulatum*
Rabbit exposure	*Francisella tularensis*
Travel to southwestern USA	*Coccidioidomycosis;* hantavirus in selected areas
Exposure to farm animals or parturient cats	*Coxiella burnetii* (Q fever)
Postinfluenza pneumonia	*S. pneumoniae, S. aureus, H. influenzae*
Structural disease of lung (e.g., bronchiectasis, cystic fibrosis)	*P. aeruginosa, P. cepacia, or Staphylococcus aureus*
Sickle cell disease, asplenia	Pneumococccus, *H. influenzae*
Suspected bioterrorism	Anthrax, tularemia, plague
Travel to Asia	Severe acute respiratory syndrome (SARS), tuberculosis, melioidosis

enteric gram-negatives include residence in a nursing home, underlying cardiopulmonary disease, multiple medical comorbidities, and recent antibiotic therapy. In predicting the likely etiologic pathogens for those admitted to the ICU, patients are divided into a population at risk for pseudomonal infection and a population without this organism being likely. The risk factors for *P. aeruginosa* infection are structural lung disease (bronchiectasis), corticosteroid therapy (>10 mg prednisone/day), broad-spectrum antibiotic therapy for more than 7 days in the past month, and malnutrition.[1]

Table 83-4 shows that certain clinical conditions are associated with specific pathogens, and these associations should be considered in all patients when obtaining a history. For example, if the presentation is subacute, following contact with birds, rats, or rabbits, then the possibility of psittacosis, leptospirosis, tularemia, or plague should be considered. Certain exposures should also raise concern about specific organisms. Thus, *Coxiella burnetii* (Q fever) is a concern with exposure to parturient cats, cattle, sheep, or goats; *Francisella tularensis* is a concern with rabbit exposure; hantavirus with exposure to mice droppings; *Chlamydia psittaci* with exposure to turkeys or infected birds; and *Legionella* with exposure to contaminated water sources (saunas). Following influenza, superinfection with pneumococcus, *S. aureus,* and *H. influenzae* should be considered. With travel to endemic areas in Asia, the onset of respiratory failure after a preceding viral illness should lead to suspicion of SARS. Endemic fungi (coccidioidomycosis, histoplasmosis, and blastomycosis) occur in well-defined geographic areas and may present acutely as symptoms that overlap with acute bacterial pneumonia.

Although a variety of radiographic patterns can be seen in pneumonia, specific findings cannot generally be used to predict the microbial etiology in CAP, but there are certain patterns to keep in mind.[35] Focal consolidation can be seen with infections caused by pneumococcus, *Klebsiella* species, aspiration (especially if in the lower lobes or other dependent segments), *S. aureus, H. influenzae, M. pneumoniae,* and *C. pneumoniae.* Interstitial infiltrates should suggest viral pneumonia as well as infection due to *M. pneumoniae, C. pneumoniae, C. psittaci,* and *P. carinii.* Lymphadenopathy with an interstitial pattern should raise concerns about anthrax, *F. tularensis,* and *C. psittaci,* whereas adenopathy can be seen with focal infiltrates in tuberculosis, fungal pneumonia, anthrax, and bacterial pneumonia. Cavitation can be the result of an aspiration lung abscess, infection with *S. aureus* or aerobic gram-negatives (including *P. aeruginosa*), tuberculosis, fungal infection, nocardiosis, and actinomycosis.

FEATURES OF SPECIFIC PATHOGENS

Streptococcus pneumoniae

This is the most common pathogen for CAP and is a gram-positive, lancet-shaped diplococcus, of which there are 84 different serotypes, each with a distinct antigenic polysaccharide capsule. Eighty-five percent of all infections are caused by one of 23 serotypes, which are now included in a vaccine. Infection is most common in the winter and early spring, which may relate to the finding that up to 70% of patients have a preceding viral illness.[64] The organism spreads from person to person and commonly colonizes the oropharynx of patients before it leads to pneumonia. Pneumonia develops when colonizing organisms are aspirated into a lung that is unable to contain the aspirated inoculum. The classic radiographic pattern is a lobar consolidation, but bronchopneumonia can also occur, and in some series this is the most common pattern.[65] Bacteremia is present in up to 20% of hospitalized patients, and extrapulmonary complications include meningitis, empyema, arthritis, endocarditis, and brain abscess.

In the past decade, antibiotic resistance among pneumococci has become increasingly common, and penicillin resistance, along with resistance to other common antibiotics (macrolides, trimethoprim/sulfamethoxazole, selected cephalosporins), is present in over 40% of these organisms.[1,46,48,51] Fortunately, most penicillin resistance is of the "intermediate" type (penicillin minimal inhibitory concentration [MIC] of 0.1 to 1.0 mg/L) and not of the high level type (penicillin MIC of 2.0 or more). Although the clinical impact of in vitro resistance is uncertain, one large database has data showing that only organisms with a penicillin MIC of more than 4 mg/L can lead to an increased risk of death.[1,47,49]

Whereas early studies could not show an increased mortality rate, after adjusting for disease severity, in patients with resistance, more recent studies have not been so clear.[50,66,67] Turrett and colleagues studied a population of 462 patients with pneumococcal bacteremia, of which more than half

were HIV positive and high-level resistance was a predictor of mortality.[66] Other investigators did not find an increased risk of death from infection with resistant organisms but did find an enhanced likelihood of suppurative complications (empyema) and a more prolonged hospital length of stay.[48,67] The conflicting data in earlier reports may have been the result of studying relatively few patients. Feikin and colleagues studied the impact of pneumococcal resistance in 5837 patients with bacteremic CAP.[49] They found an increased mortality for patients with a penicillin MIC of at least 4 mg/L or greater or with a cefotaxime MIC of 2.0 mg/L or more. However, this increased mortality was only present if patients who died in the first 4 days of therapy were excluded from analysis. Fortunately, very few organisms are currently at this level of resistance, but to prevent more organisms of this type from emerging it may be necessary to identify patients with risk factors for resistance and to target them with highly active antipneumococcal regimens. One limitation of the Feikin study was the failure to account for severity of illness or therapy choices. More recently, Moroney and associates used both cohort study and matched control methods and found that severity of illness, and not resistance or accuracy of therapy, was the most important predictor of mortality.[68] Interestingly, in the case-control part of the study, severity of illness was greater in patients without resistant organisms, implying a loss of virulence among organisms that become resistant, a finding echoed in another study that found absence of invasive illness to be a risk factor for pneumococcal resistance.[52]

The relationship of prior antibiotic use to subsequent pneumococcal resistance has been known, and prior therapy with macrolides, beta-lactams, and quinolones has been identified as a predisposing factor for subsequent resistance to the same class of antibiotic.[52,69-73] One recent study has tried to define if usage of certain specific antibiotic classes was more relevant than others in causing penicillin resistance and how long in the past the usage of antibiotics would predispose to resistance.[73] In this study, 303 patients with pneumococcal bacteremia were evaluated and 98 had penicillin-nonsusceptible strains. The use of penicillins, sulfonamides, and macrolides within either 1 or 6 months before infection was associated with an increased risk of bacteremia with penicillin-nonsusceptible *S. pneumoniae* (PNSP). The odds ratio of increased risk was from threefold to sixfold for beta-lactams and pneumococci. Interestingly, the risk was no lower for therapy in the past 6 months compared with therapy in the past 1 month. Although quinolones were associated with a slightly increased risk of infection with PNSP, this increase was not statistically significant, but other studies have shown that quinolone therapy can predispose to subsequent pneumococcal resistance to this class of antibiotics.[71,72] Prolonged and repeated courses of therapy may be particular risk factors for promoting pneumococcal resistance to beta-lactams, sulfonamides, and macrolides.[73]

Legionella pneumophila

This small, weakly staining, gram-negative bacillus was first characterized after an epidemic in 1976 and can occur either sporadically or in epidemic form. At present, 12 different serogroups of the species *L. pneumophila* have been described, and these account for 90% of all cases of legionnaires' disease, with serogroup 1 causing the most cases. The other species that commonly causes human illness is *L. micdadei*. The organism is water-borne and can emanate from air-conditioning equipment, drinking water, lakes and river banks, water faucets, and shower heads.[74] Infection is generally caused by inhalation of an infected aerosol generated by a contaminated water source. When a water system becomes infected in an institution, endemic outbreaks may occur. In its sporadic form, *Legionella* may account for 7% to 15% of all cases of CAP, being a particular concern in patients with severe forms of illness.[1,11,74]

The classic *Legionella* syndrome is characterized by high fever, chills, headache, myalgias, and leukocytosis.[74] The diagnosis is also suggested by the presence of a pneumonia with preceding diarrhea, along with mental confusion, hyponatremia, relative bradycardia, and liver function abnormalities, but this syndrome is usually not present. Symptoms are rapidly progressive, and the patient may appear to be quite toxic, so this diagnosis should always be considered in patients admitted to the ICU with CAP and in those with rapidly progressive radiographic abnormalities.

Other Organisms

CAP can also be caused by *S. aureus*, which can lead to severe illness and to cavitary lung infection. This organism can also seed the lung hematogenously from a vegetation in the patient with right-sided endocarditis. The incidence of viral pneumonia is difficult to define; but during epidemic times, influenza should be considered. It can lead to a primary viral pneumonia or to secondary bacterial infection with pneumococcus, *S. aureus*, or *H. influenzae*.[75] Viral illness may be responsible for 5% to 15% of CAP cases, and viruses that can lead to respiratory failure, in addition to influenza, include respiratory syncytial virus (which can affect the elderly), varicella (a particular concern in pregnant females with chickenpox), and hantavirus (endemic in the Four Corners area of New Mexico.[75,76] Finally, it important to always consider the diagnosis of tuberculosis in patients with CAP and, in endemic areas, fungal infection with coccidioidomycosis and histoplasmosis, especially in HIV-infected persons.

Several rickettsiae can cause CAP, including Q fever *(Coxiella burnetii)*, which occurs worldwide, Rocky Mountain spotted fever (RMSF), and scrub typhus (*Rickettsia tsutsugamushi)* in Asia and Australia.[77] Transmission typically involves an intermediate vector, often ticks (Q fever, RMSF) or mites (scrub typhus) but also sheep, cows, and contaminated milk (Q fever). These infections have a variable incubation period, ranging from days to a few weeks, and are characterized by a febrile syndrome that may have a pneumonic component and a maculopapular rash (Q fever and RMSF).

Severe Acute Respiratory Syndrome

In late 2003, a respiratory viral infection, caused by a coronavirus, emerged in parts of Asia and was termed *severe acute respiratory syndrome* (SARS). The illness affected people from a variety of endemic areas in Asia but was seen in North America when an outbreak occurred in Toronto, Canada. Importantly, worldwide as many as 20% of affected patients were health care workers, particularly those caring for patients admitted to the ICU. Transmission risk was greatest during emergent intubation and was also possible during noninvasive ventilation, making this latter modality of therapy contraindicated if SARS is suspected.[78] Infection control may be quite effective in preventing the spread of SARS to health care workers and includes the careful handling of respiratory secretions, ventilator circuits, the use of N-95

respirator masks, and careful gowning and gloving.[79] Even more elaborate infection control measures, including personal air exchange units, are needed for health care workers involved in high-risk procedures such as intubation.

Clinically, SARS patients present after a 2- to 11-day incubation period with fever, rigors, chills, dry cough, dyspnea, malaise, headache, and, frequently, pneumonia and ARDS. Laboratory data show not only hypoxemia but also elevated results of liver function tests. In the Toronto experience, about 20% of hospitalized patients were admitted to the ICU and 15% were mechanically ventilated. Respiratory involvement typically began on day 3 of the hospital stay, but respiratory failure was not until day 8.[79] The mortality rate for ICU-admitted SARS patients was over 30%; and when patients died it was generally from multiple system organ failure and sepsis. There is no specific therapy, but anecdotal reports have suggested a benefit to the use of pulse doses of corticosteroids and ribavirin.

Bioterrorism Considerations

Certain airborne pathogens can cause pneumonia as the result of deliberate dissemination by the aerosol route, in the form of a biologic weapon, and present a clinical syndrome of CAP. The pathogens that are most likely to be used in this fashion and that can lead to severe pulmonary infection are *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), and *F. tularensis* (tularemia).[51,80-84] The Centers for Disease Control and Prevention (CDC) has classified these agents as category A pathogens because of their high mortality rate and their potential impact on public health.[80] Other pneumonic pathogens could also serve as agents of biologic warfare but are potentially less serious and are categorized as category B and include *C. burnetii* and *Brucella* species. Certain emerging pathogens are categorized as category C agents and are not widely available as weapons but have the potential for high morbidity and mortality and include hantavirus and multi-drug–resistant tuberculosis.[81] Some agents of bioterrorism can be spread via the aerosol route but do not generally present as pneumonia and include smallpox and viral hemorrhagic fevers (Ebola, Marburg).

In the fall of 2001 in the United States a series of intentional attacks with anthrax led to 11 confirmed cases of inhalational illness.[82,83] Anthrax is an aerobic gram-positive, spore-forming bacillus that had rarely led to disease before 2001. Particle size is essential in determining the infectiousness of the spores, and a size of 1 to 5 μm is required for inhalation into the alveolar space, but generally infection requires an inoculum size of 8000 to 40,000 spores. The organisms initially enter alveolar macrophages and are transported to mediastinal lymph nodes, where they can persist and germinate and produce two toxins (lethal toxin and edema toxin). Illness follows rapidly after germination.[82,83] Although respiratory symptoms are often present, anthrax is not a typical pneumonic illness but rather a disease characterized by hemorrhagic thoracic lymphadenitis, hemorrhagic mediastinitis, and pleural effusion. Whereas the incubation period of anthrax has varied from 2 to 43 days in prior outbreaks, in the October 2001 series the incubation period was from 4 to 6 days.[82] In the U.S. experience, all patients had chills, fever, and sweats and most had nonproductive cough, dyspnea, nausea, vomiting, and chest pain. Chest radiographs were abnormal in all of the first 10 patients, 7 had mediastinal widening, 8 had pleural effusions (generally bloody), and 7 had pulmonary infiltrates.[82,83] Blood cultures were positive in all 8 patients in whom they were obtained before therapy, but sputum culture and Gram's stain are unlikely to be positive. Five of the 11 patients died.

Therapy for anthrax includes supportive management and antibiotics, with possibly some role for corticosteroids if meningeal involvement or mediastinal edema is present. Recommended therapy is ciprofloxacin (400 mg i.v. bid) or doxycycline (100 mg i.v. bid). Until the patient is clinically stable, one to two additional agents should be added, including clindamycin, vancomycin, imipenem, meropenem, chloramphenicol, penicillin, ampicillin, rifampin, and clarithromycin.[82] Therapy should be continued after an initial response, with either ciprofloxacin or doxycycline for at least 60 days.[82] Postexposure prophylaxis can be done with ciprofloxacin or, alternatively, doxycycline or amoxicillin for a total of 60 days.

DIAGNOSTIC EVALUATION

In the patient with severe CAP, diagnostic testing is done to define the presence of pneumonia, the severity of illness and its complications, and the etiologic pathogen. Most studies of severe CAP have not found that establishing an etiologic diagnosis can lead to improved outcome, and mortality is lowest when patients are given empirical therapy that is likely to be effective and that leads to a good clinical response within 48 to 72 hours.[14] As discussed, the diagnosis of CAP is suggested by the history and physical examination and confirmed by chest radiograph. The history may suggest certain pathogens on the basis of epidemiologic considerations (see Table 83-4), but the clinical features and chest radiograph cannot give an exact etiologic diagnosis. An etiologic diagnosis is best established if blood or pleural fluid cultures identify a pathogen, if bronchoscopic techniques demonstrate an organism in high concentrations, or if serologic testing confirms a fourfold rise in titers to specific pathogens (comparing acute and convalescent samples collected weeks apart).

Although defining a specific etiologic diagnosis of CAP allows for focused antibiotic therapy, most patients do not have a specific pathogen identified, and many who do, have this diagnosis made days or weeks later, as the results of cultures or serologic testing become available. In addition, recent studies have emphasized the mortality benefit of prompt administration of effective antibiotic therapy, with a goal of administering intravenous antibiotics within 4 to 8 hours of admission to the hospital for those with moderate to severe illness.[85] Thus, therapy should never be delayed for the purpose of diagnostic testing, and the diagnostic workup should be streamlined, with all patients receiving empirical therapy based on algorithms as soon as possible. With such empirical regimens, as many as 90% of admitted patients will have a prompt response to therapy.[86]

For admitted patients, after a chest radiograph defines the presence of pneumonia, testing should include an assessment of oxygenation (pulse oximetry or blood gas, the latter if retention of carbon dioxide is suspected), routine admission blood work, and two sets of blood cultures (Table 83-5).[1] If the patient has a pleural effusion, this should be tapped and the fluid sent for culture and biochemical analysis. Although blood cultures are positive in only 10% to 20% of CAP patients, they can be used to define a specific diagnosis and to define the presence of drug-resistant pneumococci.[1,47] Sputum culture should be limited to patients suspected of infection with a drug-resistant or unusual pathogen.[1] Urinary antigen testing for pneumococcus or *Legionella* has

TABLE 83–5. DIAGNOSTIC TESTING FOR COMMUNITY-ACQUIRED PNEUMONIA

Test	Sensitivity	Specificity	Comment
Chest radiograph	65%–85%	85%–95%	Computed tomography is more sensitive to infiltrates. Recommended for all patients.
Computed tomography	Gold standard	Not infection specific	Should not be done routinely but helpful to identify cavitation and loculated pleural fluid. Recommended in the evaluation of nonresponding patients.
Blood cultures	10%–20%	High when positive	Usually shows pneumococcus (in 50%-80% of positive samples) and defines antibiotic susceptibility. Recommended in patients with severe CAP.
Sputum Gram's stain	40%–100% depending on criteria	0–100% depending on criteria	Can correlate with sputum culture to define predominant organism and can use to identify unsuspected pathogens. Recommended if sputum culture obtained. May not be able to narrow empirical therapy choices.
Sputum culture			Use if suspect drug-resistant or unusual pathogen, but positive result cannot separate colonization from infection.
Oximetry or arterial blood gas			Both define severity of infection, need for oxygen; if hypercarbia is suspected, a blood gas sample is needed. Recommended in severe community-acquired pneumonia.
Serologic testing for *Legionella, Chlamydia pneumoniae, Mycobacterium pneumoniae,* viruses			Accurate, but usually requires acute and convalescent titers collected 4 to 6 weeks apart. Not routinely recommended.
Legionella urinary antigen	50%–80%		Specific to serogroup 1, but the best acute diagnostic test for *Legionella*
Pneumococcal urinary antigen	70%–100%	80%	False positives if recent pneumococcal infection. Can increase sensitivity with concentrated urine

some potential value for providing a rapid diagnosis. *Legionella* urinary antigen is specific to serogroup 1 infection and is positive in a little more than half of all infected patients, but it is the test that is most likely to be positive in the setting of acute illness.[87] Pneumococcal urinary antigen has a high sensitivity and specificity for diagnosing pneumococcal pneumonia, especially if concentrated urine is examined, but false-positive tests can occur in patients who have had recent pneumococcal infection.[88]

The role of Gram's stain of sputum to guide initial antibiotic therapy is controversial, but this test has its greatest value in guiding the interpretation of sputum culture and can be used to define the predominant organism present in the sample. The role of Gram's stain in focusing initial antibiotic therapy is uncertain because the accuracy of the test to predict the culture recovery of an organism such as pneumococcus depends on the criteria used. If the finding of any gram-positive diplococcus is used to define a positive test, then the test will be sensitive but not very specific. On the other hand, the finding of a predominance of gram-positive diplococci will be specific but not sensitive for predicting the culture recovery of pneumococcus.[1,89] In a recent study, the practical limitations of the test were clear: of 116 patients with CAP, only 42 could produce a sputum sample, of which 23 were valid and only 10 samples were diagnostic, with antibiotics directed to the diagnostic result in only 1 patient.[90] Even if Gram's stain findings were used to focus antibiotic therapy, this would not allow for empirical coverage of atypical pathogens that might be present with pneumococcus, as part of a mixed infection. In spite of these limitations, Gram's stain can be used to broaden initial empirical therapy by enhancing the suspicion for organisms that are not covered in routine empirical therapy (such as *S. aureus* being suggested by the presence of clusters of gram-positive cocci, especially during a time of epidemic influenza).[1]

Routine serologic testing is not recommended.[1,91] However, in patients with severe illness, the diagnosis of legionellosis can be made by urinary antigen testing, which is the test that is most likely to be positive at the time of admission but a test that is specific only for serogroup 1 infection.[87] Bronchoscopy is not indicated as a routine diagnostic test and should be restricted to immune compromised patients and to selected individuals with severe forms of CAP. In the patient admitted to the ICU with CAP, bronchoscopy with quantitative cultures is often done, to be sure that all efforts are being made to define the etiologic agent, but the benefit of this approach is unclear. As mentioned, several studies[9,14,86] have not shown any improvement in outcome when a specific etiologic diagnosis is made for patients with severe CAP. Rather, outcome is improved if the initial empirical therapy is accurate and the patient has a prompt clinical improvement.[14] However, patients who have rapidly progressive lung infection, in spite of therapy, may benefit from invasive diagnostic testing, but again a favorable impact of this testing on patient outcome has not been demonstrated. One population that should be considered for invasive testing is the corticosteroid-treated COPD patient who has a slowly responding or nonresponding pneumonia, because these individuals are at risk for infection with *Aspergillus* and this organism can be recovered from a bronchoscopic sample.[92] In addition, bronchoscopy may have value for the nonresponding patient or other immune-suppressed individuals; and in one study it provided diagnostically useful information for such patients.[93]

One recent study of severe CAP demonstrated the value of diagnostic testing for guiding modifications of antibiotic therapy, rather than focusing on the impact of these methods on initial therapy.[94] In this study, 214 patients with severe CAP were studied and a microbiologic diagnosis was established in 57.3%. When the yield of specific tests was examined, the investigators found that sputum or tracheal aspirate

cultures had the highest yield of any microbiologic investigation, being positive in 44.4% of all patients in which a sample was collected. Blood cultures were positive in 21.1% of the 189 patients sampled, whereas bronchoscopic protected specimen brush was positive in 25% of the 62 patients who were sampled and bronchoalveolar lavage was positive in 34% of the 41 patients who were sampled. When diagnostic testing identified a cause, antibiotics were changed in 74.3% of patients, compared with 32.7% of patients without an etiologic diagnosis ($P<.05$). In most instances, the change in therapy was a simplification of the initial empirical antibiotic regimen that occurred in 65 patients.

THERAPY

Initial antibiotic therapy for severe CAP is necessarily empirical, with the goal of targeting the likely etiologic pathogens, based on the considerations in Tables 83-3 and Table 83-4, which categorize patients on the basis of severity of illness and risk factors for specific pathogens. The likelihood of organisms such as DRSP, enteric gram-negative organisms, and *P. aeruginosa* is determined by the presence of cardiopulmonary disease or "modifying factors."[1] Although a set of likely pathogens can be predicted for each patient (see Table 83-3), and this information can be used to guide initial empirical therapy, if diagnostic testing shows the presence of a specific pathogen, then therapy can be focused.

In choosing empirical therapy of CAP, certain principles and therapeutic approaches should be followed (Table 83-6). For the non-ICU inpatient, therapy can be with an intravenous macrolide (azithromycin) alone, provided that the patient has no underlying cardiopulmonary disease and no risk factors for infection with DRSP, enteric gram-negative organisms, or anaerobes. Although very few patients of this type are admitted to the hospital, macrolide monotherapy has been documented to be effective in this population.[95] The majority of admitted patients will have cardiopulmonary disease and/or modifying factors, and they can be treated with either a selected intravenous beta-lactam (ampicillin/sulbactam, cefotaxime, ceftriaxone, ertapenem, or high-dose ampicillin) combined with a macrolide, or they can receive an intravenous antipneumococcal quinolone (gatifloxacin, levofloxacin, or moxifloxacin) alone.[1,47,51] From the available data, it appears that either regimen is therapeutically equivalent; and, although not proven, it may be useful to use these two types of regimens interchangeably, striving for "antibiotic heterogeneity" in the hospital, so that one regimen is not used exclusively in all patients.[1,51] The choice between these two options may best be determined by using a regimen that is different from what the patient has recently received.

In the ICU population, all individuals should be treated for DRSP and atypical pathogens but only those with appropriate risk factors (see earlier) should have coverage for *P. aeruginosa*.[1] Because the efficacy (especially for meningitis complicating pneumonia), effective dosing, and safety of quinolone monotherapy has not been established for ICU-admitted CAP patients, the therapy for such patients, in the absence of pseudomonal risk factors, should be with a selected intravenous beta-lactam (see earlier), combined with either an intravenous macrolide or an intravenous quinolone. For patients with pseudomonal risk factors, therapy can be with a two-drug regimen, using an antipseudomonal beta-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) plus ciprofloxacin (the most active antipseudomonal quinolone) or, alternatively, with a three-drug regimen, using an antipseudomonal beta-lactam plus an aminoglycoside plus either an intravenous nonpseudomonal quinolone or a macrolide.[1]

Although they should not be used as monotherapy for ICU-admitted CAP patients, the antipneumococcal quinolones have assumed great importance because they can cover pneumococcus (including DRSP), nonpseudomonal gram-negative organisms, and atypical pathogens.[96] Quinolones penetrate well into respiratory secretions and are highly bioavailable, achieving the same serum levels with oral or intravenous therapy and thereby allowing rapid switch to oral therapy in responding patients. Among the antipneumococcal quinolones, there are differences in their intrinsic activity against pneumococcus.[1,96,97] On a MIC basis, the available intravenous agents can be ranked from most to least active as moxifloxacin, gatifloxacin, and levofloxacin. Some data suggest a lower likelihood of both clinical failures and the induction of pneumococcal resistance to quinolones, if the more active agents are used in place of the less active agents.[71,97,98] In addition, there are now reports of failures in pneumococcal pneumonia with levofloxacin, and these have occurred in patients who were infected with levofloxacin-resistant organisms, which arose either after a recent course of quinolone therapy or with the acquisition of resistance during therapy.[71,72]

In addition to the general approach to therapy outlined earlier, there are several other therapeutic issues in the management of CAP.

TIMELINESS OF INITIAL THERAPY OF HOSPITALIZED PATIENTS

For inpatients with CAP, the use of timely and accurate therapy is essential to reduce mortality. In patients with severe CAP, improved survival has occurred if initial empirical therapy is accurate and if it leads to a rapid clinical response.[14,61,85] In one study, if initial therapy led to a clinical response within 72 hours, mortality of severe CAP was approximately 10%, compared with a mortality rate of 60% in patients who had initially ineffective therapy.[14] Another recent finding is the need to provide initial intravenous

TABLE 83–6. EMPIRICAL THERAPY REGIMENS FOR SEVERE COMMUNITY-ACQUIRED PNEUMONIA

No Pseudomonal Risk Factors
Selected beta–lactam (cefotaxime, ceftriaxone)
plus
Intravenously administered macrolide *or* quinolone
Pseudomonal Risk Factors Present
Selected antipseudomonal beta-lactam (cefepime, piperacillin/tazobactam, imipenem, meropenem)
plus
Ciprofloxacin
or
Selected antipseudomonal beta-lactam
plus
Aminoglycoside
plus
Intravenously administered macrolide or antipneumococcal quinolone

antibiotic therapy within 8 hours of the patient's arrival to the hospital.[85] In a large Medicare study of 14,069 patients, mortality at 30 days was significantly reduced for the 75% of patients who received their first dose of therapy within 8 hours of coming to the hospital.[85] Although this has become a target time frame for initial therapy, there was additional benefit for therapy given even sooner, and the new standard is to provide initial therapy within 4 hours of arrival to the hospital.

THE NEED TO TREAT ALL POPULATIONS FOR ATYPICAL PATHOGEN INFECTION

Although the term *atypical* does not accurately describe a specific clinical pneumonia syndrome, the term can be used to refer to a group of pathogens that includes *M. pneumoniae*, *C. pneumoniae*, and *Legionella;* and this group of organisms cannot be reliably eradicated by beta-lactam therapy (penicillins and cephalosporins) but must be treated with a macrolide, tetracycline, or a quinolone. In the current North American CAP guidelines, initial empirical therapy for all patients requires therapy for the possibility of atypical pathogen infection, either as primary infection or as part of a mixed infection.[1,47,51] This recommendation is based on a number of studies, as mentioned earlier, that show a high frequency of these pathogens, when using serologic diagnosis, often in the form of mixed infection, coexisting with a bacterial pathogen.[57-59] In one study of inpatients in the United States, infection with atypical pathogens was more common in older individuals (65 to 79 years) than in those younger than 35 years, and other studies have shown these pathogens to be common in patients with severe CAP.[11,57]

In addition to these data, a number of studies of large populations of inpatients have shown that when therapy includes a macrolide or a quinolone, outcomes, including mortality, are improved, compared with when a beta-lactam is used by itself.[61,62] In the setting of severe CAP, Rello and colleagues evaluated 466 patients and found that when a macrolide was added to a beta-lactam, the mortality and length of stay were improved compared with therapy that did not provide coverage for atypical pathogens.[99] Although these findings are not definitive, they do suggest the need for routine therapy of atypical pathogens, a strategy that may even be needed in patients with bacteremic pneumococcal pneumonia. To date, two studies have suggested that when patients with this infection receive a beta-lactam alone, the mortality is higher than if they receive a beta-lactam combined with a macrolide.[100,101]

Legionella is a potentially important pathogen in patients with severe CAP, and there are many drugs available with in vitro activity against *L. pneumophila*, but there are limited prospective, comparative data on the role of therapy in the outcome of this infection.[74] Retrospective data and long clinical experience support the use of erythromycin at a dose of 4 g/day in the hospitalized patient with *L. pneumophila.* Rifampin should be added in patients with multilobar disease, organ failure, or severe immunosuppression and be administered for the first 3 to 5 days.[1,102] Other macrolides (clarithromycin and azithromycin) are also effective, and azithromycin is available in an intravenous form. Alternatives to the just presented regimen include quinolone antibiotics (ciprofloxacin , levofloxacin, gatifloxacin, and moxifloxacin) or doxycycline.[51] Quinolones are particularly effective in animal models of *Legionella* pneumonia.[102]

There is little information on the proper duration of therapy in patients with CAP, especially those with severe illness. Even in the presence of pneumococcal bacteremia, short durations of therapy may be possible, with a rapid switch from intravenous to oral therapy in responding patients.[103] Generally, *S. pneumoniae* can be treated for 5 to 7 days if the patient is responding rapidly and has received the correct dose of an accurate therapy. The presence of extrapulmonary infection (e.g., meningitis), and the identification of certain pathogens (such as bacteremic *S. aureus* and *P. aeruginosa)* may require longer durations of therapy. Identification of *L. pneumophila* pneumonia may require at least 14 days of therapy, depending on severity of illness and host defense impairments. Most therapy in the ICU will be given intravenously; however, recent studies, using a variety of antibiotics, have suggested that oral therapy may be instituted after as early as 2 to 3 days of parenteral therapy, assuming that the patient's condition has stabilized and is afebrile.[104,105] The switch to oral therapy, even in severely ill patients, may be facilitated by the use of quinolones that are highly bioavailable and achieve the same serum levels with oral therapy as with intravenous therapy.

ADJUNCTIVE THERAPY MEASURES

In addition to antibiotic therapy, the patient with severe CAP may require chest physiotherapy, especially if the patient has either an excessive volume of purulent sputum (>30 mL/day) or severe respiratory muscle weakness resulting in ineffective cough.[106] Aerosolized humidification has been used to reduce sputum viscosity, thereby enhancing clearance in patients who have generally ineffective cough. However, it is likely that much of the generated water vapor is deposited in the upper airway where it is likely to stimulate cough but unlikely to influence the rheologic properties of sputum. Bronchodilator therapy, which also enhances mucociliary clearance, and ciliary beat frequency, is most likely to be of benefit in patients with pneumonia complicating COPD. Activated protein C infusion has been shown to reduce 28-day mortality in patients with severe sepsis and an APACHE II score of more than 26, but in the original trial over half of the treated patients had pneumonia as the cause of sepsis, suggesting a role for this therapy in patients with severe CAP.[107] Adjunctive immune therapy with granulocyte colony-stimulating factor has also been used in severe CAP, with no benefit in mortality or in the course of illness resolution.[108]

EVALUATION OF RESPONSE TO THERAPY

The majority of patients will respond rapidly to accurate empirical therapy within 24 to 72 hours. Clinical response is defined as improvement in symptoms of cough, sputum production, and dyspnea, along with ability to take medications by mouth, declining white blood cell count, and an afebrile status for at least two occasions 8 hours apart.[103-105] In the critically ill patient, improvement in oxygenation may be one of the earliest signs of response to therapy, although few studies have examined mechanically ventilated patients. When a patient has met criteria for clinical response, it is appropriate to consider a switch to an oral therapy regimen, if the patient is otherwise medically and socially stable.[1,104,105] Radiographic improvement lags behind clinical improvement and, in a responding patient, a chest radiograph is not

necessary until 2 to 4 weeks after starting therapy. In general, 50% of patients with pneumococcal pneumonia have radiographic clearing at 5 weeks, whereas the majority clear in 2 to 3 months. With bacteremic disease, 50% have a clear chest radiograph at 9 weeks and most are clear by 18 weeks.[109,110] Radiographic resolution is most influenced by the number of lobes involved and the age of the patient. Radiographic clearance of CAP decreases by 20% per decade after age 20, and patients with multilobar infiltrates take longer to clear than those with unilobar disease.[109]

If the patient fails to respond to appropriate therapy in the expected time interval, then it is necessary to consider infection with a drug-resistant or unusual pathogen (tuberculosis, *C. burnetii*, *Burkholderia pseudomallei*, *C. psittaci*, endemic fungi, or hantavirus); a pneumonic complication (lung abscess, endocarditis, empyema); or a noninfectious process that mimics pneumonia (bronchiolitis obliterans with organizing pneumonia, hypersensitivity pneumonitis, pulmonary vasculitis, bronchoalveolar cell carcinoma, lymphoma, pulmonary embolus).[1] The evaluation of the nonresponding patient should be individualized but may include CT of the chest, pulmonary angiography, bronchoscopy, and, occasionally, open lung biopsy.

PREVENTION

Prevention of CAP is important for all groups of the population but especially the elderly patient, who is at risk for both a higher frequency of infection and a more severe course of illness. Appropriate patients should be vaccinated with both pneumococcal and influenza vaccines, and cigarette smoking should be stopped in all at-risk patients. Even for the patient who is recovering from CAP, immunization while in the hospital is appropriate to prevent future episodes of infection and the evaluation of all patients for vaccination need and the provision of information about smoking cessation are now performance standards used to evaluate the hospital care of CAP patients.[51]

PNEUMOCOCCAL VACCINE

Pneumococcal capsular polysaccharide vaccine can prevent pneumonia in otherwise healthy populations, as was initially demonstrated in South African gold miners and American military recruits.[111-115] The benefits in those of advanced age or with underlying conditions in nonepidemic environments are less clearly defined. The vaccine efficacy has ranged from 65% to 84% in patients with diabetes mellitus, coronary artery disease, congestive heart failure, chronic pulmonary disease, and anatomic asplenia.[1,111-113] In immunocompetent patients over the age of 65, effectiveness has been documented to be 75%. In the immunocompromised patient, effectiveness has not been proven, and this includes patients with sickle cell disease, chronic renal failure, immunoglobulin deficiency, Hodgkin's disease, lymphoma, leukemia, and multiple myeloma. One recent retrospective cohort study evaluated 47,365 patients older than 65 years to determine the impact of pneumococcal vaccination on three different clinical events: hospitalization for CAP, outpatient therapy for CAP, and documented pneumococcal bacteremia.[116] The use of vaccination was associated with a significant reduction in the incidence of pneumococcal bacteremia (OR = 0.56) but no change in the frequency of pneumonia treated in or out of the hospital.

A single revaccination is indicated in a person who is older than age 65 years who initially received the vaccine more than 5 years earlier and was younger than age 65 on first vaccination.[1,51] If the initial vaccination was given at age 65 or older, repeat is not indicated unless the patient has anatomic or functional asplenia or has one of the immune compromising conditions listed earlier. In these patients, revaccination is indicated and the second dose is given at least 5 years after the original dose.

The available pneumococcal vaccine is widely underutilized, but the 23-valent pneumococcal vaccine contains 23 pneumococcal serotypes that cause 85% of all infections due to pneumococcus. A protein-conjugated pneumococcal vaccine has been licensed, and it appears more immunogenic than the older vaccine, but it contains only 7 serotypes, is recommended for healthy children, and has not yet been adequately tested in adults.[51,114] Hospital-based immunization could be highly effective, because over 60% of all patients with CAP have been admitted to the hospital, for some indication, in the preceding 4 years, and hospitalization could be defined as an appropriate time for vaccination.[115] Pneumococcal vaccine can be given simultaneously with other vaccines such as influenza vaccine, but each should be given at a separate site, and the vaccine can, and often should, be given before discharge in the patient admitted for CAP.

INFLUENZA VACCINATION

Influenza epidemics contribute to morbidity and mortality both by causing direct infection and by leading to postinfluenza complications. The influenza vaccine preparations are revised annually to account for changes in the antigenic nature of the virus (antigenic drift) that is present each season. Three strains are represented in each vaccine preparation: an influenza A strain (H3N2); an influenza A strain (H1N1); and one influenza B strain. Vaccination should be given to all patients older than age 65 and to those with chronic medical illness (including nursing home residents) and to those who provide health care to patients at risk for complicated influenza.[1,117] It is given yearly, usually between September and mid November. While the traditional influenza vaccine contains an inactivated virus, there is now an intranasal vaccine containing a live attenuated influenza virus. It is currently approved for individuals ages 5 to 49 years who are not immune suppressed or chronically ill and who do not have asthma.[51]

When the vaccine matches the circulating strain, it can prevent illness in 70% to 90% of healthy persons younger than age 65.[1,118] For older persons with chronic illness, the efficacy is less but the vaccine can still attenuate the influenza infection and lead to fewer lower respiratory tract infections and the associated morbidity and mortality that follow influenza. In many studies, the vaccine has been shown to be cost effective and able to prevent severe illness and death and it can reduce the occurrence of secondary pneumonia and hospitalization.[118]

ANNOTATED REFERENCES

El-Solh AA, Pietrantoni C, Bhat A, et al: Microbiology of severe aspiration pneumonia in institutionalized elderly. Am J Respir Crit Care Med 2003;167:1650-1654.

Prospective microbiologic evaluation of elderly patients admitted to the ICU from a nursing home with severe CAP in the setting of risk factors

for aspiration. The predominant organisms were gram negative and not anaerobic; and even when anaerobes were identified, specific antibiotic therapy did not appear to be necessary.

Ewig S, Ruiz M, Mensa J, et al: Severe community-acquired pneumonia: Assessment of severity criteria. Am J Respir Crit Care Med 1998;158: 1102-1108.

Retrospective single-center study of patients hospitalized with CAP to identify what features were present in those admitted to the ICU. ICU care was best predicted by the presence of one of two major criteria (need for mechanical ventilation or septic shock) or two of three minor criteria (multilobar infiltrates, PaO_2/FiO_2 ratio <250, and systolic BP <90 mm Hg).

Niederman MS, Mandell LA, Anzueto A, et al: Guidelines for the management of adults with community-acquired lower respiratory tract infections: Diagnosis, assessment of severity, antimicrobial therapy and prevention. Am J Respir Crit Care Med 2001;163:1730-1754.

Evidence-based guideline of CAP, focusing on epidemiology, bacteriology and management. A definition of severe CAP is provided, along with a discussion of the limitation of available prognostic scoring systems. For patients with severe CAP, the likely etiologic pathogens are identified and accompanied by suggestions for initial empirical therapy.

Ruiz M, Ewig S, Torres A, et al: Severe community-acquired pneumonia: Risk factors and follow-up epidemiology. Am J Respir Crit Care Med 1999; 160:923-929.

In this single-center study of severe CAP, the etiologic pathogens were defined in two consecutive decades. In both time periods, pneumococcus was the most common pathogen, and atypical organisms were also identified in nearly 20% of all patients. However, the identity of the specific atypical pathogens varied over time, with Legionella *species predominating in one period and being replaced by* Mycoplasma *and* Chlamydia *in the other period.*

Waterer GW, Somes GW, Wunderink RG: Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 2001; 161:1837-1842.

Retrospective study of patients with bacteremic pneumococcal pneumonia showing reduced mortality if patients received a dually effective antibiotic therapy regimen, compared with a single effective antimicrobial agent. The explanation for the benefit of combination therapy was unclear, but patients who received a second agent that provided for atypical pathogen coverage generally did better than patients who did not receive coverage for these organisms, a surprising finding because all patients had proven bacteremic pneumococcal infection.

Chapter 84
NOSOCOMIAL PNEUMONIA

Jean-Yves Fagon • Jean Chastre

KEY POINTS

1. **Nosocomial pneumonia is a common complication occurring in ICU patients.** The risk of nosocomial pneumonia is considerably higher in patients treated with mechanical ventilation.
2. **Etiologic agents differ** according to the population of ICU patients, duration of hospital stay, and prior antimicrobial therapy. Local microbiologic data must be considered when choosing and adapting treatment.
3. **Nosocomial pneumonia is associated with high mortality and morbidity,** particularly in case of infection due to high-risk pathogens such as *Pseudomonas aeruginosa* and *Acinetobacter* species and when initial antimicrobial therapy is inappropriate.
4. **Any strategy designed to manage patients suspected of nosocomial pneumonia** should be able to select appropriate therapy initiated at an early stage of infection and to avoid the overuse of antibiotics. Bronchoscopic techniques, when performed before introduction of new antibiotics, enable physicians to identify patients who need immediate treatment and help to select optimal therapy.
5. **Very simple, no-cost measures may have tremendous impact** on the frequency of nosocomial pneumonia.

Nosocomial pneumonia (NP) or hospital-acquired pneumonia (HAP) is defined as pneumonia occurring more than 48 hours after hospital admission and excluding any infection that is incubating at the time of hospital admission. NP is the second most frequent nosocomial infection and represents the leading cause of death from infection that is acquired in the hospital. ICU-acquired pneumonia is pneumonia that arises more than 48 hours after ICU admission. The term *ventilator-associated pneumonia* (VAP) refers to pneumonia that occurs in patients intubated and treated with mechanical ventilation. There are patients with severe NP who are transferred to the ICU and become intubated; similarities between the management of such patients and patients with VAP exist; they are, however, not included in the definition of VAP. Most studies cited in this chapter have examined VAP.

EPIDEMIOLOGY

INCIDENCE

The majority of studies have reported incidence rates of NP in general ICU populations varying between 8% and 20%.[1] The risk of pneumonia seems to be considerably higher in the subset of ICU patients treated with mechanical ventilation. Cross and Roup have published specific data on overall rates of nosocomial pneumonia in relation to the use of respiratory devices.[2] Pneumonia rates in patients with an endotracheal tube and mechanical ventilation were increased 10-fold over patients with no respiratory therapy devices. Prolonged mechanical ventilation is the most important factor associated with NP. However, VAP may occur within the first 48 hours after intubation.[3] It is usual to distinguish early-onset VAP, which occurs during the first 4 or 5 days of mechanical ventilation, from late-onset VAP, which develops 5 days or more after initiation of mechanical ventilation. Not only are the causative pathogens commonly different but the disease is usually less severe and the prognosis better in early-onset VAP.[4] By using an actuarial method, the cumulative risk of pneumonia in this context was estimated to be 6.5% at 10 days and 19% at 20 days after the onset of mechanical ventilation. Furthermore, the incremental risk of pneumonia was virtually constant throughout the entire ventilation period, with a mean rate of about 1% per day.[5] In contrast, Cook and colleagues demonstrated in a large series of 1014 mechanically ventilated patients that, although the cumulative risk for developing VAP increased over time, the daily hazard rate decreased after day 5.[6] The risk per day was evaluated at 3% on day 5, 2% on day 10, and 1% on day 15. However, the daily risk for developing VAP is highly dependent on the population being studied (including underlying illnesses, comorbid disease, severity of illness) and also on many other factors, including therapeutic interventions and particularly the number of patients in the given population who received antibiotics after their admission to the ICU.

VAP is thought to be a common complication of the acute respiratory distress syndrome (ARDS). Most clinical studies have found that pulmonary infection affects between 34% and 70% or more of patients with ARDS, often leading to the development of sepsis, multiple organ failure, and death.[1,7-11] In one study on 56 ARDS patients, protected specimen brush and bronchoalveolar lavage were used to define pneumonia and the VAP rate was 55%,[9] whereas it was only 28% for 187 non-ARDS patients diagnosed with the same criteria during the same period. It was specified that early-onset VAP was relatively rare in ARDS patients: only 10% of the first VAP episodes, as opposed to 40% in non-ARDS patients.

MORTALITY, MORBIDITY, AND COST

Crude ICU mortality rates of 24% to 76% have been reported for VAP at a variety of institutions. The results of several studies conducted between 1986 and 2001 have confirmed that observation: despite variations among studies that partly reflect the populations considered, overall mortality rates for patients with or without VAP were, respectively, 55% versus 25%,[12] 71% versus 28%,[13] 33% versus 19%,[14] 38% versus 9%,[15] and 44% versus 19%.[16] These rates correspond to increased risk ratios of mortality of VAP patients of 2.2, 2.5, 1.7, 4.4, and 2.3, respectively. They are increased by age, severity of illness, late onset, medical diagnosis, resistant pathogens, and inappropriateness of initial antimicrobial therapy. Studies evaluating the attributable mortality of VAP are difficult to interpret because they were conducted in different populations that used different diagnostic criteria to identify patients with infection and different methods to control for confounding factors.

The prognosis for aerobic, gram-negative bacilli VAP is considerably worse than that for infection with gram-positive pathogens, which are fully susceptible to antibiotics. Death rates associated with *Pseudomonas* pneumonia are particularly high, ranging from 70% to more than 80% in several studies.[13,17,18] Concerning gram-positive pathogens, in a study comparing VAP due to methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-sensitive *S. aureus* (MSSA), mortality was found to be directly attributable to pneumonia for 86% of the former cases versus 12% of the latter, with a relative risk of death equal to 20.7 for MRSA pneumonia.[19]

Using multiple logistic regression analysis, Torres and coworkers emphasized the complex relationships among the severity of pneumonia itself, the severity of underlying disease leading to ICU admission and the adequacy of initial antimicrobial treatment.[14] The important prognostic role played by the appropriateness of the initial empirical antimicrobial therapy was analyzed by several other investigators.[20-24]

Thus, considering many different kinds of evidence, VAP seems indeed associated with a 20% to 30% higher risk of death than that due to the underlying disease alone.

It is impossible to accurately evaluate the morbidity and excess costs associated with nosocomial pneumonia. However, with respect to morbidity measures, the prolonged hospital stay as a direct consequence of pneumonia has been estimated in several studies; it ranges from 4 to 8 days in the majority of studies.[25,26] These prolonged hospitalizations underscore the considerable financial burden imposed by the development of VAP.[27]

ETIOLOGIC AGENTS

Nosocomial pneumonia may be caused by a variety of pathogens and, in many patients, more than one pathogen may be isolated. Microorganisms responsible for nosocomial pneumonia may differ according to the population of ICU patients, the durations of hospital and ICU stays, and the specific diagnostic method(s) used. Several studies have reported that greater than 60% of VAP are caused by aerobic, gram-negative bacilli, such as *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae,* or *Acinetobacter* species.[1,5,14,27-32] More recently, however, some investigators have reported that gram-positive bacteria have become increasingly more common in this setting, with *S. aureus* being the predominant gram-positive isolate. For example, *S. aureus* was responsible for most episodes of nosocomial pneumonia in the European Prevalence of Infection in Intensive Care (EPIC) study, accounting for 31% of the 836 cases with identified responsible pathogens.[33] The data from 24 investigations conducted on ventilated patients, for whom bacteriologic studies were restricted to uncontaminated specimens, confirmed those results: gram-negative bacilli represented 58% of recovered organisms, and a relatively high rate of gram-positive pneumonias was also reported in those studies, with *S. aureus* involved in 20% of the cases (Table 84-1).[1]

The high rate of polymicrobial infection in VAP has been emphasized repeatedly. In a study on 172 episodes of bacteremic nosocomial pneumonia, 13% of lung infections were caused by multiple pathogens.[34] Similarly, when the protected specimen brush (PSB) technique was used to identify the causative agents in 52 consecutive cases of VAP, a 40% polymicrobial infection rate was found,[5] a value similar to that observed in another study conducted at the same time on a comparable population of ventilated patients.[35]

Underlying diseases may predispose patients to infection with specific organisms. Patients with chronic obstructive pulmonary disease (COPD) are, for example, at increased risk for *Haemophilus influenzae, Moraxella catarrhalis,* or *S. pneumoniae* infections; cystic fibrosis increases the risk of *P. aeruginosa* and/or *S. aureus* infections, whereas trauma and neurologic patients are at increased risk for *S. aureus* infection.[4,19,27,36] Furthermore, the causative agent for pneumonia differs among ICU surgical populations,[37] with 18% of the nosocomial pneumonias being due to *Haemophilus* or pneumococci, particularly in trauma patients.

Despite somewhat different definitions of early-onset pneumonia, varying from less than 3 to less than 7 days,[4,32] high rates of *H. influenzae, S. pneumoniae,* MSSA, or susceptible Enterobacteriaceae were constantly found in early-onset VAP, whereas *P. aeruginosa, Acinetobacter* species, MRSA, and multiresistant gram-negative bacilli were significantly more frequent in late-onset VAP.[4,31,32] This different distribution pattern of etiologic agents between early- and late-onset VAP is also linked to the frequent administration

TABLE 84–1. ETIOLOGY OF VENTILATOR-ASSOCIATED PNEUMONIA AS DOCUMENTED BY BRONCHOSCOPIC TECHNIQUES IN 24 STUDIES FOR A TOTAL OF 1689 EPISODES AND 2490 PATHOGENS

Pathogen	Frequency (%)
Pseudomonas aeruginosa	24.4
Acinetobacter spp.	7.9
Stenotrophomonas maltophilia	1.7
Enterobacteriaceae*	14.1
Haemophilus spp.	9.8
Staphylococcus aureus†	20.4
Streptococcus spp.	8.0
Streptococcus pneumoniae	4.1
Coagulase-negative staphylococci	1.4
Neisseria spp.	2.6
Anaerobes	0.9
Fungi	0.9
Others (<1% each)‡	3.8

*Distribution when specified: *Klebsiella* spp., 15.6%; *Escherichia coli,* 24.1%; *Proteus* spp., 22.3%; *Enterobacter* spp., 18.8%; *Serratia* spp., 12.1%; *Citrobacter* spp., 5.0%; *Hafnia alvei,* 2.1%.
†Distribution when specified: MRSA, 55.7%; MSSA, 44.3%.
‡Including *Corynebacterium* spp., *Moraxella* spp., and *Enterococcus* spp.

of prior antimicrobial therapy in many patients with late-onset VAP. In a prospective study that included 129 episodes of nosocomial pneumonia documented by PSB specimens, the distributions of responsible pathogens were compared according to whether the patients had received antimicrobial therapy before pneumonia onset.[28] The most striking finding was that the rate of pneumonia caused by gram-positive cocci or *H. influenzae* was significantly lower ($P < .05$) in patients who had received antibiotics, whereas the rate of pneumonia caused by *P. aeruginosa* was significantly higher ($P < .01$). A stepwise logistic regression analysis retained only prior antibiotic use (OR = 9.2, $P < .0001$) as significantly influencing the risk of death from pneumonia.[28] Very similar results were obtained when multivariate analysis was used to determine risk factors for VAP caused by potentially drug-resistant bacteria such as MRSA, *P. aeruginosa, A. baumannii,* and/or *S. maltophilia* in 135 consecutive episodes of VAP.[32] Only three variables remained significant: duration of mechanical ventilation before VAP onset for 7 days or more (OR = 6.0), prior antibiotic use (OR = 13.5), and prior use of broad-spectrum drugs (third-generation cephalosporin, fluoroquinolone, and/or imipenem) (OR = 4.1).[32] Not all studies, however, have confirmed this distribution pattern. Their finding may, in part, be due to the prior hospitalization and use of antibiotics in many patients developing early-onset VAP before their transfer to the ICU.

The incidence of multiresistant pathogens is also closely linked to local factors and varies widely from one institution to another. Consequently, each ICU has to continuously collect meticulous epidemiologic data. With these aims, variations of VAP etiology among three Spanish ICUs were analyzed[31] and compared with data collected in Paris.[32] The authors concluded that VAP pathogens varied widely among these four treatment centers, with marked differences in all of the microorganisms isolated from VAP episodes in Spanish centers as compared with the French site. Clinicians must clearly be aware of the common microorganisms associated with both early-onset and late-onset VAP in their own hospitals to avoid the administration of initial inadequate antimicrobial therapy.

Legionella species,[38] anaerobes,[39] fungi,[40] viruses,[41] and even *Pneumocystis carinii* should be mentioned as potential causative agents but are not considered to be common in the context of pneumonia acquired during mechanical ventilation. However, several of these causative agents may be more common and potentially underreported because of difficulties involved with the diagnostic techniques used to identify them, including anaerobic bacteria and viruses.[39,41] By examining currently available data, the clinical significance of anaerobes in the pathogenesis and outcome of VAP remains unclear, except as etiologic agents in patients with necrotizing pneumonitis, lung abscess, or pleuropulmonary infections. *Legionella pneumophila* as a cause of nosocomial pneumonia is variable but probably more frequent in immunocompromised patients, particularly organ transplant recipients, and in hospitals with the organism present in the hospital water supply. Isolation of fungi, most frequently *Candida* species, at significant concentrations poses interpretative problems. Invasive disease has been reported in VAP but, more frequently, yeasts are isolated from respiratory tract specimens in the apparent absence of disease. One prospective study examined the relevance of isolating *Candida* species from 25 non-neutropenic patients who had been mechanically ventilated for at least 72 hours.[40] Just after death, multiple culture and biopsy specimens were obtained with bronchoscopic techniques. Although 10 patients had at least one biopsy specimen positive for *Candida* species, only 2 had evidence of invasive pneumonia as demonstrated by histologic examination.

PREDISPOSING FACTORS

A number of factors have been suspected or identified to increase the risk of pneumonia in ICU, including those identified in the subset of mechanically ventilated patients. The data indicated specific high-risk populations (i.e., patients with COPD, ARDS, serum albumin level less than 2.2 g/dL, patients undergoing mechanical ventilation for more than 3 days, those requiring intracranial pressure monitoring, those with coma or impaired consciousness, burns, or trauma, and more generally those with severe underlying medical conditions as evaluated by a high APACHE II or APACHE III score or presence of organ failure) and specific treatment modalities or therapeutic intervention (i.e., use of H_2 blockers or antacids, previous antibiotics, use of drugs that are markers for severe underlying disease such as dopamine, dobutamine, or paralytic agents or continuous sedation, re-intubation, and frequent changes of ventilator circuits, bronchoscopy, or nasogastric tube) as being independently associated with nosocomial pneumonia.

SURGERY

Postsurgical patients are at increased risk for pneumonia.[15,37,42] A history of smoking, low albumin level, longer preoperative stays, longer surgical procedures, and thoracic or upper abdominal operative sites were significant risk factors for postoperative pneumonia. In their study comparing adult critical-care populations, Cunnion and colleagues demonstrated that surgical ICU patients were found to have consistently higher rates of nosocomial pneumonia than medical ICU patients with a risk ratio equal to 2.2.[26] The relative importance of the surgical procedure itself versus intubation, prophylactic antibiotics, and/or other variables therefore remains to be clearly elucidated in surgical patients.

MEDICATION

Antimicrobial Agents

The use of antibiotics in the hospital setting has been associated with an increased risk of nosocomial pneumonia and selection of resistant pathogens.[15,28,32,33,36,43] In a cohort study of 320 patients, prior antibiotic administration was identified by logistic regression analysis to be one of the four variables independently associated with VAP along with organ failure, age older than 60 years, and the patient's head positioning (i.e., flat on his back or supine vs. head and thorax raised 30 to 40 degrees or semirecumbent).[15] However, other investigators found that antibiotic administration during the first 8 days was associated with a lower risk of early-onset VAP.[44,45] For example, Sirvent and coworkers showed that a single dose of a first-generation cephalosporin given prophylactically was associated with a lower rate of early-onset VAP in patients with structural coma.[46] Finally, the results of the multicentric Canadian study on the incidence of and risk factors for VAP indicated that antibiotic treatment conferred protection against VAP.[6] This apparent protective effect of antibiotics disappears after 2 to 3 weeks,

suggesting that a higher risk of VAP cannot be excluded beyond this point.

In contrast, prolonged antibiotic administration to ICU patients for primary infection is thought to favor selection and subsequent colonization with resistant pathogens responsible for superinfections.[5,32,43,47,48] According to our data on 567 ventilated patients, those who had received antimicrobial therapy within the 15 days preceding lung infection were not at higher risk for development of VAP[5] but 65% of the lung infections that occurred in patients who had received broad-spectrum antimicrobial drugs versus only 19% of those developing in patients who had not received antibiotics were caused by *Pseudomonas* or *Acinetobacter* species. Therefore, strong arguments suggest that the prophylactic use of antibiotics in the ICU increases the risk of superinfection with multiresistant pathogens while only delaying the occurrence of nosocomial infection.

Stress Ulcer Prophylaxis

According to meta-analyses of the efficacy of stress-ulcer prophylaxis in ICU patients, respiratory tract infections were significantly less frequent in patients treated with sucralfate than those receiving antacids or H_2 blockers.[49-52] However, this conclusion was not fully confirmed in a very large, multicenter, randomized, blinded, placebo-controlled trial that compared sucralfate suspension (1 g q6h) with the H_2-receptor antagonist ranitidine (50 mg q8h) for the prevention of upper gastrointestinal bleeding in 1200 patients who required mechanical ventilation.[53] Clinically relevant gastrointestinal bleeding developed in 10 of the 596 (1.7%) patients receiving ranitidine, as compared with 23 of the 604 (3.8%) receiving sucralfate (RR, 0.44; 95% CI, 0.21 to 0.92; $P = 0.02$). In the ranitidine group, 114 of 596 (19.1%) patients had VAP, as diagnosed by an adjudication committee using a modified version of the CDC criteria, versus 98 of 604 (16.2%) in the sucralfate group (RR, 1.18; 95% CI, 0.92 to 1.51; $P = 0.19$). Thus, although pneumonia rates were similar for the two groups, the relative risks suggest a trend toward a lower pneumonia rate for patients receiving sucralfate. Furthermore, VAP occurred significantly less frequently in patients receiving sucralfate when the diagnosis of pneumonia was based on Memphis VAP Consensus Conference criteria (if there was radiographic evidence of abscess and a positive needle aspirate, or histologic proof of pneumonia at biopsy or autopsy) ($P = .03$).[53]

Sucralfate appears to have a small protective effect against VAP because stress-ulcer prophylactic medications that raise the gastric pH might themselves increase the incidence of pneumonia. This contention is supported by direct comparisons of trials of H_2-receptor antagonists versus no prophylaxis, which showed a trend toward higher pneumonia rates among the patients receiving H_2-receptor antagonists (OR, 1.25; 95% CI, 0.78 to 2.00).[51] Furthermore, the comparative effects of sucralfate and no prophylaxis are unclear. Among 226 patients enrolled in two randomized trials, those receiving sucralfate tended to develop pneumonia more frequently than those given no prophylaxis (OR, 2.11; 95% CI, 0.82 to 5.44).[54,55]

ENDOTRACHEAL TUBE, RE-INTUBATION, AND TRACHEOSTOMY

The presence of an endotracheal tube by itself circumvents host defenses, causes local trauma and inflammation, and increases the probability of aspirating nosocomial pathogens from the oropharynx around the cuff. Clearly, the type of endotracheal tube may also influence the incidence of aspiration. With low-volume, high-pressure endotracheal cuffs, an incidence of 56% was reported, which decreased to 20% with the advent of high-volume, low-pressure cuffs.[56]

In addition to the presence of endotracheal tubes, re-intubation is, per se, a risk factor for nosocomial pneumonia, as indicated by Torres and colleagues.[57] This result is probably related to an increased risk of aspiration of colonized oropharyngeal secretions into the lower airways in patients with glottic dysfunction and/or impaired consciousness after several days of intubation. Another explanation is direct aspiration of gastric contents into the lower airways, particularly when a nasogastric tube is kept in place after extubation. In their case-control study, Torres and colleagues found a 47% pneumonia rate in reintubated patients as compared with 4% in controls matched for the duration of prior mechanical ventilation ($P = .0007$).

The role of early tracheotomy in VAP prevention remains controversial, with only a few studies that examined this issue.[58-60] Whereas some studies found a reduction in the rate of VAP in patients with early tracheotomy,[59] others could not demonstrate any benefit.[58,60] For example, in a randomized, prospective, multicenter trial on 112 patients who were thought to need prolonged mechanical ventilation, there were no differences, at least until day 14, between ICU length of stay, pneumonia rate, or mortality between the 53 patients who underwent early (day 3 to 5) tracheotomy and the 59 who were managed using translaryngeal intubation. In the absence of any meaningful data, until a properly constructed randomized trial is performed to define the timing and utility of tracheotomy in the ICU, its true impact on decreasing VAP will remain merely speculative.[61]

NASOGASTRIC TUBE, ENTERAL FEEDING, AND PATIENT POSITION

Nearly all patients receiving mechanical ventilation have a nasogastric tube inserted to manage gastric and enteral secretions, prevent gastric distention, or provide nutritional support. The nasogastric tube is not widely considered to be a potential risk factor for pneumonia, but it may increase oropharyngeal colonization, cause stagnation of oropharyngeal secretions, and increase reflux and the risk of aspiration. Using multivariate analysis, Joshi and colleagues identified the presence of a nasogastric tube as one of the three independent risk factors for nosocomial pneumonia in a series of 203 patients admitted to the ICU for 72 hours or more.[62]

Early initiation of enteral feeding is generally regarded as beneficial in critically ill patients, but it may increase the risk of gastric colonization, gastroesophageal reflux, aspiration, and pneumonia.[63] Winterbauer and colleagues described a 38% incidence of aspiration in enterally fed, critically ill patients with small-bore nasogastric tubes, but all patients were fed by the bolus technique.[64] Recent data suggest that aspiration is infrequent when small-bore feeding tubes and continuous infusion are used.[65,66] The aspiration rate generally varies as a function of differences in the patient population, neurologic function, type of feeding tube, location of the feeding port, and the method of evaluating aspiration.[67] Clinical impression and preliminary data suggest that postpyloric or jejunal feeding entails less risk of aspiration and may therefore

be associated with fewer infectious complications than gastric feeding, although this point remains controversial.[68,69]

Maintaining mechanically ventilated patients with a nasogastric tube in place in the supine position is also a risk factor for aspiration of gastric contents into the lower airways. Torres and colleagues injected radioactive material via a nasogastric tube directly into the stomach of 19 mechanically ventilated patients and found that mean radioactive counts in endobronchial secretions were higher in a time-dependent fashion in samples obtained while patients were in the supine position than in those obtained while patients were in the semirecumbent position.[70] The same microorganisms were isolated from stomach, pharynx, and endobronchial samples in 32% of the specimens taken while patients were semirecumbent and in 68% of those taken while patients were in the supine position. These results suggest that placing mechanically ventilated patients in the semirecumbent position is a simple and effective means to minimize aspiration of gastric contents into lower airways and hence constitutes a recommendable, no-cost prophylactic measure for those who can tolerate this position. Such experimental results were indirectly confirmed by Kollef, who demonstrated that supine patient head positioning during the first 24 hours of mechanical ventilation was an independent risk factor for acquiring VAP.[15] However, another study published by the same group that demonstrated the effect of body position on gastric content aspiration reported disappointing results, strongly supporting that gastroesophageal reflux in mechanically ventilated patients with a nasogastric tube occurs irrespective of body position.[71] A randomized trial conducted by the same group was stopped after the planned interim analysis because the frequency and the risk of VAP were significantly lower for the semirecumbent group.[72]

RESPIRATORY EQUIPMENT

Respiratory equipment itself may act as a source of bacteria responsible for nosocomial pneumonia. In past years, the major risk of infection was associated with contaminated reservoir nebulizers, designed to deliver small-sized particles suspended in the effluent gas.[12] These observations led to the current trends in respiratory therapy with the use of cascade humidifiers, which do not generate microaerosols. Nevertheless, respiratory equipment continues to provide a source of bacterial contamination. For example, medication nebulizers inserted into the inspiratory phase tube of the mechanical ventilator circuit may produce bacterial aerosols after a single use.[73]

Mechanical ventilators with humidifying cascades often have high levels of tubing colonization and condensate formation that may also be risk factors for pneumonia. Craven and colleagues examined condensate colonization in 20 circuits and found a median level of 2.0×10^5 organisms/mL, and 73% of the 52 gram-negative isolates present in the patient's sputum were subsequently isolated from condensate.[74] As most of the tubing colonization was derived from the patient secretions, the highest bacterial counts were present near the endotracheal tube. Simple procedures such as turning the patient or raising the bed rail may accidentally wash contaminated condensate directly into the patient's tracheobronchial tree. Inoculation of large amounts of fluid with high bacterial concentrations is an excellent way of overwhelming pulmonary defense mechanisms and producing pneumonia. Heating ventilator tubing markedly reduces the rate of condensate formation, but heated circuits are often nondisposable and are expensive. To date, no scientific evidence confirms that heated circuits reduce the incidence of VAP. In-line devices with one-way valves to collect condensate are probably the easiest way to handle this problem. They should be correctly positioned into disposable circuits and emptied regularly.

Similarly, there is not sufficient evidence to suggest that heat and moisture exchangers (HME) are superior to cascade humidifiers in terms of the risk of VAP. Dreyfuss and colleagues reported similar rates of pneumonia in 61 patients allocated to humidification with a HME and 70 patients with a heated humidifier (10% vs. 11%, NS).[75] When HME was used, changing the HME every 48 hours did not affect ventilator circuit colonization, and the authors suggest that the cost of mechanical ventilation may be substantially reduced without any detriment to the patient by extending the time between HME changes from 24 to 48 hours.[76] In recent years, several authors have reported no difference in pneumonia rates with ventilator circuit changes at 48-hour and 7-day intervals or with no change.[77-79]

SINUSITIS

While many studies have compared the risk of nosocomial sinusitis as a function of the intubation method used and the associated risk of VAP,[80-84] only a few were adequately powered to give a clear answer. In one study on 300 patients who required mechanical ventilation for at least 7 days and were randomly assigned to undergo nasotracheal or orotracheal intubation, computed tomographic (CT) evidence of sinusitis was observed slightly more frequently in the nasal than oral endotracheal group ($P = .08$), but this difference disappeared when only bacteriologically confirmed sinusitis was considered.[85] The rate of infectious maxillary sinusitis and its clinical relevance were also prospectively studied in 162 consecutive critically ill patients, who had been intubated and mechanically ventilated for 1 hour to 12 days before enrollment.[84] All had a paranasal CT scan within 48 hours of admission that was used to divide them into three groups (no, moderate, or severe sinusitis), according to the radiologic appearance of the maxillary sinuses. Patients who had no sinusitis at admission (n = 40) were randomized to receive endotracheal and gastric tubes via the nasal or oral route and, based on radiologic images, respective sinusitis rates were 96% and 23% ($P < .03$); yet, no differences in the rates of infectious sinusitis were documented according to the intubation route. However, VAP was more common in patients with infectious sinusitis, with 67% of them developing lung infection in the days after the diagnosis of sinusitis.[84] Therefore, whereas it seems clear that infectious sinusitis is a risk factor for VAP, no studies have yet been able to definitively demonstrate that orotracheal intubation decreases the infectious sinusitis rate compared with nasotracheal intubation, and thus no firm recommendations on the best route of intubation to prevent VAP can be advanced.

INTRAHOSPITAL PATIENT TRANSPORT

A prospective cohort study conducted on 531 mechanically ventilated patients evaluated the impact of transporting the patient out of the ICU to other sites within the hospital.[86] Results showed that 52% of the patients had to be moved at

least once for a total of 993 transports and that 24% of the transported patients developed VAP compared with 4% of the patients confined to the ICU ($P < .001$). Multiple logistic regression analysis confirmed that transport out of the ICU was independently associated with VAP (OR = 3.8; $P < .001$).

EPIDEMIOLOGY

Diagnosis of ventilator-associated pneumonia is a controversial subject.[87,88] This debate is the result of differences in the analysis of three important questions: interpretation of clinical signs and symptoms suggestive of lung infection, differentiation between colonization and infection of the lower respiratory tract, and use of antibiotics in the ICU.

The first major difficulty in diagnosing VAP is that the presence of signs suggestive of pneumonia in non-ICU patients are too nonspecific to be of diagnostic value for ventilated patients.[1,89,90] The systemic signs of infection, such as fever, tachycardia, and leukocytosis, are nonspecific findings and can be caused by any condition that releases cytokines.[91] In trauma and other surgical patients, fever and leukocytosis should prompt the physician to suspect infection, but during the early post-traumatic or postoperative period (i.e., during the first 72 hours), these findings usually are not conclusive. However, later, fever and leukocytosis are more likely to be caused by pulmonary or nonpulmonary (vascular catheter infection, gastrointestinal infection, urinary tract infection, sinusitis, or wound infection) infections, but even then, other events associated with an inflammatory response (e.g., devascularized tissue, open wounds, pulmonary edema, and/or infarction) can be responsible for these findings. Although the plain (usually portable) chest radiograph remains an important component in the evaluation of hospitalized patients with suspected pneumonia, it is most helpful when it is normal and rules out pneumonia. When infiltrates are evident, the particular pattern is of limited value for differentiating among cardiogenic pulmonary edema, noncardiogenic pulmonary edema, pulmonary contusion, atelectasis (or collapse), and pneumonia. Because atelectasis is common in ICU patients, the contribution of repeating the chest radiograph after vigorous pulmonary physiotherapy was emphasized to differentiate infiltrates caused by atelectasis from those due to infection.[92] Very few studies have examined the accuracy of the portable chest radiograph in the ICU.[90,92-95] In a review of 24 patients with autopsy-proven pneumonia who were receiving mechanical ventilation, no single radiographic sign had a diagnostic accuracy greater than 68%.[93] When the group was divided into patients with and without ARDS, however, a significant difference was noted. The presence of air bronchograms or alveolar opacities in patients without ARDS correlated with pneumonia, whereas no such correlation was found for patients with ARDS. A variety of causes other than pneumonia can explain asymmetrical consolidation in patients with ARDS, and marked asymmetry of radiographic abnormalities has also been reported in patients with uncomplicated ARDS.[96] Several clinical studies confirmed the poor correlation between clinical signs and bacteriologic demonstration of VAP. Meduri and associates demonstrated the presence of lung infection in only 42% of the patients with clinically suspected VAP and frequent occurrence of multiple infectious and noninfectious processes.[97] In 1991, a composite clinical score was proposed, based on seven variables (temperature, blood leukocyte count, volume and purulence of tracheal secretions, oxygenation, pulmonary radiography, and semiquantitative culture of tracheal aspirate) accorded 0, 1, or 2 points.[98] That study on 28 patients requiring prolonged mechanical ventilation showed a good correlation ($r = .84$, $P < .0001$) between this clinical score and quantitative bacteriology of bronchoalveolar lavage (BAL) samples, with a threshold value of 6 enabling identification of patients with infection. However, this scoring system is quite tedious to calculate and difficult to use in clinical practice, because several variables, such as progression of pulmonary infiltrates and results of semiquantitative cultures of tracheal secretions, can lead to different calculations depending on the observer. Furthermore, its value remains to be validated in a large prospective study, especially in patients with bilateral pulmonary infiltrates.

The second major obstacle to be confronted for the diagnosis of VAP is that, unlike patients developing community-acquired pneumonia, the presence of bacteria in the lower airways of intubated patients is not sufficient to diagnose true lung infection. Most VAP seems to result from aspiration of potential pathogens that have colonized the oropharyngeal airways. Intubation facilitates the entry of bacteria into the lung by pooling and leakage of contaminated secretions around the endotracheal cuff.[99] The tracheobronchial tree and the oropharynx of mechanically ventilated patients are frequently colonized by enteric gram-negative bacilli.[4,100,101] Based on specimens simultaneously obtained from the deep trachea and lung for culture from 48 patients with respiratory failure undergoing open-lung biopsy, culture results agreed for only 40% of these paired samples.[102] For patients with histologically documented pneumonia, endotracheal aspirate sensitivity was 82%, but its specificity was only 27%. The relationship between tracheal colonization and lung infection, however, remains unclear. Johanson and associates demonstrated that only 23% of colonized patients subsequently developed nosocomial pneumonia.[100]

Whereas simple qualitative culture of endotracheal aspirates is a technique with a high percentage of false-positive results due to bacterial colonization of the proximal airways observed in most ICU patients, some recent studies using quantitative culture techniques suggest that endotracheal aspirate cultures may have an acceptable overall diagnostic accuracy, similar to that of several other more invasive techniques.[103-107] In one study, the operating characteristics of endotracheal aspirate quantitative cultures, using 10^6 colony-forming units (cfu)/mL of respiratory secretions as the interpretative cutoff point, compared favorably with those of the PSB technique, with slightly higher sensitivity (82% vs. 64%) and lower specificity (83% vs. 96%).[103] To assess the reliability of that method, fiberoptic bronchoscopy with protected specimen brush and bronchoalveolar lavage was used to study 57 episodes of suspected lung infection in 39 ventilator-dependent patients with no recent changes of antimicrobial therapy.[106] The operating characteristics of endotracheal aspirate cultures were calculated over a range of cutoff values (from 10^3 to 10^7 cfu/mL) and the threshold of 10^6 cfu/mL appeared to be the most accurate, with a sensitivity of 68% and a specificity of 84%. However, when this threshold was applied to the study population, almost one third of the patients with pneumonia were not identified. Furthermore, only 40% of microorganisms cultured in endotracheal aspirate samples coincided with those obtained from PSB specimens. Other authors have emphasized that, although quantitative endotracheal aspirate cultures can correctly identify patients with pneumonia, microbiologic

results cannot be used to infer which microorganisms present in the trachea are really present in the lungs. In a study comparing quantitative endotracheal aspirate culture results with postmortem quantitative lung-biopsy cultures, only 53% of the microorganisms isolated from the former samples at concentrations greater than 10^7 cfu/mL were also found in the latter cultures.[108]

The third major problem with the management of patients suspected of having VAP concerns the use of antibiotics. Most epidemiologic investigations have clearly demonstrated that the indiscriminate administration of antimicrobial agents to patients in the ICU has immediate and long-term consequences, which contribute to the emergence of multiresistant pathogens and increase the risk of severe superinfections with potentially increased morbidity and mortality, in addition to antibiotic-related toxicity and higher cost.[15,109-111] On the other hand, patient survival may improve if pneumonia is treated correctly and rapidly.[1,112,113] Using multivariate analysis, it was demonstrated that inappropriate therapy was strongly associated with fatality.[14,114] More precisely, the prognostic importance of the appropriateness of initial antimicrobial therapy has been underlined in many, mostly recent, studies: an inadequate antibiotic regimen, initiated before obtaining the results of cultures from respiratory secretions, was associated with greater hospital mortality rate compared with an antibiotic regimen, which provided adequate antimicrobial coverage of all identified pathogens from obtained cultures.[20-24] Unfortunately, two factors seem to render the choice of antibiotics difficult in this setting. First, VAP is likely to result from highly resistant organisms, especially in patients who were previously treated with antibiotics[115] or in case of pneumonia occurring more than 7 days after initiation of mechanical ventilation.[32] Second, multiple organisms are frequently cultured from the pulmonary secretions of patients considered to have pneumonia, especially when the sampling technique is not specific enough to differentiate colonizing from infecting pathogens.[5,14,116]

Ideally, any diagnostic strategy intended to be used in patients clinically suspected of having developed hospital-acquired pneumonia should be able to reach the three following objectives:

1. Accurately identify patients with true pulmonary infection, and, in case of infection, isolate the causative microorganisms (to initiate immediate appropriate antimicrobial treatment and then to optimize therapy based on pathogen susceptibility patterns).
2. Identify patients with extrapulmonary sites of infection.
3. Withhold and/or withdraw antibiotics in patients without infection.

Two diagnostic algorithms can be used in cases in which HAP is suspected. One option is to treat every patient clinically suspected of having a pulmonary infection with new antibiotics even when the likelihood of infection is low. In this option, the selection of appropriate empirical therapy is based on risk factors and local resistance patterns and involves qualitative testing to identify possible pathogens, with antimicrobial therapy being adjusted according to culture results or clinical response (Fig. 84-1). This "clinical" approach has two potential advantages: (1) no specialized microbiologic techniques are required and (2) the risk of missing a patient who needs antimicrobial treatment is minimal, at least when all suspected patients are treated with new antibiotics. However, such a strategy leads to overestimation of the incidence of HAP. Qualitative endotracheal aspirate cultures contribute indisputably to the diagnosis of HAP only when they are completely negative for a patient with no modification of prior antimicrobial treatment. In such a case, the negative-predictive value is very high and the probability of the patient having pneumonia is close to null.[24]

Concern about the inaccuracy of clinical approaches to HAP recognition had led numerous investigators to postulate that "specialized" diagnostic methods, including quantitative cultures of endotracheal aspirates or specimens obtained with bronchoscopic or nonbronchoscopic techniques including BAL and/or PSB, could improve identification of patients with true HAP and facilitate decisions whether to treat, and thus clinical outcome.[23,25-28] Using such a strategy, the decision algorithm is similar to the one described in Figure 84-1 except that therapeutic decisions are taken based on results of direct examination of distal pulmonary samples and results of quantitative cultures (Fig. 84-2).

EVALUATION OF DIAGNOSTIC STRATEGIES

Other than decision-analysis studies[117,118] and one retrospective study,[119] only four trials have so far assessed the impact of a diagnostic strategy on antibiotic use and outcome of patients suspected of having HAP using a randomized scheme.[23,120-122] No differences in mortality and morbidity were found when either invasive (PSB and/or BAL) or noninvasive (quantitative endotracheal aspirate cultures) techniques were used to diagnose HAP in three Spanish randomized studies.[23,120,122] However, those studies were based on relatively few patients (51, 76, and 88, respectively) and antibiotics were continued in all patients despite negative cultures, thereby neutralizing one of the potential advantages of any diagnostic test in patients clinically suspected of having HAP. Concerning the latter, several prospective studies have concluded that antibiotics can indeed be stopped in patients with negative quantitative cultures with no adverse effects on the recurrence of HAP and mortality.[21,119,123-125] One of the first studies to clearly demonstrate a benefit in favor of invasive techniques was a prospective, randomized trial that compared the two strategies in 413 patients suspected of having VAP.[121] Compared with patients managed clinically, those receiving invasive management had a lower mortality rate on day 14 (16% and 25%; $P = .02$), and lower mean sepsis-related organ failure assessment scores on days 3 and 7 ($P = 0.04$). At 28 days, the invasive-management group had significantly more antibiotic-free days (11 ± 9 vs. 7 ± 7; $P < 0.001$), and only multivariate analysis showed a significant difference in mortality (hazards ratio, 1.54 [CI, 1.10 to 2.16]; $P = 0.01$).[26] Thus, implementation of bronchoscopic techniques for the diagnosis of VAP may reduce antibiotic use and improve patient outcome.

The choice of procedure(s) may eventually depend on the preferences and experiences of individual physicians and the patient's underlying disease(s). Despite broad clinical experience with the PSB and BAL techniques, it remains, nonetheless, unclear which one should be used in clinical practice. Most investigators prefer to use BAL rather than PSB to diagnose bacterial pneumonia, because BAL (1) has a slightly higher sensitivity to identify HAP-causative microorganisms, (2) enables better selection of an empirical antimicrobial treatment before culture results are available, (3) is less dangerous for many critically ill patients, (4) is less

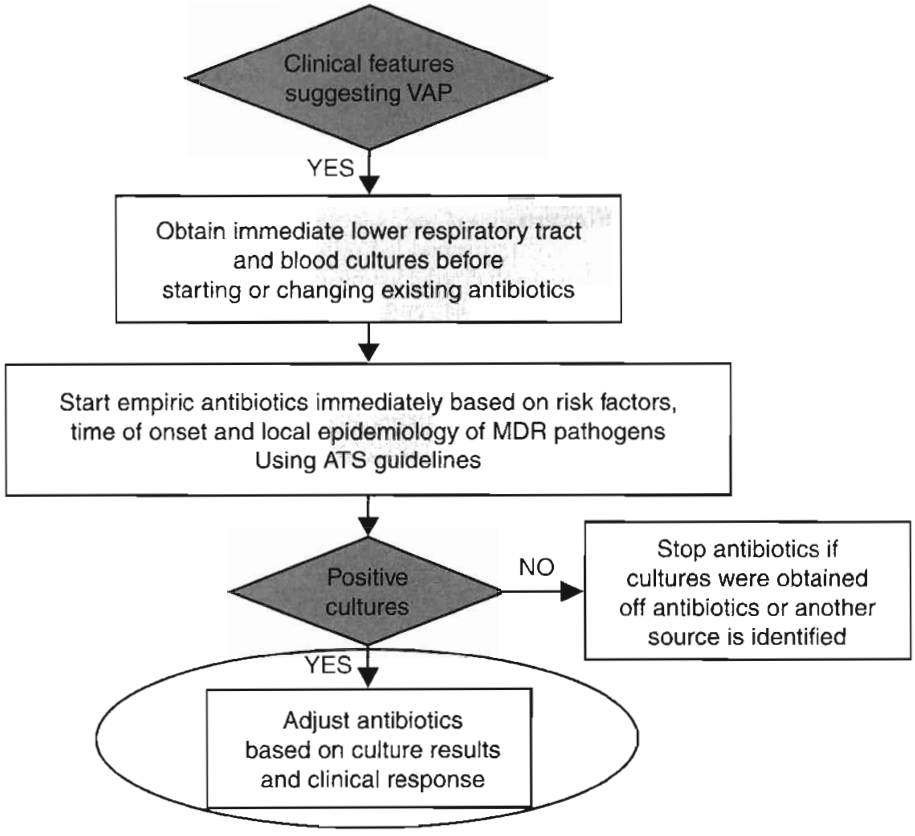

FIGURE 84–1. Clinical VAP strategy.

costly, and (5) may provide useful clues for the diagnosis of other types of infections. However, it must be acknowledged that a very small return on BAL may contain only diluted material from the bronchial rather than alveolar level and thus give rise to false-negative results, particularly for patients with very severe COPD. In these patients, the diagnostic value of BAL techniques is greatly diminished and the PSB technique should be preferred.[126]

Cultures of pulmonary secretions for diagnostic purposes after initiation of new antibiotic therapy in patients suspected of having developed HAP can clearly lead to a high number of false-negative results, regardless of the way in which these secretions are obtained. Using a lower threshold to define a positive quantitative result in such a setting may be inaccurate, because follow-up cultures can be completely negative in at least 40% of true cases of VAP.[127,128] Pulmonary secretions therefore need to be obtained before new antibiotics are administered, as is the case for all microbiologic samples.

The diagnosis of bacterial pneumonia in the severely ill, mechanically ventilated patient remains a difficult dilemma for the clinician. Our personal bias is that the use of bronchoscopic techniques to obtain PSB and/or BAL specimens from the affected area in the lung of ventilated patients with signs suggestive of pneumonia allows definition of a therapeutic strategy superior to that based exclusively on clinical evaluation (see Figs. 84–1 and 84–2). When performed before introduction of new antibiotics, these bronchoscopic techniques enable physicians to identify most patients who need immediate treatment and help to select optimal therapy, in a manner that is safe and well tolerated by patients. Furthermore, these techniques prevent resorting to broad-spectrum drug coverage in all patients who develop a clinically suspected infection. Although the true impact of this decision tree on patient outcome remains controversial, available data clearly suggest that being able to withhold antimicrobial treatment from some patients without infection may constitute a distinct advantage in the long term, by minimizing the emergence of resistant microorganisms in the ICU and redirecting the search for another (the true) infection site.

In patients with clinical evidence of severe sepsis with rapidly deteriorating organ dysfunction, hypoperfusion, or hypotension, the initiation of antibiotic therapy should not be delayed while awaiting fiberoptic bronchoscopy, and patients should be treated immediately with antibiotics. It is probably in this latter situation that simplified nonbronchoscopic diagnostic procedures could be most justified, because distal pulmonary secretions can be obtained on a 24-hour basis, just before starting new antimicrobial therapy. Because several studies have indicated that delays in the administration of effective antibiotic therapy may impact on VAP outcome, antibiotic therapy should not be postponed for more than a few hours (<6 hours) pending performance of fiberoptic bronchoscopy, even when the patient is clinically stable.

When fiberoptic bronchoscopy is not available to physicians treating patients clinically suspected of having VAP, we recommend using either a simplified nonbronchoscopic diagnostic procedure, replacing fiberoptic bronchoscopy in the algorithm depicted in Figure 84-1 by one of these techniques, or following the strategy described by Singh and associates,[129] in which decisions regarding antibiotic therapy are based on a clinical score constructed from seven variables, the CPIS score. Such an approach avoids prolonged treatment of patients with a low likelihood of infection, while allowing immediate treatment of patients with VAP. However, two conditions must rigorously be respected when

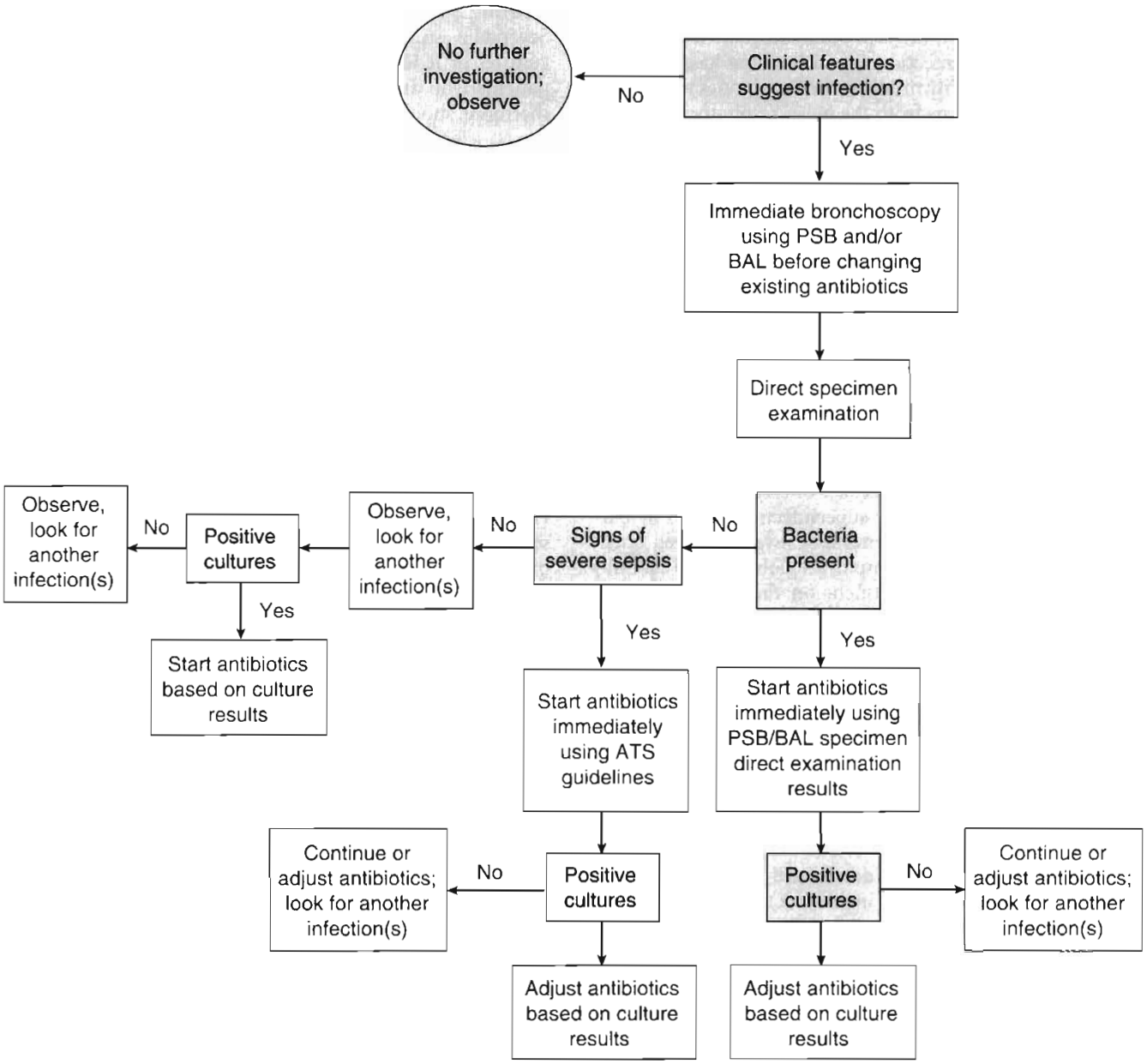

FIGURE 84–2. "Invasive" (microbiologic) strategy.

implementing this strategy. First, selection of the initial antimicrobial therapy should be based on predominant flora responsible for VAP at each institution. It is highly probable that ciprofloxacin would not be the right choice in numerous institutions due to the high prevalence of MRSA infections in many of them.[130] Second, it should be made clear to physicians that antimicrobial treatment should be reevaluated on day 3, when susceptibility patterns of the microorganism(s) considered to be VAP causative are available, in order to select treatment with a narrower spectrum.

TREATMENT

EVALUATION OF CURRENT ANTIMICROBIAL STRATEGIES

Despite many advances in antimicrobial therapy, successful treatment of patients with nosocomial pneumonia remains a difficult and complex undertaking. No consensus has been reached concerning issues as basic as the optimal antimicrobial regimen for therapy or duration of treatment. Although some investigators have recommended two-drug parenteral therapy for most cases, recent data have demonstrated the efficacy of a monotherapy for some patients. Similarly, the efficacy of endotracheal or aerosolized antibiotics as either the sole or adjunctive therapy for gram-negative pneumonia remains controversial. In fact, to date, evaluation of various antimicrobial strategies for the treatment of bacterial pneumonia in mechanically ventilated patients has been difficult for several reasons.

First, nearly all previous therapeutic investigations have relied solely on clinical diagnostic criteria and therefore have probably included patients who did not have pneumonia. Second, most of these studies used cultures of tracheal secretions as the major source of samples for microbiologic analysis despite the fact that the respiratory tract of most

ventilated patients is usually colonized with multiple potential pathogens. Finally, the lack of an adequate technique to directly sample the infection site in the lung has hampered assessment of the ability or inability of antibiotics to eradicate the causative pathogens from the lower respiratory tract and therefore the ability to predict their bacteriologic efficacy.

Montravers and colleagues evaluated the bacteriologic and clinical efficacy of antimicrobial therapies, selected on the basis of the etiologic microorganisms identified by cultures of PSB samples obtained during bronchoscopy, for the treatment of nosocomial bacterial pneumonia in 76 patients receiving mechanical ventilation.[127] Using a follow-up PSB sample culture to directly assess the site of infection in the lung, their results demonstrated that the administration of an antimicrobial therapy combining, in most cases, two effective agents, was able to sterilize or control the lower respiratory tract infection after only 3 days of treatment in 67 (88%) of the patients included in the study. The only two bacteriologic failures were observed in patients who did not receive adequate treatment because of errors in the selection of antimicrobial drugs. Early superinfection caused by bacteria resistant to the initial antibiotics was, however, documented in 7 (9%) patients, emphasizing the need to carefully monitor the impact of treatment on the initial microbial flora for optimal management of such patients when the clinical response is suboptimal. Furthermore, results of cultures of follow-up PSB samples were well correlated with the clinical outcome noted during the 15-day observation period, making this test a good prognostic indicator in patients with VAP.

FACTORS CONTRIBUTING TO SELECTION OF INITIAL TREATMENT

Important factors to be considered for the optimal selection of initial antibiotic therapy include (1) putative causative pathogens and their patterns of antibiotic susceptibilities, based on the clinical setting and previous epidemiologic studies, (2) data obtained by surveillance cultures in the same patient, (3) information given by direct microscopic examination of pulmonary secretions, and (4) intrinsic antibacterial activities of antimicrobial agents and their pharmacokinetic characteristics.

Clinical Setting

Underlying diseases and specific risk factors may predispose patients to infection with specific organisms, as well as some intrinsic factors linked to each hospital or ICU.[4] Therefore, selection of initial antimicrobial therapy needs to be tailored to each institution's local patterns of antimicrobial resistance.[31,130] Based on the results of a French prospective study in which the responsible microorganisms for infection in 135 consecutive episodes of VAP observed in the ICU were documented using bronchoscopic specimens, the distribution of infecting pathogens was markedly influenced by prior duration of mechanical ventilation and prior antibiotic use.[32] Taking these epidemiologic characteristics into account allowed the authors to devise a rational decision-tree for selecting initial treatment in this setting that prevents using broad-spectrum drug coverage in all patients. A computerized decision-support program linked to computer-based patient records can facilitate the dissemination of such information to physicians for immediate use in therapy decision-making and improve the quality of care.[131,132]

Routine Surveillance Culture Results

Several investigators have recommended routine surveillance cultures of ICU patients because they may be predictive of patients who are at high risk of invasive disease and, furthermore, should invasive disease develop, empirical therapy can be selected based on the predominant pathogens identified by these cultures.[4,133] However, the accuracy of this approach for selecting initial antimicrobial treatment for ICU patients requiring new antibiotics for VAP has not yet been established. This hypothesis was recently retested in a prospective study conducted on 125 patients who required mechanical ventilation for more than 48 hours and for whom strict bronchoscopic criteria were applied to diagnose pneumonia and identify the causative pathogens.[134] Although a large number of various prior microbiologic specimen culture results were obtained before fiberoptic bronchoscopy for each HAP episode, only 33% of the 220 HAP-causative microorganisms were isolated by these routine analyses with susceptibility patterns available to guide initial antimicrobial treatment. When the analysis focused on HAP episodes for which prior (within 72 hours) respiratory secretion culture results were available, results were better but still disappointing because all causative pathogens were recovered for fewer than 60% of cases. Such a strategy may also considerably increase the workload of the microbiology laboratory without having any positive impact on patient management.

Colonization with potentially drug-resistant pathogens, such as MRSA or extended-spectrum β-lactamase–producing strains of *K. pneumoniae* or other Enterobacteriaceae, is associated with an increased risk of infection caused by the corresponding microorganism. These results were confirmed in the study by Hayon and associates, with positive-predictive values of recovering such a microorganism from a specimen of 62%, 52%, or 24% for VAP caused by MRSA, *P. aeruginosa*, or *A. baumannii*, respectively.[134] However, because the sensitivity of prior microbiologic culture results for identifying bacteria causing HAP do not exceed 70%, selection of initial antimicrobial therapy for patients with HAP can hardly be based only on these results, especially for deciding to use (or not to use) vancomycin and/or a broad-spectrum β-lactam effective against *P. aeruginosa* and/or *A. baumannii*.

Information Given by Direct Examination of Pulmonary Secretions

Direct microscopy of pulmonary secretions is extremely important not only to identify patients with true VAP but also to select appropriate treatment, especially when BAL specimens are used to prepare cytocentrifuged Gram-stained smears.[135] In patients with pneumonia, the morphology and Gram staining of bacteria are closely correlated to the results of bacterial cultures, enabling early formulation of a specific antimicrobial regimen before the culture results are available. In a study of 94 mechanically ventilated patients with suspected HAP who underwent fiberoptic bronchoscopy with BAL and PSB, direct BAL fluid examination results were available within 2 hours, BAL and PSB culture results were available after 24 hours, and antibiotic susceptibility was learned after 48 hours.[136] At each step in the strategy, the senior physician and the resident in charge of the patient were asked their diagnoses and their therapeutic plans based on the available data. Using a threshold of 1% infected cells, direct BAL examination discriminated well between patients with and those without VAP (sensitivity

94%, specificity 92%, area under the ROC curve 0.95). Therefore, a strategy based on bronchoscopy and direct examination of BAL fluid may lead to more rapid and appropriate treatment of HAP than a strategy based only on clinical evaluation.

Intrinsic Antibacterial Activities of Antimicrobial Agents

Effective antibiotic treatment of bacterial pneumonia depends on adequate delivery of antibacterial agents to the infection site; therefore, scrupulous attention must be given to optimal doses, routes of administration, and pharmacodynamic characteristics of each agent used to treat this infection. Owing to major methodologic problems, published data concerning the penetration of most antibiotics into the lung should probably be viewed with caution, and only general trends concerning concentrations achievable at the infected site in lung tissue can be derived from those studies.[137,138]

For penicillins and cephalosporins, the bronchial secretion-to-serum drug-concentration ratios range between 0.05 and 0.25. Fluoroquinolones have better penetration characteristics, and bronchial secretion concentrations are between 0.8 and 2 times those in serum. Aminoglycosides and tetracyclines have ratios of 0.2 to 0.6. Host-related as well as drug-related factors may, however, influence the penetration of antimicrobial drugs across the blood/bronchus and alveolar/capillary barriers. Thus, for those drugs, such as the β-lactams and glycopeptides, which do not cross membranes readily, penetration might increase in the presence of inflammation because of enhanced membrane permeability.[139]

Several published reports have demonstrated a relationship among serum concentrations of β-lactams or other antibiotics, the in vitro minimal inhibitory concentration (MIC) of the infecting organism, and the rate of bacterial eradication from respiratory secretions in patients with lung infection, thereby emphasizing that clinical and bacteriologic outcomes can be improved by optimizing the therapeutic regimen according to pharmacokinetic properties of the agent(s) selected for treatment.[140-144] Most investigators distinguish between antimicrobial agents that kill by a concentration-dependent mechanism (e.g., aminoglycosides and fluoroquinolones) from those that kill by a time-dependent mechanism (e.g., β-lactams and vancomycin).

Development of a priori dosing algorithms based on MIC, patient creatinine clearance and weight, and a clinician-specified pharmacokinetic-pharmacodynamic variable, such as the 24-hour area under the concentration/time curve divided by the MIC (AUIC), might therefore be a valid way to improve treatment of these patients, leading to a more precise approach than current guidelines for optimal use of antimicrobial agents.

DE-ESCALATION

Once the microbiologic data become available, it is also necessary to de-escalate therapy to avoid prolonged use of a broader spectrum of antibiotic therapy than is justified by the available information. For many patients, including those with late-onset infection, the culture data will not show the presence of highly resistant pathogens, and in these individuals therapy can be narrowed, or even reduced, to a single agent in light of the susceptibility pattern of the causative pathogens without risking inappropriate treatment. While a de-escalating approach to antibiotic therapy (i.e., culture-guided treatment) may not help individual patients, it could benefit the ICU as a whole by reducing the selection pressure for resistance. Every possible effort should therefore be made to obtain, before new antibiotics are administered, reliable pulmonary specimens for direct microscope examination and cultures from each patient clinically suspected of having developed HAP.[145]

MONOTHERAPY VERSUS COMBINATION THERAPY

Several studies have examined the use of a single antibiotic (e.g., a third-generation cephalosporin, imipenem–cilastatin, or a fluoroquinolone) to treat HAP.[146-150] In general, monotherapy has proved to be a useful alternative to combination therapy, with the same success rate and no more superinfections or colonizations by multiresistant pathogens. Because those studies included nonhomogeneous populations of patients with different types of infections and given the potential inaccuracy of using only clinical criteria to diagnose lung infection, further trials are needed to clarify all these uncertainties. Furthermore, for patients with severe infection due to *P. aeruginosa* or other multiresistant bacteria, such as *Klebsiella* species or *Acinetobacter* species, combining an antipseudomonal β-lactam with an aminoglycoside or ciprofloxacin is likely to obtain a much better outcome than monotherapy, as previously shown. In a prospective clinical study on 200 patients with *P. aeruginosa* bacteremia, mortality rates for patients with pneumonia receiving monotherapy or combination therapy as the initial empirical treatment were 88% (7/8 patients) or 35% (7/20 patients), respectively ($P = .03$).[151] Similarly, for the subgroup of 55 patients who experienced hypotension within 72 hours prior to or on the day of the positive blood culture in a prospective observational study on 230 *Klebsiella* bacteremias, the mortality rate was significantly lower for those patients who received combination therapy (24%) than those given monotherapy (50%).[152] It should be noted, however, that the β-lactam agents used in those studies were older agents, with less potent activity than the advanced cephalosporins or the carbapenems available today.

Based on these data, it is probably safer to use a β-lactam antibiotic in combination with an aminoglycoside or a quinolone for patients with severe HAP, at least for the first days of therapy, while culture results of pulmonary secretions are pending. It may be that monodrug therapies for nosocomial pneumonia would best be reserved for infections in which *P. aeruginosa* or other multiresistant microorganisms, such as *Klebsiella, Enterobacter, Citrobacter, Serratia,* or *Acinetobacter* species, have been excluded as the etiologic agents.

DURATION OF ANTIMICROBIAL THERAPY

The optimal antimicrobial regimen and duration of therapy for patients who develop pneumonia has not been established. Most experts recommend that the duration be adapted to the severity of the disease, the time to clinical response, and the microorganism(s) responsible.[4] A "long" treatment, that is, a minimum of 14 to 21 days, is prescribed for the following situations: multilobular involvement, malnutrition, cavitation,

gram-negative necrotizing pneumonia, and isolation of *P. aeruginosa* or *Acinetobacter* species, which correspond to the majority of pulmonary infections occurring in patients requiring mechanical ventilation. This duration is essentially justified by the high theoretical risk of relapse, especially in case of infection caused by *P. aeruginosa* and MRSA, which are particularly difficult to eradicate from the respiratory tract.[153] Thus, at present, a short-term regimen is rarely prescribed in patients who develop HAP, despite the potential major advantages it could have in terms of bacterial ecology and the prevention of the emergence of multiresistant bacteria. Lowering the amount of antibiotics administered to patients hospitalized in ICUs is indeed a primary objective of every strategy aimed at reducing the emergence and dissemination of such bacteria.[111,154]

A prospective, randomized, multicenter trial was recently conducted in France to compare the clinical efficacy of two predefined durations of antimicrobial treatment (an 8-day and a 15-day course of antibiotics) in patients with microbiologically proven VAP.[155] This trial was designed to demonstrate both the noninferiority of the effect of the short course regimen on mortality and recurrence of pulmonary infection, and its superiority in terms of antibiotic use, as assessed by the number of days alive and free of antibiotics. These outcome measures were all assessed 28 days after the onset of pneumonia. Of 401 patients enrolled, 197 were randomly assigned to receive a short (8-day) course of antibiotics and 204 to receive a long (15-day) course of therapy. Compared with patients who received a long course of therapy, patients who received a short course had neither excess mortality (18.8% vs. 17.2%; 90% CI for the difference, −3.7 to +6.9 percentage points) nor excess pulmonary infection recurrence (28.9% vs. 26.0%; 90% CI for the difference, −3.2 to +9.1 percentage points), but they had significantly more antibiotic-free days (13.1 ± 7.4 vs. 8.7 ± 5.2 days, $P < .0001$). Therefore, an 8-day regimen can probably be the standard for the duration of antibiotic therapy in patients with HAP. Such an approach might help to control health care costs and to contain the development of bacterial resistance in ICUs.

PREVENTION

Because VAP has been associated with increased morbidity, longer hospital stay, increased health care costs, and higher mortality rates, prevention of this infection is a major challenge for intensive care medicine. A number of recommendations published for the prevention of nosocomial pneumonia are empirical rather than based on controlled observations for several reasons that make evaluation of the impact of such interventions difficult:

1. The difficulty of obtaining an accurate diagnosis of VAP, that is, to distinguish patients with true infection from patients with tracheal colonization and/or other pathologic processes since only patients who develop true VAP are likely to benefit from preventive measures.
2. The difficulty of precisely determining the impact of a prophylactic measure on the overall mortality of a general ICU population, that is, to identify preventable deaths, directly attributable to VAP, among all deaths occurring in a population of ventilated ICU patients.
3. The difficulty of evaluating the effects of a preventive measure on a potentially pathogenic mechanism, for example, to evaluate the exact role played by prevention or reduction of tracheal colonization in modifying the development of VAP.[156-161]

CONVENTIONAL INFECTION-CONTROL APPROACHES

These measures should be the first step taken in any prevention program.[162] The design of the ICU has a direct effect on the potential for nosocomial infections. Adequate space and lighting, proper functioning of ventilation systems, and facilities for hand washing lead to lower infection rates.[163] It should, however, be kept in mind that physical upgrading of the environment does not per se reduce the infection rate unless personnel attitude and practices are improved. In any ICU, one of the most important factors is probably the team that staffs it—the number, quality, and motivation of its medical, nursing, and ancillary members. The team should include a sufficient number of nurses to avoid having them move from one patient to another and to avoid working under constant pressure. The importance of personal cleanliness and attention to aseptic procedures must be emphasized at every possible opportunity. At the same time, unnecessarily rigid restrictions should be avoided. It is clear that careful monitoring, decontamination, and compliance with the usage guidelines of respiratory equipment decrease the incidence of nosocomial pneumonia.[164] In any case, hand washing or hand rubbing with alcohol-based solution remains uncontested as the most important infection control practice.[165,166]

A bacterial monitoring policy facilitates the early recognition of colonization and infection and has been associated with statistically significant reductions in nosocomial infection rates.[167] The focal point for infection control activities in the ICU is a surveillance system designed to establish and maintain a database that describes endemic rates of nosocomial infection. Awareness of the endemic rates enables the recognition of the onset of an epidemic when infection rates rise above a calculated threshold.

Preventing infection by modifying host risk has focused on treatment of underlying diseases and complications and control of antibiotic use. Adoption of an antibiotic policy restricting the prescription of broad-spectrum agents and useless antibiotics is of major importance.[168] Simple, safe, inexpensive, logical, but unproven measures, including the use of physiotherapy,[169] the judicious use and prompt removal of a useless nasogastric tube, and removal of tubing condensate, may have tremendous impact on the frequency of nosocomial pneumonia in mechanically ventilated patients.

SPECIFIC PROPHYLAXIS AGAINST VENTILATOR-ASSOCIATED PNEUMONIA

Because invasive mechanical ventilation is a risk factor for VAP, strategies that reduce its duration might reduce its incidence. Optimization of weaning protocols is a first way to reduce the duration of exposure to risk.[170,171] Noninvasive ventilation is an alternative approach to the use of artificial airways to avoid infectious complications and injury of the trachea in patients with acute respiratory failure. Many observations and studies, unfortunately small and not blinded, suggest that patients who tolerate noninvasive ventilation

have a lower incidence of pneumonia than those tracheally intubated.[172-175] However, although seven randomized trials have compared noninvasive ventilation with conventional mechanical ventilation for prevention of pneumonia, only one could demonstrate a statistically significant benefit in favor of noninvasive ventilation.[171,176-181]

Apart from these protocols aiming at reducing the duration of mechanical ventilation, seven prophylactic approaches have been studied: semi-recumbent positioning, oscillating and rotating beds, continuous or intermittent aspiration of subglottic secretions, ventilator circuits management, methods of enteral feeding, stress ulcer prophylaxis, and antibiotic use including selective digestive decontamination.

Semi-Recumbent Positioning

Supine patient positioning has been shown to be independently associated with the development of VAP.[182] Placing ventilated patients in a semi-recumbent position to minimize reflux and aspiration of gastric contents is a simple measure, although some practical problems can occur in unstable patients. Three trials have evaluated the efficacy of semi-recumbent positioning,[183-185] but only one measured the incidence of VAP: Drakulovic and colleagues clearly indicated significantly lower rates of both clinically suspected and bacteriologically confirmed VAP and identified supine positioning as an independent risk factor for VAP with enteral nutrition, mechanical ventilation for 7 days or more, and a Glasgow Coma Scale score of less than 9 points. These results explained the higher risk of VAP observed in patients receiving enteral nutrition in the supine position. There was no difference in mortality in this study.[184] No adverse effects were observed in patients assigned to semi-recumbent positioning.

Oscillating and Rotating Bed

Immobility in critically ill patients treated with mechanical ventilation results in atelectasis and impaired secretions drainage, and potentially predisposes to pulmonary complications including VAP. Oscillating and rotating beds may help in preventing pneumonia.[186] Six randomized trials,[187-192] including mostly surgical and trauma patients, ventilated or not, summarized in a meta-analysis by Choi and Nelson[193] have compared continuous lateral rotational therapy with standard beds for the prevention of nosocomial pneumonia. The meta-analysis found a statistically significant reduction in the risk for pneumonia, principally concerning early-onset (<5 days) pneumonia and a decreased duration of ICU stay. Notably, the only randomized, controlled trial (not included in the meta-analysis) conducted on a general ICU population did not show any differences in pneumonia rates but showed a significantly shorter length of ICU stay.[194] Some adverse events have been described with these beds, including disconnection of catheters or pressure ulceration; in addition, nursing care is potentially complicated with oscillating beds. Finally, in spite of the cost of such beds, cost-benefit analyses performed in those studies suggested favorable results, mainly caused by the reduction of ICU length of stay.

Aspiration of Subglottic Secretions

Repeated microinhalations of colonized oropharyngeal (subglottic) secretions are the major well-documented mechanism resulting in the development of VAP. Continuous or intermittent aspiration of oropharyngeal secretions has been proposed to avoid chronic aspiration of secretions through the tracheal cuff of intubated patients. Aspiration of subglottic secretions requires the use of specially designed endotracheal tube with a separate lumen that opens into the subglottic region. Three randomized controlled trials have studied aspiration of subglottic secretions for the prevention of VAP.[195-197] Mahul and associates found that pneumonia was significantly less frequent in patients with an endotracheal tube having a separate dorsal lumen for hourly suctioning of stagnant secretions above the cuff than in others and that VAP development was delayed.[195] Similarly, in a 3-year prospective, randomized, controlled study, Valles and coworkers documented a lower VAP rate when continuous subglottic aspiration was performed.[196] However, this difference was fully explained by VAP occurring during the first week, whereas late-onset pneumonias were more frequent in the aspiration group. Furthermore, detailed microbiologic analysis demonstrated that this reduction concerned only pneumonia due to *H. influenzae* or gram-positive cocci. The incidence of VAP due to *P. aeruginosa* or Enterobacteriaceae did not differ between the two groups. Kollef and colleagues performed a randomized trial on 343 post-cardiac surgery patients to compare continuous subglottic aspiration and standard postoperative medical care.[197] Although those authors found similar rates of VAP in both groups, VAP episodes occurred significantly later in patients receiving subglottic aspiration than in those treated conventionally. No difference in mortality rates was observed in these three studies. No adverse events were reported with aspiration of subglottic secretions in studied patients; however, experimental data suggest the possibility of tracheal damages in sheep intubated with this type of tube.

Ventilator Circuit Management

Decreased frequency of ventilator-circuit change, replacement of heated humidifiers by heat and moisture exchangers, decreased frequency of heat and moisture exchanger change, and closed suctioning systems have been tested for preventing VAP. Four randomized trials of decreased frequency of ventilator circuit changes have been published[198-201] comparing changes every 2 days, 7 days, and no scheduled change and did not find significant difference in the rate of VAP as summarized in a recent meta-analysis.[202] One meta-analysis summarized the results of five randomized, controlled trials that compared the effects of heated humidifiers and heat and moisture exchangers on the risk of VAP.[161] Only one of these five studies found a significant reduction of VAP rate with the use of heat and moisture exchangers.[203] Efficacy of both humidification strategies seems comparable; however, two studies reported increased rates of endotracheal tube occlusion with the use of heat and moisture exchangers,[161] and increased resistive load resulting in difficulties in the ventilation and weaning process of patients with severe ARDS—related with larger dead space—has been reported in observational studies.[204] No other adverse effects were observed. No effect on mortality was reported. Finally, one study has evaluated the impact of less frequent changes (daily vs. every 5 days) in heat and moisture exchangers on the development of VAP.[205] No difference in the VAP rates was observed.

To avoid hypoxia, hypotension, and contamination of suction catheters entering the tracheal tube, investigators have examined closed suctioning systems.[206,207] They found a nonsignificantly lower prevalence rate of VAP for patients managed with the closed system compared with those with

the open system without demonstrating any adverse effect[206] or not only failed to show a statistically significant protective effect of the closed system on the incidence of VAP but also observed an increased frequency of endotracheal colonization associated with the closed device.[207]

Methods of Enteral Feeding

Nearly all patients receiving mechanical ventilation have a nasogastric tube inserted to manage gastric and enteral secretions, prevent gastric distention, or provide nutritional support. The nasogastric tube may increase the risk for gastroesophageal reflux, aspiration, and VAP.[208]

Four randomized, controlled trials have evaluated methods of enteral feeding aimed at preventing VAP: postpyloric or jejunal feeding (vs. gastric feeding), the use of motility agents (metoclopramide vs. placebo), acidification of feeding (with addition of hydrochloric acid), and intermittent (vs. continuous) feeding.[209-212] These studies did not find differences in incidence of VAP and/or mortality rates. Potentially serious adverse affects have been observed in patients receiving acidified feeding (gastrointestinal bleeding) or intermittent enteral feeding (increased gastric volume and lower volumes of feeding). Thus, to date, methods of enteral feeding aimed to reduce the incidence of VAP cannot be recommended for routine use.

Stress Ulcer Prophylaxis

Gastric colonization by potentially pathogenic organisms has been shown to increase with decreasing gastric acidity.[213] Thus, medications that decrease gastric acidity (antacids, H_2 blockers) may increase organism counts and increase the risk for VAP. In contrast, medications that do not affect gastric acidity (sucralfate) may not increase this risk.

Seven meta-analyses of more than 20 randomized trials have evaluated the risk for VAP associated with the methods used to prevent gastrointestinal bleeding in critically ill patients.[214-220] These studies reported a significant reduction in four, or nonsignificant trends in reduction in three, of VAP incidence with sucralfate therapy compared with H_2 blockers. Three studies reported a statistically significant mortality benefit in patients given sucralfate.[215-217]

The relationships between prophylaxis of stress ulcer and prophylaxis of VAP are complex:

1. VAP is a possible indirect consequence of the use of drugs that raise the stomach pH.
2. Gastrointestinal bleeding is a serious complication in critically ill patients at high risk for stress ulcer (i.e., patients with coagulopathy or need for prolonged mechanical ventilation) but is extremely rare in patients at low to moderate risk.
3. The largest randomized trial comparing ranitidine to sucralfate showed ranitidine was superior in preventing gastrointestinal bleeding and did not increase the risk of VAP.[221]
4. The risk of VAP is unknown when accurate methods of enteral feeding or other preventive measures are used in combination with stress ulcer prophylaxis.

Clinicians must weigh the potential benefit of sucralfate (with potentially less VAP and more gastrointestinal bleeding) versus H_2 blockers (with potentially more VAP and less gastrointestinal bleeding) and probably limit stress ulcer prophylaxis to high-risk patients.

Antibiotic Use and Selective Digestive Decontamination

There is theoretical interest in using topical antibiotics to sterilize the oropharynx and stomach in mechanically ventilated patients, with the goal of reducing the incidence of VAP.[222] Several groups have used topical prophylactic antibiotics for selective decontamination of the oropharynx and digestive tract (SDD) in patients at high risk for nosocomial pneumonia. The SDD regimen usually includes a short course of systemic antibiotic therapy, such as cefotaxime, trimethoprim, or a fluoroquinolone, and nonabsorbable local antibiotic prophylaxis consisting of a combination of an aminoglycoside, polymyxin B, and amphotericin.[222] Since the original studies published by Stoutenbeek and coworkers in 1984,[223,224] which demonstrated a decrease of the overall infection rate in patients receiving the SDD regimen, more than 40 randomized, controlled trials and seven meta-analyses have been published.[225-231] All seven meta-analyses reported a significant reduction in the risk of VAP, and four reported a significant reduction in mortality.[227,228,230,231] No mortality benefit occurred with topical prophylaxis alone.[225,227,230,231] However, a clear consensus as to the effectiveness of SDD has not been established, owing to discordances among these meta-analyses related to limitations and methodologic deficiencies of analyzed studies, particularly the use of clinical diagnosis of pneumonia as a study endpoint; the heterogeneity of the populations studied; the wide variety of oral regimens; inconsistent addition of systemic administration of antibiotics (cefotaxime or ceftazidime); and differences in analytic methods.[232,233]

Conclusions drawn based on meta-analyses of SDD studies may be summarized as follows:

1. SDD reduces the incidence of VAP and, when a combined topical and systemic regimen is used, may reduce mortality.
2. An inverse relationship has been described between methodologic quality of the studies and benefits questioning the overall value of results reported in meta-analyses.
3. The long-term effects of SDD on emergence of resistance and risk of superinfections is unknown.
4. The impact of SDD on the duration of mechanical ventilation, ICU stay, and hospital stay appear to be limited.

Early attempts at systemic prophylaxis by using parenteral antibiotics alone against pneumonia were clearly unsuccessful.[234,235] In contrast, recent studies showed that a short-course of antibiotic regimen in patients with structural coma or severe burns was an effective prophylactic strategy to decrease the VAP rate.[236] In addition, indirect arguments from SDD studies, including systemic antibiotic therapy, and a recent study evaluating a short course of antibiotic therapy for patients with a low probability of developing VAP[129] suggest that antibiotic prophylaxis merits being more precisely investigated in this setting.

The influence of rotating of antibiotics (generally associated with restrictive use) in the ICU on VAP prevalence has been investigated by comparing successive periods during which one antibiotic was used in place of another for the empirical treatment of suspected gram-negative bacterial infections. Some investigators found that VAP occurred significantly less frequently during the after period compared with the before period.[168,237]

CONCLUSION

Effective antimicrobial therapy and adequate supportive measures remain the mainstay of treatment for VAP. More active and less toxic antibacterial agents are still needed, especially for some problematic pathogens, such as multiresistant nonfermenting gram-negative bacteria or MRSA. However, it should be emphasized that, in the event that one or several specific etiologic agents are identified by a reliable diagnostic technique, the choice of antimicrobial drugs is much easier, because the optimal treatment can be selected in light of the susceptibility pattern of the causative pathogens without resorting to broad-spectrum drugs or risking inappropriate treatment. Every possible effort should therefore be made to obtain, before new antibiotics are administered, reliable pulmonary specimens for direct microscope examination and cultures from each patient clinically suspected of having developed VAP.

ANNOTATED REFERENCES

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The first study clearly identifying duration of mechanical ventilation and previous antibiotic usage as risk factors for multi-drug resistant pathogens in VAP.

Chapter 85

PULMONARY INFECTIONS IN THE IMMUNOCOMPROMISED PATIENT

Carlos Agustí • Ana Rañó • Antoni Torres

KEY POINTS

1. Pulmonary infections are the **most frequent complications** in immunocompromised patients and have **a high mortality,** especially when intubation and mechanical ventilation are required.
2. The evaluation of the **patient's net state of immunosuppression** is key for the proper management of the pulmonary complication. Particularly important is the specific type of underlying immune deficiency, the immunosuppressive therapy received, and the potential epidemiologic exposures.
3. **Bacteria** are the most frequent cause of pulmonary infections in the different groups of immunocompromised patients. However, **opportunistic fungi are emerging as a common cause of pneumonia** in neutropenic patients and are associated with an elevated mortality.
4. Periodic surveillance of **serum galactomannan** and early implementation of **thoracic CT** in patients at high risk for invasive pulmonary aspergillosis may improve outcome.
5. A **marked decrease in the incidence of *Pneumocystis carinii*** pneumonia has been observed over the past years owing to prescription of *P. carinii* prophylaxis in patients at risk. Similarly, with the introduction of highly active antiretroviral therapy (HAART), the incidence of **pulmonary tuberculosis** in HIV-infected patients has dropped significantly.
6. Major emphasis must be placed on the **prevention of CMV disease in high-risk patients. CMV antigenemia** based on the detection of the pp65CMV antigen in peripheral blood leukocytes and **quantitative PCR** for early detection of viral DNA/RNA in serum have been implemented for early detection of active infection. Both assays have a sensitivity and specificity for the diagnosis of active infection of greater than 80% and diagnose active infection 1 to 3 weeks before conventional tools.
7. A confident diagnosis can seldom be made based on clinical and conventional radiology in immunocompromised patients. **Fiberoptic bronchoscopy** needs to be considered early after the appearance of the pulmonary infiltrates. **Bronchoalveolar lavage** is a very reliable technique, can provide a specific diagnosis in 50% to 80% of cases, and can also give the diagnosis of alternative noninfectious causes.
8. **Early implementation of noninvasive ventilation** is indicated in early stages of hypoxemic acute respiratory failure, because it decreases the requirement of intubation and the incidence of nosocomial pneumonia.
9. **Empirical treatment of pneumonia** in immunocompromised patients will vary depending on factors influencing the net state of immunosuppression. The selection of antimicrobial agents must be adapted to local patterns of microbial resistance.

The number of immunocompromised patients has increased over the past decade.[1-3] Improvements in solid-organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) techniques, the expanded use of chemotherapeutic treatments and glucocorticoids,[4] and the appearance of new immunomodulatory therapies are among the main reasons for this increase. The recognition and management of pulmonary complications, particularly infections that result from immunosuppression, is a challenging task for clinicians. Despite the introduction of potent broad-spectrum antimicrobial agents, complex supportive care modalities, and the use of preventive measures, pulmonary infections continue to be the most frequent complications in these patients and are associated with high mortality,[5-7] especially when intubation and mechanical ventilation are required. Early diagnosis and intervention are essential because they are associated with better outcome.

EVALUATING THE NET STATE OF IMMUNOSUPPRESSION

The proper assessment of factors involving the patient's state of immunosuppression is of paramount importance (Table 85-1). Most important are the specific type of underlying immune deficiency, the immunosuppressive therapy received, and the epidemiologic exposures the patients encounter (in both the community and the hospital). A timetable with intervals during which each type of infection and of noninfectious pulmonary complication tends to be most prevalent is shown in Table 85-2. A proper knowledge

TABLE 85–1. VARIABLES TO BE CONSIDERED IN EVALUATING THE NET STATE OF IMMUNOSUPPRESSION

Specific type of underlying immune deficiency:
Neutrophil defect: aplasia, neutropenia, leukemia
Immunoglobulin defect: multiple myeloma
T-cell defect: AIDS, solid organ transplant, lymphoma
Type, dose, and duration of immunosuppressive therapy
Type of organ transplanted
Presence or absence of leukopenia
Integrity of the mucocutaneous barriers
Timing between transplantation and development of pulmonary infiltrates
Disturbances secondary to transplant: graft-vs.-host disease
Environmental exposures
Infection with immunomodulating viruses: cytomegalovirus, Epstein-Barr virus
Other metabolic conditions: uremia, diabetes

TABLE 85–2. TIMETABLE OF THE MOST LIKELY PULMONARY COMPLICATIONS IN IMMUNOCOMPROMISED TRANSPLANT PATIENTS

First 30 Days after Transplant
Bacterial and fungal infections
Herpesvirus, respiratory viruses
Noninfectious complications: pulmonary edema, diffuse alveolar hemorrhage
2 to 6 Months after Transplant
Bacterial and fungal infections
Immunomodulatory viruses: cytomegalovirus, Epstein-Barr virus
Opportunistic infections: *Pneumocystis carinii*, *Listeria monocytogenes*
More than 6 Months after Transplant
Community-acquired respiratory viruses and bacteria
In patients with poor allograft function: consider opportunistic infections.

of these temporal-related complications, as well as the particular considerations involving each patient, will help guide diagnostic tests and implement appropriate empirical therapy.

ETIOLOGY OF PNEUMONIA IN IMMUNOCOMPROMISED PATIENTS

BACTERIAL INFECTIONS

Bacteria are the most frequent cause of pulmonary infections in the different groups of immunocompromised patients. Encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae* are particularly prevalent in patients with immunoglobulin defects, such as those suffering from multiple myeloma. In HIV-infected patients, bacteria are the most common cause of pulmonary infection, with the most common microorganisms being *S. pneumoniae*, *H. influenzae*, and *Staphylococcus aureus*. Many other bacteria must also be considered in ICU patients, particularly *Staphylococcus aureus* (including methicillin-resistant [MRSA]) and multi-resistant gram-negative bacilli (*Pseudomonas aeruginosa*,[8] *Acinetobacter* species,[9] and *Stenotrophomonas maltophilia*).[10] Epidemiologic studies have shown that *Legionella* pneumonia is nine times more prevalent in the immunocompromised host,[11] particularly among recipients of renal allografts.[12] Occasionally, uncommon opportunistic bacteria such as *Nocardia* must be considered in the differential diagnosis, especially in organ transplant patients (most notably, renal).[13]

FUNGAL INFECTIONS

Aspergillus species are among the most common microorganisms causing pneumonia in the immunocompromised patient.[14] A high clinical suspicion and the prompt institution of specific therapy are the only chances to control dissemination of disease. Because neutrophils are the key cells in the defense against *Aspergillus*, the neutropenic patient (e.g., HSCT patient) is at a highest risk for dissemination. In these patients, periodical surveillance of serum galactomannan[15] (a polysaccharide antigen of the wall of *A. fumigatus*) permits early detection of the infection. Early use of thoracic CT in patients at high risk for invasive pulmonary aspergillosis may also improve outcome.[16]

Candida species colonize the respiratory tract and are often recovered from pulmonary specimens in immunocompromised patients, but they are only considered as truly pathogenic if fungemia occurs or lung tissue invasion can be demonstrated. With the expanded use of new antifungal therapies, a higher incidence of infections due to *C. krusei* and *C. glabrata* has been reported.[17] Other fungi expand rapidly in response to environmental exposures, causing lethal infections, such as those due to *Penicillium purpurogenum* and *Scedosporium prolificans*.[18-21] Mucormycosis occurs almost always in the presence of immunosuppression, most notably diabetes, and often causes tissue invasion and destruction requiring surgical resection. The deep-seated fungal infections due to *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis* must be considered in endemic areas, mostly in the United States.

A marked decrease in the incidence of *P. carinii* pneumonia has been observed owing to the use of *P. carinii* prophylaxis in patients at risk and the use of highly active antiretroviral therapy (HAART) in HIV-infected patients.[22-24] A $CD4^+$ count less than 200 cells/mm^3 is associated with a markedly increased risk for *P. carinii* pneumonia. In SOT recipients, the risk for *P. carinii* is higher in the first 6 months after intense immunosuppression, particularly in heart-lung recipients but can appear later on in patients treated for rejection (HSCT patients with graft-versus-host disease). *P. carinii* pneumonia in patients with AIDS has a longer median duration of symptoms and a better outcome than in patients with SOT and HSCT. The chest radiograph can vary from normal to any type of infiltrates, although diffuse bilateral infiltrates is the most common presentation. An increase in serum lactate dehydrogenase and, particularly, the presence of pneumothorax raises the suspicion of *P. carinii* pneumonia.

MYCOBACTERIUM INFECTIONS

Pulmonary tuberculosis has experienced a marked decrease in HIV-infected patients with the introduction of HAART[25]; however, remarkable geographic differences are observed. A high level of suspicion is necessary to diagnose pulmonary

tuberculosis in immunocompromised patients. It should be suspected in patients with a T-cell defect (see Table 85-1). The typical radiologic pattern is often replaced by diffuse, basal or miliary infiltrates as well as mediastinal lymph nodes. Although sputum is a good noninvasive test for *Mycobacterium* staining, most patients will undergo bronchoscopy with a diagnostic yield of more than 90%. Different polymerase chain reaction (PCR) techniques have been developed to try to circumvent the problem of diagnostic delay in tuberculosis; however, false-positive results in patients shedding nonviable microorganisms limit the clinical use of these techniques. Atypical mycobacterial infections, particularly *M. avium* complex, were common in HIV-infected patients with less than 50 $CD4^+$ cells/mm^3. With the introduction of HAART, the incidence of these infections has dropped significantly. With the exception of lung transplant patients, atypical mycobacterial infections are rare in SOT recipients.

VIRUSES

Cytomegalovirus (CMV) is the most prevalent and lethal virus causing pneumonia in immunocompromised patients. The incidence of CMV infection will depend on several factors: (1) type of transplant (highest in allogeneic HSCT recipients), (2) degree of immunosuppression (highest when graft rejection is present and/or additional immunosuppressive treatment is required), and (3) previous serologic status. Thus, the incidence of CMV infection is as high as 60% to 70% during the first 3 months after allogeneic HSCT when graft donor or patients are pre-transplantation CMV seropositive. The incidence of CMV disease among SOT patients ranges from 8% to 35% in kidney, heart, and liver transplant recipients but is considerably higher in pancreas (50%) and lung or heart-lung recipients (50% to 80%). By contrast, introduction of HAART has resulted in a drastic decrease in the number of cases of CMV disease in HIV-infected patients and is extremely rare in patients with cancer.[26] Because one third of patients with evidence of CMV infection will develop CMV pneumonia, major emphasis must be placed on the prevention of CMV disease in high-risk patients. CMV also may contribute to the net state of immunosuppression, resulting in an increased susceptibility to other infectious agents. CMV antigenemia based on the detection of the pp65CMV antigen in peripheral blood leukocytes and quantitative PCR for early detection of viral DNA/RNA in serum have been implemented for early detection of active infection. Both assays have a sensitivity and specificity for the diagnosis of active infection of greater than 80% and diagnose active infection 1 to 3 weeks before conventional tools.[27] As a rule, symptomatic infection will not develop before 2 to 3 weeks after transplantation, and the peak incidence occurs between 4 and 8 weeks after the transplant. Although late symptomatic cases are well described, more than 90% of cases occur in the first 4 months after transplantation. The clinical and radiologic findings of CMV pneumonia are nonspecific. Occasionally, involvement of other organ systems with hepatitis, ulcerative gastroenteritis, hemorrhagic colitis, or retinitis may be a clue to the etiology of the pulmonary disease. Before the development of surveillance and prophylactic measures, CMV pneumonia had a high mortality that reached 85%. Currently, mortality is between 30% and 50%.

Recent developments in molecular-based diagnostic tools have shown that conventional respiratory viruses (influenza, parainfluenza, respiratory syncytial virus, adenoviruses, enteroviruses, and rhinoviruses) are frequent causes of respiratory illnesses and are associated with high rates of morbidity and mortality among immunocompromised patients.[28]

DIAGNOSTIC APPROACH

The evaluation of pulmonary infiltrates in the immunocompromised host is often a diagnostic challenge. Diagnosis can seldom be made based on clinical findings or conventional radiology in immunocompromised patients. Sputum cultures have a low sensitivity but are certainly indicated because organisms isolated in the upper respiratory tract are likely to be the cause of the pneumonia. Because immunocompromised patients with pulmonary infection are at risk for rapid dissemination of the disease with accompanying acute respiratory failure, fiberoptic bronchoscopy needs to be considered early after the appearance of the pulmonary infiltrates. The early use of fiberoptic bronchoscopy may add to the prompt identification of the specific etiologic agent, facilitating an etiology-guided treatment and avoiding unnecessary and potentially harmful additional treatment. In this sense, it has been shown that early diagnosis of both viral and fungal infections decreases mortality.[29,30] Fiberoptic bronchoscopy is a low-risk procedure that can be safely performed in most patients, including those with hypoxemia, with the application of supplemental oxygen. The use of fiberoptic bronchoscopy in immunocompromised patients provides a specific diagnosis in 50% to 80% of the cases.[31-33] Bronchoalveolar lavage (BAL) is a very reliable technique for detecting opportunistic infections such as *P. carinii*, CMV, and fungi but also bacteria, mycobacteria, and other pathogens.[34-36] BAL is particularly efficient in that it still recovers resistant pathogens after several days of empirical treatment, allowing modifications of the primary antimicrobial regimen. Bronchoscopy also provides material to diagnose alternative noninfectious causes, such as diffuse alveolar hemorrhage[37] or alveolar proteinosis,[38] which often afflict immunocompromised patients. The protected specimen brush (PSB) does not seem to add diagnostic information to BAL. By contrast, a simple, safe, and cost-effective technique such as tracheobronchial aspirate may constitute a good complement to BAL in the diagnosis of the etiology of pneumonia in immunocompromised patients.[32] Very rarely, an open lung biopsy will be needed for diagnostic purposes.[39] Although its diagnostic yield is high, and often leads to changes in therapy, the indications and proper moment must be selected carefully owing to potential morbidity and mortality.

Thoracic computed tomography (CT) is an important diagnostic tool in invasive pulmonary aspergillosis. The halo sign (hemorrhagic pulmonary nodule) and air-crescent sign (cavitation) are early radiologic signs typical of invasive pulmonary aspergillosis. This technique is also quite valuable in detecting pneumonic infiltrates in febrile neutropenic patients, particularly in transplant recipients, because it very often detects pulmonary infiltrates when a chest radiograph is normal.[40] Neutropenic patients with fever, showing a normal high-resolution CT scan, have a very low risk of pneumonia. A potential drawback of CT in the evaluation of pulmonary infiltrates in immunocompromised patients is the incapacity to detect polymicrobial infections. The possibility of more than one etiologic agent can be as high as 15% in some groups of immunocompromised patients.

TABLE 85–3. VARIABLES RELATED TO MORTALITY IN DIFFERENT GROUPS OF IMMUNOCOMPROMISED PATIENTS

APACHE II score > 20
Bilateral infiltrates in chest radiography
Mechanical ventilation requirement
Inadequate empirical treatment
Delay in diagnosis

PROGNOSTIC FACTORS OF PNEUMONIA IN IMMUNOCOMPROMISED PATIENTS

Pneumonia in immunocompromised patients is associated with high mortality irrespective of the factors leading to the altered immune status. Those with the highest mortality rate are recipients of an HSCT. Different factors have been identified that portend a poor prognosis.[41] Some of these factors are common to the different groups of the ICU patients whereas others relate to specific groups (Table 85-3). Particularly relevant is the requirement of mechanical ventilation. Needing mechanical ventilation bears a grim prognosis, particularly in HSCT recipients, where the mortality rate is >90% and very few survive 6 months after the onset of the pulmonary complication.[42] A prognostic factor that has a decisive influence on the clinical practice is the inadequacy of the empirical treatment. The difficulty of making an antibiotic selection in light of growing resistance and the wide spectrum of potential etiologic factors emphasizes the importance of designing strategies aimed at obtaining an early diagnosis. The impact of diagnostic delay on mortality is an important theme in the care of seriously ill patients, particularly as it affects the adequacy of initial therapy.[43] Early implementation of fiberoptic bronchoscopy may have prognostic implications.

THERAPEUTIC STRATEGIES

NONINVASIVE VENTILATION

The requirement of mechanical ventilation portends a poor prognosis in immunocompromised patients. Patients requiring mechanical ventilation may have a worse prognosis than similar patients matched for general severity-of-illness scoring systems such as Acute Physiology and Chronic Health Evaluation II (APACHE II), because mechanical ventilation may be directly injurious through increasing the risk for nosocomial pneumonia. Early implementation of noninvasive mechanical ventilation is indicated in immunocompromised patients because it decreases the requirement of intubation and the incidence of nosocomial pneumonia.[44-47]

EMPIRICAL TREATMENT OF SUSPECTED PNEUMONIA

Empirical treatment of pneumonia in immunocompromised patients will vary depending on factors influencing the net state of immunosuppression (see Tables 85-1 and 85-2). For neutropenic patients with fever, the administration of empirically chosen intravenous antibiotics is a widely accepted clinical practice.[48-51] The selection of antimicrobial agents must be adapted to local patterns of microbial resistance. Broad-spectrum antibiotics with activity against gram-negative bacilli, including *P. aeruginosa*, and gram-positive pathogens are indicated. Therapy must be modified to cover fungi based on identification or increased likelihood of this infection (long-term neutropenia), lack of response to initial antibiotics, or clinical worsening. Early performance of fiberoptic bronchoscopy must be always considered for a specific, etiologic-based therapy, avoiding unnecessary and potentially harmful additional treatments.

CONCLUSION

Pneumonia represents a serious challenge for clinicians caring for immunocompromised patients. Mortality in immunocompromised patients is high, particularly in patients undergoing HSCT and those requiring mechanical ventilation. A great diversity of diagnostic and laboratory procedures is available, and the clinician must determine the tests that should be performed based on the net state of immunosuppression. Early diagnosis is advantageous, and fiberoptic bronchoscopy substantially increases the diagnostic yield, causing changes in the empirical treatment in the majority of patients. Neutropenic patients with fever of unknown origin and normal chest radiographs should undergo high-resolution CT. Early application of noninvasive ventilation is warranted to avoid intubation and improve prognosis.

ANNOTATED REFERENCES

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This prospective study was performed in febrile neutropenic patients with unknown focus of infection with persisting fever for more than 48 hours despite empirical antibiotic treatment. The high frequency of inflammatory pulmonary disease after a suspicious high resolution CT scan (>50%) proved that pneumonia is not excluded by a normal chest radiograph. Patients with normal HRCT scan, particularly transplant recipients, have a very low risk of pneumonia during follow-up.

Hilbert G, Gruson D, Vargas F, et al: Noninvasive ventilation in immunocompromised patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med 2001;95:358-364.

This is a prospective, randomized trial of intermittent noninvasive ventilation, as compared with standard treatment with supplemental oxygen, in a population of immunocompromised patients with pulmonary infiltrates, fever, and an early stage of hypoxemic acute respiratory failure. The study shows that early initiation of noninvasive ventilation was associated with significant reduction in the rate of endotracheal intubation and serious complications.

Huaringa AJ, Leyva FJ, Giralt SA: Outcome of bone marrow transplantation patients requiring mechanical ventilation. Crit Care Med 2000;28:1014-1017.

This retrospective study demonstrates that the ICU survival rate of bone marrow patients who develop pulmonary complications and require mechanical ventilation is less than 20%.

Stover DE, Zaman MB, Hajdu SI, et al: Bronchoalveolar lavage in diagnosis of diffuse pulmonary infiltrates in the immunocompromised host. Ann Intern Med 1984;101:1-7.

This is a classical prospective study that demonstrated that bronchoalveolar lavage is a valuable procedure for evaluation of pulmonary disease in the immunosuppressed host.

Pizzo PA: Fever in immunocompromised patients. N Engl J Med 1999; 341:893-900.

This review article focuses on some of the challenges clinicians face in the management of fever in immunocompromised patients.

Chapter 86
LUNG TRANSPLANTATION

David Weill

KEY POINTS

1. **Lung transplantation is a viable option** for patients with end-stage lung disease.
2. **Careful monitoring** of patient input and output is critical in the early postoperative period to avoid pulmonary edema.
3. In patients receiving a **single-lung transplant for emphysema,** ventilator strategies that avoid native lung hyperinflation should be employed.
4. **Extubation should occur as early as possible** to avoid the deleterious effects of the mechanical ventilator on the transplanted lung.

HISTORICAL PERSPECTIVE

Lung transplantation evolved from heart-lung transplantation as a method by which donor organs could be used more efficiently. Heart-lung transplantation was first performed in 1981[1] and was initially the procedure of choice for diseases that are now more commonly treated by transplant using either bilateral sequential lung transplantation or even single-lung transplantation. The appeal of developing the isolated lung transplant technique was the improvement in donor organ utilization. Specifically, by using each of the three thoracic organs available from a single donor (i.e., two lungs and a heart), donor organ utilization can be maximized while achieving acceptable outcomes.

The double-lung transplant procedure, originally accomplished by en bloc replacement using a tracheal anastomosis, was first performed in 1983 in Toronto. The bilateral procedure is now performed as a sequential transplant using bilateral bronchial anastomoses. The bilateral sequential technique, as compared with the en bloc tracheal anastomotic technique, has been associated with fewer airway anastomotic complications, likely as a result of the superior blood supply from retrograde pulmonary artery flow.

In a report by the Toronto Transplant Group, single-lung transplantation was first described in 1986.[2] The advantage of the procedure is that it has allowed maximal donor utilization while being associated with good patient outcomes. The single-lung procedure has historically been accepted as the procedure of choice for common transplant indications, such as emphysema and idiopathic pulmonary fibrosis, and is currently performed as commonly as the bilateral procedure.[3]

SURVIVAL AND DEMOGRAPHICS

Worldwide, 1200 to 1400 patients receive a lung transplant each year. Despite the yearly increase in patients on the transplant waiting list (recently nearly 4000 patients), the number of transplant procedures performed each year has been relatively stable over the past several years (Fig. 86-1).[3] Significant discussion and research regarding methods to expand the donor pool are ongoing,[4] but, until strategies to increase lung donor procurement are actually employed, the number of transplants performed each year will likely remain stable.

Long-term survival after lung transplantation is limited by the development of the bronchiolitis obliterans syndrome (BOS), which is commonly referred to as chronic rejection. BOS, defined by declining spirometry below the best postoperative level achieved, is variable in time to onset but increases in frequency as duration post transplant lengthens. Unfortunately, the etiology of BOS remains elusive, but it likely involves both immune and nonimmune mechanisms, including frequent early acute rejection episodes, infection with cytomegalovirus (CMV), severe early postoperative lung injury, and donor factors. Largely because the mechanism of BOS is unknown, satisfactory treatment is currently not available.

INDICATIONS AND PROCEDURE CHOICE

Indications for lung transplant are listed in Table 86-1 according to the generally accepted procedure choice. Although there are many end-stage lung diseases that can potentially be amenable to lung transplantation, four diseases compose the vast majority of lung transplant recipients: emphysema (both cigarette-induced and due to alpha$_1$-antitrypsin deficiency), cystic fibrosis, primary pulmonary hypertension, and idiopathic pulmonary fibrosis.[3] Contraindications to transplant include evidence of extrapulmonary disease such as significant kidney, liver, or cardiac disease; poor nutritional or rehabilitation status; recent or current malignancy; and a poor psychosocial profile.

Generally the procedure of choice is the one that can be performed safely while utilizing the available donor organs most efficiently. Emphysema is the most common lung transplant indication and has consistently been associated with the best survival post transplant.[3] While some controversy exists regarding the optimal procedure choice (single vs. double) in this group of patients,[5] most patients with emphysema who have undergone a lung transplant have received a single-lung transplant. Bilateral lung transplant has traditionally been reserved for suppurative lung diseases,

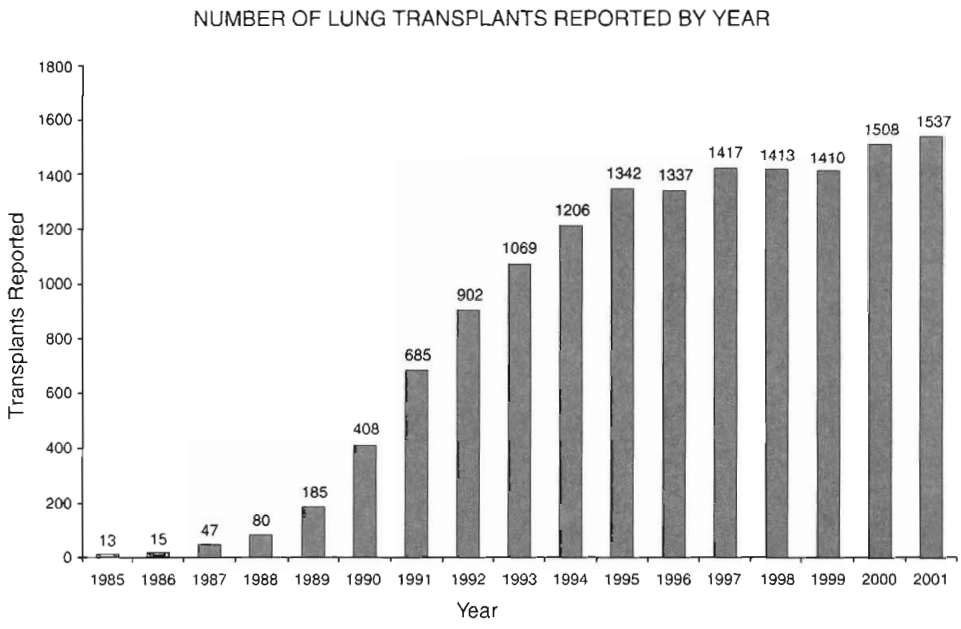

FIGURE 86-1. Number of lung transplants reported by year.

such as cystic fibrosis and other bronchiectatic diseases, where replacing as much infected lung tissue as possible is the primary goal. Also, patients with primary pulmonary hypertension generally receive a bilateral lung transplant, because this prevents the potentially life-threatening situation that occurs when, in performing a unilateral transplant, nearly all of the cardiac output flows to the allograft, given its relatively lower vascular resistance as compared with the native primary pulmonary hypertension lung. In the early transplant period when single lungs were transplanted for this indication, the result in most centers was profound unilateral pulmonary edema in the allograft.

CANDIDATE SELECTION

Because of the rigors of a major thoracic surgery, such as lung replacement, an extensive evaluation process occurs in all potential lung transplant recipients. The majority of the preoperative testing is directed toward excluding significant extrapulmonary disease, particularly those diseases that would lessen the chances of survival in the immediate postoperative period or make tolerance of the commonly used postoperative immunosuppression difficult. Occult coronary artery disease or malignancies are not uncommonly uncovered as the evaluation proceeds, particularly in those patients who have significant cigarette smoking histories. Other important goals of the evaluation process are to determine the likelihood of compliance with the complicated postoperative medical regimen and the existence of a solid support system to help with medical care once the patient leaves the hospital.

TABLE 86–1. LUNG TRANSPLANT BY PROCEDURE TYPE (IN ORDER OF FREQUENCY)

Single Lung Transplant	Double Lung Transplant
Emphysema/COPD	Cystic fibrosis
Idiopathic pulmonary fibrosis	Emphysema/COPD
Alpha$_1$-antitrypsin deficiency	Alpha$_1$-antitrypsin deficiency
Re-transplant	Idiopathic pulmonary fibrosis
	Primary pulmonary hypertension
	Bronchiectasis

WAITING LIST CONSIDERATIONS

TIME ON WAITING LIST

Waiting times for lung transplant recipients are highly unpredictable and vary considerably geographically. Waiting list priority is strictly according to time, or "seniority," on the list. Currently, there is no waiting list status system, although there likely will continue to be significant efforts to give priority to those on the waiting list who are more ill and who are most likely to do well post transplant. Unfortunately, devising such a system for lung allocation is problematic, primarily owing to the lack of compelling data correlating likelihood of waiting list mortality among the various disease groups with the highest probability of survival after transplantation. At most centers, as patients referred for transplant increase and patients on the waiting list increase, waiting times continue to increase and mortality on the waiting list will increase as well.

CARE OF PATIENTS ON WAITING LIST

Management of patients on the lung transplant waiting list involves close interaction with the referring physician. Treatment is directed toward the underlying disease process and is not generally affected by the patient's waiting list status. However, clinical activities that may affect transplant outcome should be a prominent aspect of the medical care plan. For instance, enrollment and participation in a cardiopulmonary rehabilitation program is of paramount importance so that waiting patients can develop or maintain the best cardiovascular fitness possible. Furthermore, weight management is often an important issue and regular exercise can help avoid excessive weight gain, which is associated with poor outcomes after transplantation. Conversely, in patients with cystic fibrosis, weight maintenance can be achieved by regular consultation with nutritional support

personnel familiar with patients in whom specific dietary needs exist. Other considerations requiring the attention of the transplant team include substantial increases in corticosteroid use, which, although never definitively linked to poor outcomes post transplant, remain a theoretical concern in terms of bronchial anastomotic and wound healing. As lung transplant waiting lists grow at most centers, regular outpatient clinic visits to monitor patients on the waiting list will likely become more important so that clinical issues that may affect transplant success can be detected and addressed.

DONOR ISSUES

DONOR CRITERIA

The expansion of lung transplantation as a therapy for end-stage lung disease is not limited by the number of potential recipients but rather by the availability of suitable donor organs. The standard, or "classic," lung donor criteria are well known, if not closely followed, among lung transplant practitioners. Although some of these criteria certainly make good sense (i.e., a clear chest radiograph, no bronchoscopic evidence of aspiration), nearly all the others are controversial, often ignored, and not based on convincing research data.[4] The standard or classic lung donor criteria are listed in Table 86-2. Whereas certain geographic regions of this country, some countries in Europe, and Australia have adopted more aggressive donor management strategies that have resulted in more donor lungs, many areas with lung transplant programs have fewer than expected lung donors.

POSTOPERATIVE CARE

The early postoperative care of lung transplant recipients can be divided into four general categories: (1) hemodynamic management, (2) respiratory management, (3) initiation of an immunosuppression regimen, and (4) infectious disease prophylaxis. Although many basic critical care principles apply to the care of lung transplant recipients, certain special considerations apply.

HEMODYNAMIC MANAGEMENT

Fluid Administration

In the early postoperative period, proper fluid management may be the most important aspect of lung transplant care. Because the lymphatic drainage is disrupted during surgery, the transplanted lung has a propensity toward pulmonary edema, and this tendency toward pulmonary edema is exacerbated by several conditions. First, owing to the procurement and reimplantation process, lung allografts suffer a lung injury that is characterized by a diffuse capillary leak. The process, commonly referred to as ischemia-reperfusion injury or the reimplantation response, is usually mild and treated easily with supportive measures. This type of injury is characterized by diffuse pulmonary infiltrates radiographically and varying degrees of oxygenation impairment. In cases of severe injury, the pulmonary edema may be profound and require more aggressive measures, such as independent lung ventilation, inhaled nitric oxide, and, in extreme cases, extracorporeal membrane oxygenation (ECMO). Second, because intraoperative and early postoperative hypotension occurs commonly, overexuberant resuscitation with crystalloid solutions sometimes occurs and worsens the pulmonary edema. In some circumstances, hypotension or decreased urine output has been treated with starch solutions that, because of the large molecules in these solutions, results in passage of even greater amounts of fluids through the dilated capillary channels.

Especially in the first 72 hours after surgery, judicious use of intravenous fluids should be exercised and efforts should be made to minimize fluid administration while maintaining adequate urine output.

Use of pulmonary artery catheters is standard in the early postoperative care of transplant recipients and helps guide fluid management. Low central venous pressures (0 to 5 mm Hg) are the objective. Also, careful attention to input and output measurements provides additional information regarding volume status and is a reminder to administer only essential fluids. Generally, if renal function allows, a worthy goal is to keep the patient 1 L negative for the first 3 postoperative days. This is best achieved with the liberal use of loop diuretics and the limiting of extra fluid infusions.

Hypotension is common after lung transplantation. Not only is the patient, by design, intravascularly volume depleted but he or she is also receiving medications that cause hypotension, such as paralytics, sedatives, and analgesics. As a result, during the early postoperative period, patients typically will have episodes of hypotension that need to be addressed. Another important consideration is the effect of positive-pressure ventilation on the hemodynamics of a recent lung transplant recipient, particularly in those receiving a single-lung transplant for emphysema, owing to discrepancies in native lung and allograft compliance characteristics. These discrepancies, coupled with many recipients who not only have preoperative right ventricular dysfunction but also in whom postoperative intravascular volume depletion is intentionally achieved, can result in overinflation of the native lung. The concept of native lung hyperinflation is covered in more detail in the section on Ventilator and Respiratory Management, but one must consider whether early post-operative hypotension is best treated with ventilator management strategies that address overdistention of the native lung.

During periods where hypotension is found to be the result of profound intravascular volume depletion, fluid resuscitation should ideally include solutions that have the greatest tendency to remain in the vascular space and not simply migrate through the dilated pulmonary capillary channels. Colloid solutions, such as albumin, and packed red blood cells (RBCs), are ideal in this setting, as is replacement with clotting factors, particularly in the patient who has postsurgical consumption of these factors. Generally, in the

TABLE 86-2. STANDARD LUNG TRANSPLANT DONOR CRITERIA

Age < 55 yr
ABO blood group compatibility
Clear chest radiograph
PaO_2 > 300 mm Hg on fractional inspired oxygen of 1.0 and positive end-expiratory pressure = 5 cm H_2O
Less than 20 pack-year smoking history
Absence of chest trauma
No aspiration or sepsis
Gram stain shows sputum sample free of bacteria, fungus, and significant number of white blood cells

hypotensive patients with hemoglobin less than 10 g, use of packed RBCs is the treatment of choice. If a patient has very little postoperative bleeding, albumin infusions provide a temporary solution to intravascular volume depletion and can be given in conjunction with a loop diuretic to achieve a more brisk diuresis by transiently increasing effective renal blood flow. This effect is likely short-lived but nonetheless provides a temporary increase in oncotic pressure that may lessen the development of pulmonary edema.

VENTILATOR AND RESPIRATORY MANAGEMENT

The initial care of early postoperative lung transplant recipients is directed toward ventilatory stability. Ventilator mode is generally dictated by the patient's level of consciousness in the early postoperative period. For example, patients who are deeply sedated and/or under the influence of paralytic agents will obviously require full control of their ventilation. The assist-control mode meets this requirement and is generally the preferred ventilatory mode in the immediate postoperative period. However, because an effort is made at many programs to extubate patients sooner after surgery, use of less sedation and the avoidance of paralytic agents are being employed. In this group of patients, less ventilatory control is required and patients usually do well with intermittent mandatory ventilation until early extubation is achieved. In patients with poor early graft function, for example those with primary graft failure, ventilatory strategies that limit barotrauma are most efficacious and usually include pressure-control modalities. Certainly, with pressure-control ventilation, the use of sedation and paralytics is warranted, recognizing the potential deleterious neurologic effects of the latter when used in combination with high doses of corticosteroids and, in some instances, aminoglycoside antibiotics.

The Use of Positive End-Expiratory Pressure

Positive end-expiratory pressure (PEEP) can be safely used in lung transplant recipients, especially those patients who have received a bilateral lung transplant. In the double-lung recipients, the compliance characteristics of the two allografts will be similar; therefore, the positive pressure exerted on each lung will be nearly evenly distributed. PEEP of +5 to +15 is safe in this patient population. In fact, some believe that PEEP has a beneficial effect in this group in decreasing postoperative bleeding by increasing intrathoracic pressure, which would lead to tamponade of the small blood vessels in the chest. This point, however, is not widely accepted and has not been supported by conclusive data.

In single-lung recipients, the use of PEEP can be more problematic. The differing compliance characteristics of the remaining native lung and the allograft lead to the potential for a majority of the positive pressure being directed at only one lung. This is particularly true in emphysema recipients who have a highly compliant native lung and a less compliant transplanted lung. In this situation, nearly all the positive pressure is exerted on the native lung, which leads to a situation known as acute native lung hyperinflation. The hyperinflated native lung can cause both cardiac tamponade, manifested as acute hypotension associated with a reduction in cardiac index, and allograft compression, manifested by hypoxemia and hypercarbia. Because of these potential problems, the avoidance of PEEP in patients with emphysema undergoing single-lung transplantation is generally recommended. The use of PEEP in single-lung recipients with other disease processes is usually not problematic. A more complete review of the differences in ventilator management associated with single- and double-lung recipients is presented later in the chapter.

Chest Physiotherapy and Patient Positioning

Chest physiotherapy (CPT) is an essential part of postoperative respiratory management. Because the allograft is denervated, the cough reflex in lung transplant recipients is impaired. CPT therefore is imperative in the clearance of retained mucus and blood in the airway. As the postoperative recovery ensues, CPT is less important because patients learn to cough periodically, regardless of the impetus to do so. Before patients are trained to do this, aggressive CPT is used (i.e., usually every hour in the first few postoperative days while the patient is awake and every 2 hours during sleep) and includes vibratory percussion, intermittent positive-pressure ventilation, and patient-directed incentive spirometry. Whereas CPT devices that deliver excessive airway pressure are to be avoided due to concerns of potential anastomotic disruption, positive-pressure devices using less than 20 cm Hg airway pressure are generally safe.

Patient positioning in the bed can help minimize the development of pulmonary edema. The lung that is positioned toward the bed when the patient is in the lateral decubitus position receives relatively less blood flow than the upward positioned lung, primarily owing to the effects of gravity. This is especially important in single-lung transplant recipients because the vascular compliance characteristics differ between the native lung and the allograft with the newly transplanted lung receiving relatively more blood flow due to less vascular resistance. Of course, if the new lung experiences significant reperfusion injury after transplant, then the vascular resistance would likely be higher in the allograft. Regardless of the initial condition of the transplanted lung, the allograft side should be placed upward for the first 6 hours postoperatively while the patient is in the lateral decubitus position to diminish its blood flow and ideally its tendency to develop pulmonary edema. The single-lung recipient should then be positioned with the new lung down for 1 to 2 hours before being again placed with the allograft upward. Also of note, one can determine how well the allograft is functioning by comparing oxygenation when the native lung and allograft are receiving the majority of the blood flow. For instance, when the patient oxygenates better with the native lung downward (and therefore receiving the majority of the blood flow) than when the allograft is receiving most of the pulmonary blood flow, that is an indication that the new lung is not yet functioning well. In double-lung recipients, which side is positioned downward is less important and patients are simply turned from side to side periodically (e.g., every 2 hours).

Single-Lung vs. Double-Lung Issues

Management of the mechanical ventilator after lung transplant surgery is heavily influenced by the type of lung transplant procedure performed (i.e., a single- or double-lung transplant). In recipients who receive a bilateral transplant, the ventilator management is very similar to that for nontransplant recipients. However, in single-lung recipients, the compliance differences between the native lung and the allograft mandate different ventilator strategies. Different strategies

are particularly important in single-lung recipients with emphysema rather than in single-lung recipients with fibrotic lung, owing to the tendency of the native emphysematous lung to hyperinflate under the influence of positive pressure. Because of this tendency, some programs have advocated double-lung transplants routinely for patients with emphysema owing to the potential for increased mortality in the single-lung recipients with emphysema.[6] Fortunately, proper ventilator management in the single-lung recipients can prevent most of the problems with native lung hyperinflation, and concerns about this phenomenon should not influence procedure choice.[7]

Ventilator management in patients with emphysema who receive a single-lung transplant should be directed toward limiting airway pressure and allowing maximal expiratory time. The avoidance of PEEP and the use of excessively large tidal volumes limit the degree of native lung hyperinflation because any degree of positive pressure will have a tendency to be directed to the highly compliant native emphysematous lung. Because some degree of native lung hyperinflation is unavoidable, strategies to allow maximal emptying of the native lung should be employed and include reducing the set respiratory rate and increasing inspiratory flow rate to allow a longer expiratory time. If the problems associated with acute native lung hyperinflation cannot be resolved with simple ventilator maneuvers and if the patient has not experienced significant ischemia-reperfusion injury, then extubation should be strongly considered because the removal of all positive pressure will resolve the problem. By using these management strategies and by clearly understanding the physiology involved with single-lung transplant recipients, one can usually avoid the untoward effects of native lung hyperinflation and its associated morbidity and mortality.

Native lung hyperinflation is more common when acute lung injury is present in the allograft, because the compliance discrepancy between the native lung and the allograft is even more pronounced. In this rare circumstance, independent lung ventilation using a double-lumen endotracheal tube can be initiated and can provide a means to ventilate the native lung and allograft according to the compliance characteristics of each.[8] Independent lung ventilation outside of the operating room setting is associated with difficulties, particularly relating to endotracheal tube malpositioning and subsequent acute lobar or total lung collapse. Unfortunately, prevention and recognition of tube dislodgment requires constant surveillance, generally endoscopically, and is difficult unless personnel skilled with endoscopic endotracheal tube management skills are available on a continuous basis. Under these circumstances, diligent nursing care is required, including the administration of appropriate sedation and/or paralytic agents as well as the avoidance of routine repositioning of the patient.

Extubation

The extubation criteria in a lung transplant recipient are similar to those for other types of ventilated patients, particularly postsurgical patients. The patient should certainly be free of any lingering effects of the anesthetic and able to meet standard extubation criteria published elsewhere.[9] As more experience with lung transplant management has developed, the decision to extubate is being made sooner; and some centers are even trying to extubate patients in the operating suite soon after surgery.[10] Other programs, however, are reluctant to extubate this quickly because of concerns about delayed ischemia-reperfusion injury that would compromise allograft function or uncertainty about whether anesthetic medications have been completely cleared. Regardless, the dogma about leaving patients ventilated for a predetermined amount of time is now being challenged.

Chest Tube Management

Lung transplant recipients generally have two chest tubes per transplanted lung after surgery. A posterior tube is positioned to drain surgical bleeding, while the anterior tube evacuates air from the pleural space. The anterior tube is usually the first tube to be removed given that, in the absence of a bronchial anastomosis dehiscence, prolonged air leaks into the chest tube are uncommon. In fact, much of what is often mistakenly regarded as an air leak coming from the thorax is often air being introduced via the skin incision at the chest tube site. The posterior tube is removed when total 24-hour drainage from it is less than 150 mL. In a bilateral lung transplant, one should be cognizant that there is communication between the two hemithoraces because the pleural space has been opened. Because of this, chest tubes in bilateral transplants should be removed one tube per side at a time with the anterior tubes being removed first followed by the posterior tubes.

Bronchoscopy after Lung Transplantation

The initial bronchoscopy after lung transplantation typically occurs in the operating room. The goal of the procedure is to assess the bronchial anastomoses and to clear retained blood and sputum from the airway. Once the patient returns to the ICU there is generally no need to bronchoscope the patient again in the first 24 postoperative hours unless complications develop. For instance, acute ventilatory insufficiency should prompt a bronchoscopic examination of the transplanted lung or lungs to make certain that acute mucus plugging of the airways is not accounting for the ventilatory insufficiency. Because of blood in the airway from the operation and caused by retained secretions from the native lung in single-lung recipients, mucus plugging happens not uncommonly. Serious complications from bronchoscopy early after surgery are rare. Transient oxygen desaturation during bronchoscopy is common but not generally harmful to the patient.

IMMUNOSUPPRESSIVE REGIMENS

Review of Commonly Used Agents

Different transplant centers use different immunosuppressive regimens. However, general comments can be made about the more commonly used medications. Some programs use an induction strategy that involves the early administration of antibody, either directed directly at the lymphocyte ("lymphocyte-depleting") or against interleukin receptor sites.[11] Most antibodies delivered are monoclonal and are more easily tolerated than the polyclonal antibodies used in the earlier transplant era. Regardless of which induction agent is preferred, a primary advantage of this strategy involves the early avoidance of nephrotoxic immunosuppressive agents (such as calcineurin inhibitors like cyclosporine or tacrolimus), while still providing adequate immunosuppression. This benefit is particularly important during the immediate postoperative period when renal insufficiency is common owing to purposeful intravascular

volume depletion, use of nephrotoxic antibiotics and antiviral agents, and the effects of cardiopulmonary bypass (if used).

Although a thorough review of immunosuppressive medications is available elsewhere, a few basic comments about immunosuppressive strategies can be made. Most lung transplant programs use a three-drug immunosuppressive regimen. Corticosteroids are a central part of the early strategy, particularly during the period when adequate blood levels of the other immunosuppressive agents are not yet achieved. Because of the large corticosteroid doses used immediately after surgery, a variety of side effects can be expected. For example, fluid retention, systemic hypertension, and poor glucose control should be anticipated. Acute changes in mental status can also occur and clinically present as delirium or psychosis. Many of these effects can be eliminated by administrating the corticosteroids in a tapering fashion that aims to reduce the dosage as quickly as it is safe to do so.

Calcineurin inhibitors such as tacrolimus and cyclosporine-based medications comprise the second part of the three-drug strategy. These medications are typically administered intravenously early in the postoperative period for a number of reasons. First, lung transplant recipients are generally not able to take oral medications in the first 24 hours after surgery. Second, the intravenous absorption is more predictable and avoids the rapid absorption seen early after oral administration, which is highly desirable in lung recipients in whom one would like to avoid nephrotoxic effects that could impede good urine output. Finally, because the intravenous delivery is highly amenable to dose titration, turning off the intravenous drip in response to reduced urine output can quickly reestablish adequate urine output and helps achieve the goal of relative intravascular volume depletion that is critical in the early postoperative period. In the first 48 hours after surgery, a cyclosporine level equal to or less than 100 ng/mL and a tacrolimus level no greater than 5 is desirable. Once urine output is adequate and renal function is stable, drug dosage can be increased to achieve more therapeutic medication blood levels.

The third part of the immunosuppressive regimen involves the use of either azathioprine or mycophenolate mofetil. Azathioprine is generally well tolerated and is usually associated with mild, reversible side effects, such as leukopenia, anemia, thrombocytopenia, and liver function test abnormalities. Mycophenolate mofetil, a newer agent, can also cause leukopenia and anemia. Furthermore, in some circumstances, the drug can lead to nausea, vomiting, and abdominal pain, all of which can be ameliorated by reducing the dose or temporarily stopping the drug. The monitoring of mycophenolic acid blood levels is being performed in some solid organ recipients,[12,13] but the precise target levels in lung transplantation are unknown.

INFECTIOUS DISEASE PROPHYLAXIS

Infections after lung transplant are common and occur because of baseline immunosuppression, transmission from the donor, and ICU-related instrumentation (e.g., chest tubes, central venous catheters, endotracheal tubes). The antibiotic prophylactic regimen is directed toward preventing pneumonia, surgical site infections, and central line–related infections. Usually, this goal is achieved through the prophylactic use of late-generation cephalosporins and vancomycin. Because of their colonization with *Pseudomonas* species, patients with cystic fibrosis receive a third prophylactic antibiotic with good gram-negative coverage, such as an aminoglycoside.

TABLE 86–3. CMV PROPHYLAXIS PROTOCOL

	Recipient Positive	Recipient Negative
Donor Positive	6 wk GCV* (2 wk i.v. and 4 wk p.o.) CMV-IG 3 doses (1 dose every 2 wk)	12 wk GCV* (6 wk i.v., p.o.) CMV-IG† 7 doses in 6 wk
Donor Negative	No prophylaxis used	

GCV, ganciclovir; CMV IG, CMV hyperimmune globulin.
*Intravenous dose 5 mg/kg q12h adjusted for creatinine clearance.
†150 mg/kg within 72 h post transplant, then every 2 weeks for 4 doses, then 100 mg/kg every 4 weeks for 2 additional doses.

Infection with CMV after transplant can lead to deleterious acute and chronic effects. Acutely, patients are at risk to develop CMV pneumonia, which in many instances leads to severe morbidity and mortality. Also, CMV syndrome, caused by CMV replication in the bloodstream, is heralded by the onset of malaise, fever, nausea, and vomiting. Furthermore, many believe that CMV infection (even asymptomatic) can lead to more long-term sequelae, such as chronic allograft dysfunction (BOS).[14]

To prevent both the acute and chronic consequences of CMV infection, many programs have adopted an aggressive CMV prophylactic protocol. The more aggressive protocols include combination therapy using both ganciclovir and CMV hyperimmune globulin.[15] The duration of therapy is dependent on CMV serology status of the donor and the recipient and is outlined in Table 86-3. Other less aggressive strategies are also used and, although less expensive and associated with less treatment-associated toxicity, likely lead to an increased incidence of CMV-related diseases.

The prophylactic use of antifungal agents is controversial and varies among centers.[16] There are single-center studies that have demonstrated a reduction in invasive fungal disease after instituting a fungal prophylactic regimen.[17] Those programs that do use antifungal prophylaxis generally use medications in the azole class or aerosolized amphotericin.[18,19] While there have been no conclusive studies in lung transplant to support an antifungal prophylactic strategy, some lung transplant physicians use these agents primarily for their ability to raise blood levels of the calcineurin inhibitors, which ultimately results in significant cost savings because the calcineurin inhibitor dose can be reduced.[20] One concern with this strategy, however, is the potential to select for resistant fungal infections, particularly candidal species.

INTENSIVE CARE UNIT ISSUES

In the early postoperative period, while the patient is mechanically ventilated, the use of sedative medications and paralytics is common. However, in most cases, when early allograft function is adequate, the routine use of paralytic medications can be avoided. The avoidance of these drugs is desirable given that paralyzing agents have been associated with prolonged paralysis, which in lung transplant recipients can impair ability to wean from mechanical ventilation and to participate fully in the postoperative physical therapy regimen. The deleterious effects of the paralytic agents can

be exacerbated by the concomitant use of high-dose corticosteroids and aminoglycoside antibiotics,[21] both of which are commonly used in the early postoperative period in lung transplant recipients.

Strategies involving gastrointestinal prophylaxis and prophylaxis against deep vein thrombosis are similar to those employed in any thoracic surgical patients. Generally, gastrointestinal prophylaxis is achieved using H_2 blockers or a proton-pump inhibitor and is particularly important early postoperatively when the patient is exposed to high doses of corticosteroids. Most programs continue the gastrointestinal prophylactic measures indefinitely. Because of the risk of surgical bleeding, prophylaxis is initially achieved using antistasis devices to the lower extremities. As the risk of postoperative bleeding diminishes, standard prophylactic regimens for deep venous thrombosis using heparin-based drugs can be safely used until the patient is fully ambulatory.

EARLY POSTOPERATIVE COMPLICATIONS

HEMODYNAMIC INSTABILITY

As discussed earlier, the immediate hemodynamic goal in the lung transplant recipient is intravascular volume depletion. Although achieving the goal of reducing the tendency toward pulmonary edema, this strategy often results in hypotension. Furthermore, the combination of intravascular volume depletion, a poorly compliant right ventricle requiring higher filling pressures, the use of sedative and paralytic medications that cause hypotension, and positive pressure provided by the mechanical ventilator can result in exacerbation of blood pressure difficulties. Fortunately, the hypotension that occurs commonly under these circumstances can be readily reversed by a few different measures.

For example, gentle volume resuscitation with colloids such as albumin or red blood cell transfusion can reestablish an adequate blood pressure, while not contributing significantly to pulmonary edema development. Of course, in some patients with known preoperative right ventricular dysfunction, such as that seen in primary or secondary pulmonary hypertensives, maintaining adequate right ventricular filling pressures using volume expansion is important in ensuring adequate cardiac performance even in the presence of normal systemic blood pressures. The hemodynamic effect in certain situations of positive-pressure ventilation has been discussed previously. If the recipient experiences problems with positive-pressure–related hypotension, removal from the mechanical ventilator is the treatment of choice. Not only does this remove the hemodynamic effects of positive-pressure ventilation but it also obviates the need for administration of sedative and paralytic medications, all of which have hypotensive side effects. Rarely is there a need for ionotropic or cardiopressor support, except in instances of early postoperative hypothermia or profound hemorrhage.

VENTILATORY INSTABLITY

Ventilatory instability in the early postoperative period requires similar evaluation as any postsurgical patient. Initial efforts to determine the etiology of ventilatory problems should be directed at diagnosing mechanical problems related to the mechanical ventilator and the endotracheal tube. For instance, the acute onset of hypercarbia in the early postoperative setting should lead to investigation of the patency of the endotracheal tube specifically and the bronchial tree generally. Plugging of the airways, either with retained mucus or blood, is very common in this setting and can cause rapid ventilatory insufficiency. The development of this problem is suggested by acute increases in ventilatory pressure but is definitively diagnosed by bronchoscopic examination of the airways. Treatment involves the removal of mucus or blood blocking the airway. Of course, improper patient-ventilator synchrony can cause a similar clinical scenario and may result from inadequate patient sedation.

Problems with early allograft function also lead to inadequate ventilation and oxygenation. These problems are usually temporary and are best managed simply through supportive measures. However, in the case of primary graft failure, the oxygenation and ventilatory problems are more profound and require more complex management strategies. In the setting of a double-lung transplant, the management should include the application of increased levels of PEEP and, if necessary, alterations of inspiratory to expiratory ratios. In single-lung recipients, one can selectively ventilate the native lung while other measures are taken to improve allograft performance. This strategy can be accomplished through the use of double-lumen endotracheal tubes, which allow independent lung ventilation.[22] In cases of important allograft dysfunction, positioning the patient on the side with the native lung "down" can lead to increased perfusion to that side (i.e., the side with less pulmonary edema) and can lead to improvements in oxygenation.

EXTRACORPOREAL MEMBRANE OXYGENATION

In instances in which none of the measures described earlier results in hemodynamic and ventilatory stability, ECMO is an alternative treatment strategy.[23-25] Although associated with significant morbidity, ECMO can rapidly restore hemodynamic and ventilatory stability. Important morbidity as a result of this therapy includes bleeding complications secondary to the anticoagulation necessary to maintain the ECMO circuit. Bleeding can occur anywhere and is particularly evident at the cannula insertion site. However, intracranial hemorrhage is the most catastrophic complication and is the most common cause of death associated with ECMO.[26] The preferred ECMO method in lung transplant recipients is generally the venoarterial route, although the venovenous route has been used as well.[27] Insertion of the ECMO cannulas is best performed at the femoral site, because local control of bleeding can be achieved. Although associated with good hemodynamic stability, central cannulization often results in poorly controlled bleeding.

OPERATIVE COMPLICATIONS

Postoperative bleeding issues are similar to other thoracic surgical patients and are best handled by correction of coagulopathies and replacement of red blood cells. As in other thoracic patients, careful chest tube output monitoring is essential in detecting and, ultimately, treating excessive bleeding. Return to the operating room for exploration in the presence of excessive bleeding is not uncommon after lung transplantation. Bleeding complications are generally more common in patients in whom dissection to free the native lung is difficult, such as in cystic fibrosis patients or in

patients with fibrotic lung diseases. There is also a tendency toward more bleeding in patients who have required cardiopulmonary bypass.[28]

As improvements in surgical technique have developed, a decrease in airway, venous, and pulmonary artery anastomotic complications has occurred.[29] Although uncommon, anastomotic complications in the immediate postoperative period generally involve the vascular connections rather than the bronchial anastomosis. Complications with the bronchial anastomosis, such as dehiscence or stricture, usually occur later in the postoperative period. Conversely, problems with the venous[30,31] or pulmonary artery anastomosis[32] manifest immediately postoperatively and are life threatening, particularly if not detected promptly.

Pulmonary artery stricture, or narrowing, is fortunately very uncommon. When it does occur, problems with oxygenation are seen and usually occur in the absence of radiographic abnormalities. The diagnosis is initially one of exclusion, where more common causes of poor oxygenation are investigated first. Once no evidence of other causes of poor allograft function can be found, evaluation of the pulmonary artery anastomosis should occur and usually is best accomplished via pulmonary angiography. Pulmonary perfusion scanning can in some instances be helpful and is noninvasive. However, nonspecific alterations in allograft blood flow do not distinguish among the usual causes of postoperative allograft dysfunction. Pulmonary angiography, on the other hand, can anatomically demonstrate pulmonary artery narrowing and provides the means to measure pressure gradients across the pulmonary artery anastomosis.[33] If a significant gradient across the pulmonary artery anastomosis were to exist, the suspicion of a pulmonary artery stricture would be high enough to warrant surgical re-exploration.

Of the complications associated with the vascular anastomoses, problems with the venous anastomosis are most common. Because of the technical challenges associated with it and the low-flow state of the venous system, the venous anastomosis is susceptible to kinking or clot formation. Both of these complications cause impedance of venous return and back flow of blood into the pulmonary vasculature. This results in immediate and profound pulmonary edema that is refractory to all supportive measures. A clinical scenario of this kind should prompt immediate investigation, ideally via visualization and Doppler measurement of the venous anastomosis using transesophageal echocardiography.[34,35]

TRANSFER FROM ICU

In uncomplicated cases, lung transplant recipients can generally be discharged from the ICU within 24 to 48 hours. Once the respiratory status is stable, plans can be made to transfer patients to less intensive care settings. Aside from reducing the potential for ICU-related infections, discharge from an ICU setting allows more freedom of movement so that more effective pulmonary rehabilitation can occur. Additionally, from a psychosocial standpoint, patients feel less isolated and are able to visit more frequently with friends and family members in less acute care settings.

ANNOTATED REFERENCES

Garrity ER Jr, Villanueva J, Bhorade SM, et al: Low rate of acute lung allograft rejection after the use of daclizumab, an interleukin 2 receptor antibody. Transplantation 2001;71:773-777.

Garrity and his colleagues evaluated the impact of induction therapy using daclizumab on acute rejection incidence. They found that induction therapy with daclizumab significantly reduced the incidence of acute rejection and was not associated with a significantly increased incidence of infections.

Meyers BF, Sundt TM III, Henry S, et al: Selective use of extracorporeal membrane oxygenation is warranted after lung transplantation. J Thorac Cardiovasc Surg 2000;120:20-26.

The authors reviewed their experience using ECMO in post–lung transplant recipients. Although ECMO is associated with increased morbidity, it is a viable therapeutic option in patients with profound respiratory and hemodynamic embarrassment. The authors further explain the technical approach to ECMO therapy.

Weill D, Lock BJ, Wewers DL, et al: Combination prophylaxis with ganciclovir and cytomegalovirus (CMV) immune globulin after lung transplantation: Effective CMV prevention following daclizumab induction. Am J Transplant 2003;3:492-496.

The authors compared monotherapy using intravenous ganciclovir to combination therapy using intravenous ganciclovir and hyperimmune CMV globulin. Weill and colleagues found that a significant reduction in CMV disease and infection was observed in the combination therapy, as compared with using ganciclovir alone.

Weill D, Torres F, Hodges TN, et al: Acute native lung hyperinflation is not associated with poor outcomes after single lung transplant for emphysema. J Heart Lung Transplant 1999;18:1080-1087.

The authors report on the incidence and effect of acute native lung hyperinflation in the University of Colorado Lung Transplant Program. Acute native lung hyperinflation while radiographically common was not associated with increased morbidity or mortality. Consequently, aggressive measures to prevent acute native lung hyperinflation, such as dual lung ventilation, contralateral lung volume reduction surgery, or the routine use of double-lung transplant for emphysema patients are not warranted.

Yonan NA, el-Gamel A, Egan J, et al: Single lung transplantation for emphysema: Predictors for native lung hyperinflation. J Heart Lung Transplant 1998;17:192-201.

Yonan and colleagues discuss factors that predict the development of acute native lung hyperinflation. The authors conclude that acute native lung hyperinflation was common and led to increased morbidity and mortality. Yonan suggested that acute native lung hyperinflation could be avoided by the routine use of contralateral lung volume reduction surgery, double-lung transplant, or dual lung ventilation.

Chapter 87
BURNS AND INHALATION INJURY

Soman Sen • Richard L. Gamelli

KEY POINTS

1. **Careful and focused history and physical examination** including the extent of exposure and the nature of inhaled substance aid in the diagnosis and treatment of inhalation injury.
2. **Nature of the inhaled substance,** including physical properties and heat-carrying capacity, can give an indication of the level and extent of damage on the tracheobronchial tree.
3. **Pathologic changes of inhalation injury** include upper airway edema (glottic cartilage), necessitating mechanical ventilation, and damage to the epithelial lining of the tracheobronchial tree, resulting in increased recruitment of inflammatory mediators and further damage. Mortality of burn injury and inhalation injury is greater than either alone.
4. **Pulmonary complications from inhalation injury** are related to direct damage from thermal energy and toxins, infection from opportunistic organisms, damage caused by inflammatory mediators (alveolar macrophages, neutrophils), reduction in surfactant production, and mucociliary dysfunctions.
5. **Long-term complications from inhalation injury** include a persistence of symptoms such as cough, dyspnea, and symptoms of obstruction. Structural changes may include tracheal stenosis, bronchiectasis, and bronchiolitis obliterans.
6. Initial **medical management** includes adequate fluid resuscitation, maintenance of airway patency, and, when needed, effective mechanical ventilation. Regular pulmonary toilet and effective antibiotic therapy are important after the initial injury period.
7. **Mechanical ventilation** during inhalation injury involves both providing adequate oxygenation and ventilation and minimizing further damage to lung tissue. The use of high-frequency ventilation has been shown to provide some benefit in patients with acute lung injury.

Inhalation injury often occurs in combination with thermal injury and leads to serious complications that manifest at different points in the disease process. Inhalation injury alone carries a 5% to 8% mortality risk; however, when combined with burn injury the mortality can increase by 20% or more.[1] These factors when combined with a complicated pathologic course make inhalation injury a potentially difficult and dangerous disease process.

CLASSIFICATION OF INJURY

Classifications of inhalation injury have been developed according to several different schemes. One of the first schemes was developed as a result of observations made at the Cocoanut Grove fire of 1942 and grouped patients according to outcomes and their initial symptoms. Early signs of hypoxia that were directly attributable to respiratory tract injury had the highest and most immediate mortality. Signs of cyanosis and dyspnea that occurred within a few hours of the insult could be attributable to development of pulmonary edema. At 24 hours, upper airway edema was found to be increased and necessitated establishment of an airway (tracheostomy, intubation). After 48 hours, the final group of patients developed worsening respiratory symptoms due to atelectasis and subsequent pneumonia.[2]

Other classification symptoms for inhalation injury were based on the anatomic location of injury. Upper airway injury involves the nasopharyngeal and oropharyngeal regions to the larynx. This damage results in massive edema and compromise of airway patency, often necessitating intubation or tracheostomy. Injury to the distal parts of the tracheobronchial tree manifests at a later time. Tracheal and major bronchi injuries result in direct mucosal damage and desquamation of the epithelial lining. Injury to the distal alveoli results in atelectasis and predisposes to pneumonia.[3]

THE INITIAL INHALATION INSULT

The initial manifestations of inhalation injury are due to direct damage to airway surfaces that result in inflammation and edema. This damage is more often than not due to the heat content of inhaled material. For example, smoke, which is dry and has a low specific heat, causes damage to upper airways whereas steam, which has 4000 times the heat-carrying capacity, can cause more extensive tracheobronchial damage.[4] The clinical symptoms that appear initially are stridor, hypoxia, and respiratory distress.[5]

Management of the initial insult incorporates a thorough physical examination as well as careful and specific history that provides details about extent of exposure to the inhaled substance and nature of the substance itself. Evaluation of physical symptoms should include examination of the oropharynx for direct damage and documentation of stridor, cyanosis, and confusion, but it is not unusual for there

to be no obvious physical symptom of inhalation injury at the initial evaluation. Initial management includes providing adequate oxygenation as well re-evaluation and maintenance of airway patency.[6]

ENVIRONMENTAL VARIABLES THAT DETERMINE SEVERITY

The extent of inhalation injury is related to the duration of exposure and severity of trauma to the tracheobronchial tree. A major component of the degree of the initial inhalation energy is the amount of heat-carrying capacity of the inhaled substance. Dry heat has a lower heat-carrying capacity than steam and thus usually injures upper airway and supraglottic structures.[7] Thermal injury produces direct injury to the mucosa of upper airway structures. In rare occasions, the lower airway may be damaged. Clinically this manifests as upper airway edema within the first 24 hours.[3]

The level of injury produced by inhalation of particulate matter depends on the diameter of the matter. Large-diameter particles less than 100 μm enter the airway but usually do not travel beyond the upper respiratory tract. Particles less than 10 μm can reach the lower tracheobronchial tree and particles less than 5 μm can reach the terminal bronchus and alveolus. Particulate matter can cause direct mechanical damage and can also carry toxins beyond the level of the initial inhalation.[3]

The ability of gases and toxins to exert damage on the tracheobronchial tree depends on the capacity of the toxin to reach different areas of the airway.[5] Water solubility affects the location of deposit of gases and toxins. Mucous membranes line much of the upper respiratory tract, which allows gases that are highly water soluble to be absorbed in the upper tract and cause irritation to these structures. Because less soluble gases are not absorbed in the upper airway, they travel to the lower airway and cause irritation and damage to those structures.[3]

PATHOLOGY

UPPER AIRWAY INJURY

Upper airway structures that are in direct danger from inhalation injury include the mucous membranes of the nasopharynx, hypopharynx, epiglottis, glottis, and larynx. The mucous membranes of these structures can undergo a significant amount of inflammation due to direct injury. However, the cartilage of the glottis is not tolerant of edema, and damage to this structure can produce life-threatening compromise of airway patency.[7]

Injury to the upper airway occurs earliest and quickly manifests symptoms. Most of the early damage is due to direct thermal injury to mucous membranes of upper airway structures. Mucous membranes are damaged when the temperature of inhaled gases reaches 150°C. The resulting damage initiates an inflammatory cascade that leads to increased capillary permeability, histamine release, and inflow of transudative fluid, all of which results in edema. This process initiates over the course of the first 24 hours post exposure, and the resulting edema resolves in 4 to 5 days. Airway compromise occurs when edema and swelling cause the airway diameter to fall below 8 mm and mandates the need for a mechanical airway.[7]

LOWER AIRWAY INJURY

Thermal Injury. Direct thermal injury to lower airway structures is an uncommon occurrence (5%). This is due to the dissipation of heat during travel through the airway and to reflexive closing of the glottis at high temperatures (150°C). Small particulate matter (<5 μm) can travel to terminal bronchi and alveoli and cause damage to protective structures such as epithelial cells and alveolar macrophages.[8]

Tracheobronchial Injury. Cytoplasmic vacuolization and cytoplasmic blebbing are seen in epithelial cells of the bronchial tree 48 hours after severe smoke inhalation.[9] This is followed by epithelial necrosis, hemorrhage, and perivascular congestion. This damage initiates an inflammatory cascade that recruits inflammatory cells, neutrophils, and macrophages that cause further damage.[10] In addition, the congestion and increased lymphatic flow lead to obstruction of bronchial segments and impair gas exchange.

Parenchymal Damage. Direct damage to the lung epithelium causes the recruitment of inflammatory mediators that produce increased parenchymal damage. Neutrophils are among the first mediators recruited. In addition to growth factors and cytokines, neutrophils release reactive oxygen species and proteases that cause direct cellular damage. This damage triggers further inflammation and leads to pulmonary dysfunction.[11] This dysfunction begins at the cellular level with evidence of increased apoptosis of lung epithelial cells. This leads to a decrease in surfactant release and defective surfactant mechanisms, resulting in obstruction and collapse of lung segments.[12] In addition, alveolar macrophages release free radicals that cause further damage to pulmonary parenchyma.[13] With extensive destruction and inflammation, pulmonary compliance is reduced and gas exchange is impaired, leading to altered pulmonary blood flow patterns and ventilation-perfusion mismatches.[14]

DAMAGE FROM ASPHXIANTS

Smoke generates compounds—carbon monoxide (CO) and cyanide—that are absorbed systemically and impair oxygen utilization and delivery. These compounds directly interfere with oxygen uptake and delivery mechanisms, which results in cellular and local tissue hypoxia and eventually organ failure and death.

CO is an odorless nonirritating gas that is responsible for up to 600 accidental deaths per year. The pathology of CO poisoning is attributable to its ability to rapidly diffuse into the bloodstream and bind to the iron moiety of heme normally bound by oxygen. Because of higher affinity (240 times) for the heme-binding site, CO easily displaces oxygen and impairs the ability of hemoglobin to deliver oxygen. In addition, the stoichiometry of hemoglobin is altered, further impairing oxygen delivery by the other sites of hemoglobin. CO also binds to enzymes within mitochondria involved in the utilization of oxygen by cells and tissues. By binding to these enzymes, myoglobin, cytochromes, and NAPDH reductase, the cellular and local tissue acidosis increases, further impairing oxygen delivery. This results in progressive cellular dysfunction and, ultimately, organ failure.[15]

Neurologic symptoms are often the first manifestation of CO poisoning. Mild carboxyhemoglobin levels (5% to 10%) are usually well tolerated. When concentrations reach 10% to 30% symptoms begin to manifest. Headaches, nausea, and

dizziness are common initial symptoms in mild to moderate CO poisoning. With severe poisoning (50% carboxyhemoglobin levels), more dangerous neurologic symptoms occur, such as syncope, seizures, and comas. The diagnosis is made based on a combination of physical symptoms along with elevated levels of systemic carboxyhemoglobin. Pulse oximetry values do not differentiate between carboxyhemoglobin and oxyhemoglobin and thus remain paradoxically elevated. Blood P_{O_2} level remains normal because it reflects oxygen dissolved in plasma that is not affected by CO.[16] Neurologic symptoms may persist in the form of delayed neuropsychiatric sequelae. The symptoms of this syndrome include a persistent vegetative state, parkinsonism, short-term memory loss, behavioral changes, hearing loss, and psychosis. These symptoms may manifest from 3 to 240 days after recovery, and 50% to 75% of patients with delayed neuropsychiatric sequelae recover fully in 1 year.[17]

The hallmark of treatment of CO poisoning involves maintaining adequate oxygenation. The CO half-life decreases from 6 to 8 hours to 40 to 80 minutes with 1 hour of treatment with 100% oxygen. When administered in a hyperbaric chamber the half-life decreases to 15 to 30 minutes.[18] Administration of 100% oxygen can be done via facemask or by mechanical ventilation. Hyperbaric oxygen treatment has been shown to have an advantage over normobaric oxygen treatment for CO poisoning. However, given the limited number of hyperbaric chambers available, the widespread use of hyperbaric therapy is limited.[17,19]

Cyanide inhalation is a potentially life-threatening occurrence that requires immediate intervention. Once inhaled, cyanide rapidly crosses into the blood and disrupts normal cellular utilization of oxygen by binding to cytochrome oxidase, thus interfering with cellular respiration. Like CO, cellular lactic acid production is increased and cellular dysfunction soon follows.[20]

Diagnosis is made by careful review of the history of inhalation and duration of exposure as well as by clinical symptoms. Physical manifestations of cyanide poisoning include headache and confusion, followed by coma, seizures, fixed pupils, bradycardia, hypotension, arrhythmias, heart block, and cardiac failure. Diagnostic tests include measurement of blood concentrations of cyanide, which are considered toxic at levels of 0.5 mg/L.[20]

Treatment of cyanide inhalation includes administration of oxygen as well as decontamination agents. When cyanide toxicity is suggested, 100% oxygen should be administered immediately This can be done under normobaric or hyperbaric conditions, but the use of hyperbaric chambers is yet to be proven to provide a benefit.[21] Amyl and sodium nitrates can be used as decontamination agents. These compounds induce the formation of methemoglobin to which cyanide has a high affinity. Methemoglobin thus acts as a scavenger for cyanide. Other compounds include sodium thiosulfate, which transfers a sulfur group to cyanide and converts it to thiocyanate, which is excreted by the kidneys, and hydroxycobalamin (not approved by the U.S. Food and Drug Administration), which detoxifies cyanide by binding to it, forming cyanocobalamin.[22,23]

FEATURES OF SPECIFIC IRRITANTS

Smoke produces a variety of compounds that have been shown to cause or initiate damage to the lung. The mechanism of damage for many of these compounds is unknown but the location of damage within the respiratory tract is related to the ability of the compound to reach that location (Table 87-1).

TABLE 87-1. SPECIFIC LUNG IRRITANTS

Chemical Irritants	Properties	Mechanism of Toxicity
Smoke:		
Acrolein	Lipophilic	Direct epithelial damage
Industrial:		
Chlorine	Water soluble	Forms free radicals
Phosgene	Low solubility	Causes the release of arachidonic acid metabolites
Nitric oxide	Lipid soluble	Causes lipid peroxidation
Sulfur dioxide	Water soluble	Causes lipid peroxidation
Ammonia	Water soluble	Forms hydroxyl ions and causes liquefactive necrosis

Acrolein. Acrolein is a toxic compound found in the inhalation of several materials, including tobacco smoke, vehicle exhaust, and wood smoke. Acrolein is a lipophilic aldehyde carbonyl with an attached vinyl group. Its lipophilic nature allows it to pass by the upper airway and penetrate lower airway structures, where it is absorbed. Systemic acrolein is metabolized by the liver by reacting with glutathione, resulting in mercapturic acids that are renally excreted.[24] This transformation, however, does not occur as readily in the lung, and thus acrolein levels remain elevated in lung tissue and cause direct epithelial damage.[25,26]

Hydrogen Chloride. The toxicity of chlorine is related to its water solubility as well as duration of exposure. Chlorine is a moderately water-soluble gas that can penetrate deep into the lower lung structures. Within the upper airway, chlorine has a direct irritant effect that causes inflammation and edema. Within the lower airway hydrogen chloride forms reactive ions that create free radicals. These free radicals react with various compounds and lead to mucosal destruction, pulmonary edema, and parenchymal damage.[27,28]

Phosgene. Phosgene is an acylating agent found in plastics and aniline dyes. It is a low-soluble gas that when inhaled produces severe pathology within the bronchoalveolar spaces. Phosgene reacts with glutathionine and causes the release of arachidonic acid metabolites.[29-31]

Ammonia. The inhaled form of ammonia, anhydrous ammonia, is highly water soluble and is mostly absorbed in the upper airway. However, owing to its toxic nature, lower airway structures can also be affected. Ammonia exerts its effects by reacting with tissues, creating hydroxyl ions, which results in liquefactive necrosis.[32]

Nitrogen Oxide. Nitric oxides are highly lipid soluble compounds that are absorbed in the lower lung regions. Nitric oxides exert their toxic effects by the production of free radicals through lipid peroxidation, leading to parenchymal damage and pulmonary edema.[33,34]

Sulfur Dioxide. Sulfur dioxide is a highly water-soluble gas that is mainly absorbed in the upper airways. Sulfur dioxide, like nitric dioxide, reacts with tissues to produce free radicals via lipid peroxidation.[35]

THE ROLE OF A CUTANEOUS THERMAL INJURY

The combined effect of thermal injury and inhalation injury is synergistic on morbidity and mortality, creating increased pulmonary vascular changes and inflammation that lead to

decreased pulmonary compliance and pulmonary functions. Burn injury alone increases vascular permeability and can result in pulmonary edema. When associated with inhalation injury this increase in pulmonary edema is exacerbated and results in a massive influx of inflammatory mediators, which increases damage to the lung parenchyma.[36] With increasing damage to lung parenchyma, pulmonary compliance decreases and ventilation-perfusion mismatches occur. With the resulting edema, atelectasis and consolidation of the lung from the increased vascular permeability and increased lymphatic flow set the stage for secondary bacterial infections.[37-39] In addition, the pulmonary edema and decreased pulmonary compliance result in increased intrathoracic pressure, which causes a left side–dominant myocardial depression and contributes to the altered hemodynamic profile observed in combined thermal and inhalation injury.[40]

POSTINHALATION PULMONARY COMPLICATIONS

Inhalation injury directly injures upper and lower airway structures through thermal energy, toxic irritants, and particulate matter deposition. This damage causes increased vascular permeability, leading to an influx of inflammatory mediators, all of which results in parenchymal damage. This parenchymal damage leads to further pulmonary dysfunctions, leading to decreased pulmonary compliance, infection, and the acute respiratory distress syndrome (ARDS). Burn injury also increases vascular permeability and causes release of inflammatory mediators.

LOCAL FACTORS

Ciliary Dysfunctions. Inhalation injury causes direct damage to mucosal and ciliary elements, leading to dysfunctions in ciliary motility. This damage is caused by several agents, including acrolein and other aldehydes.[26] In addition, inflammatory mediators such as thromboxane have been shown to decrease mucociliary activity. Thus, inhalation injury produces mucociliary dysfunction by both direct toxic injury as well as by causing the release of inflammatory mediators.[41] This allows particles and toxins to exert their effects on other local defense mechanisms as well as initiate a cascade of parenchymal damage and bacterial infection.[42]

The Pulmonary Alveolar Macrophage. Alveolar macrophage numbers increase in smoke inhalation injury as well as production of superoxide anions that can cause extensive tissue damage.[43] In addition, phagocytic function of macrophages is decreased, which leads to increased toxin and bacterial exposure to lung parenchyma.[13,44] This combined with extensive parenchymal damage caused by alveolar macrophages contributes to pulmonary dysfunctions, infectious complications, and development of ARDS.

Surfactant. Surfactant function and production are altered with severe inhalation injury. In lung injury models, surface tension generated by surfactant is reduced, leading to a loss of force that maintains alveolar patency and results in alveolar collapse. The changes in surfactant function are related to the level of inflammation because studies have shown that increased capillary permeability leads to reduced surfactant production.[12] In addition, there is reduction in surfactant protein levels as well (SP-A, SP-B) that could lead to reduced lung defense mechanisms, further enhancing lung pathology during inhalation injury.[45]

Infections. Infectious complications are a common occurrence with burn injury, and pneumonia, in particular, can reach occurrence rates of up to 50% in severely burned patients, with the majority (65%) of these patients requiring mechanical ventilation.[46,47] Inhalation injury doubles the risk of pneumonia in these patients and leads to pulmonary complications. The mortality for the deadly duo of inhalation injury and nosocomial pneumonia can reach 50% to 86%.[48] The root cause of this synergistic effect has to do with both direct lung injury from inhalation as well as systemic inflammation and immune dysfunctions. This creates an environment that is susceptible to opportunistic hosts, such as *Pseudomonas aeruginosa* and *Acinetobacter*, and can lead to fulminant pneumonias.[49]

Pathogens. In thermal injury, pneumonias are a common complication of the clinical course.[50] With concomitant inhalation injury pulmonary infections can be a potentially devastating complication and lead to increased mortality rates.[49] Organisms that cause these infections in inhalation injury can be organized into groups according to the pathogens' exogenous/endogenous state or to the time from injury to infection. Organisms that are endogenous and cause infections are those that are present in the oral and respiratory tract or those in the gut at the time of admission. These include *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Proteus mirabilis,* and *Escherichia coli.* Those organisms that are exogenous are those acquired during the hospital course and were not present in either the gastrointestinal or respiratory tract. These include methicillin-resistant *S. aureus, Acinetobacter, Pseudomonas aeruginosa,* and other opportunistic organisms (e.g., *Candida*). Within these groupings, early infections tend to be from endogenous organisms whereas infections at a later time tend be from exogenous organisms. Another grouping scheme classifies organisms as occurring early or late in the clinical course. *S. pneumoniae* and *H. influenzae* commonly occur earlier in the clinical course, and *P. aeruginosa* and *S. aureus* occur late.[46] *P. aeruginosa* infection has been shown to significantly increase mortality rates in burn-injured patients. The emergence of *Acinetobacter* species has increased in burn injury and is an increasingly difficult and virulent organism due to its easy transmissibility and multi-drug resistance.[51] Like *P. aeruginosa*, infections by *Acinetobacter* tend to occur later in the time course of treatment and carry a high mortality rate.[52] Recognition and understanding of the pathogens involved in inhalation injury and the time course for the onset of infections are important to tailor effective antimicrobial therapy and avert serious complications.

The Acute Respiratory Distress Syndrome. ARDS is characterized by pulmonary edema not of cardiac origin and pulmonary inflammation leading to alterations in ventilation and perfusion.[53] During thermal injury, inflammatory mediators are released systemically and travel to the highly vascular lung tissue and increase vascular permeability, recruit immune cells, and reduce surfactant function.[10,54] This leads to alveolar collapse and ventilation-perfusion mismatches. This is further enhanced by inhalation injury, which causes direct lung damage and inflammation. Thus, burn and inhalation injury carry a significant risk in the development of ARDS, which results in a fairly high mortality rate (50% to 60%).[55]

THE ENDOGENOUS MEDIATORS OF LUNG INJURY

The Neutrophil. During inhalation injury there is a sequestration of neutrophils in the lungs mediated by direct lung damage. Neutrophils release oxygen radicals and proteases, which results in further damage to lung parenchyma and epithelia. This causes further release of inflammatory mediators that increase pulmonary vascular permeability, resulting in pulmonary edema.[11] Mucosal damage and pulmonary edema lead to collapse of bronchial segments, changes in pulmonary blood flow, and decreased gas exchange. The importance of neutrophil-mediated lung injury in the pathology of ARDS during inhalation injury is further corroborated by studies showing that the inhibition of neutrophil rolling reduces epithelial injury and vascular permeability and may lead to improved outcomes.[56]

Endothelium. Lung injury induces changes in endothelial function that increase vascular permeability and polymorphonuclear leukocyte recruitment, leading to increased inflammation and lung damage. These changes include a reduction of vascular endothelial growth factor that occurs during inflammation and sepsis, which may impair repair mechanisms and lead to further inflammation. In addition, endothelial damage causes release of thromboxanes that cause further inflammation and damage.[57]

Complement. In the lung, complement activation causes endothelial expression of P-selectin, a chemoattractant for neutrophils. P-selectin is up-regulated and augments the recruitment of neutrophils.[58] In addition, complement activation also causes the formation of cell lysing complexes that are activated by macrophages. These lysing complexes contribute to the damage to the lung caused by neutrophils and macrophages.[59]

Eicosanoids. Thromboxanes and leukotrienes are potent mediators of inflammation produced from the arachidonic acid pathway. Thromboxane A_2 increases permeability in the lung and results in interstitial as well as pulmonary edema. Leukotriene B_4 functions as a potent chemoattractant for neutrophils, further exacerbating the damage caused by these cells.[60] Together both thromboxanes and leukotrienes amplify the inflammatory process initiated by injury.[61,62]

Activation of the eicosanoid pathway is mediated by phospholipase A_2. Phospholipase A_2 causes the release of arachidonic acid from the phospholipids of cell membranes. Once released, arachidonic acid is metabolized by cyclooxygenases and lipoxygenases in the lung, which generates a large amount of eicosanoids. Phospholipase A_2 levels have been shown to be elevated after inhalation injury.[63] This activation pathway has been investigated as a potential therapy, and evidence shows that inhibition of phospholipase A_2 can attenuate lung injury in animal models.[64,65]

ONGOING PULMONARY DAMAGE AFTER INHALATION INJURY

Oxygen Toxicity. Oxygen toxicity can complicate the treatment of inhalation injury. After 48 hours of exposure to elevated oxygen levels (FiO_2 of 90%), damage to endothelial cells and an increase in interstitial edema occur.[66] After 72 hours of exposure, type I epithelial cells show evidence of damage. The mechanism by which this occurs is the generation of highly reactive oxygen radicals, which cause direct DNA damage and induce cells to undergo apoptosis, leading to necrosis of epithelial structures.[67,68]

Fluid Management. A key to the initial management of inhalation injury and burns is adequate fluid resuscitation.[6] The parameters used to determine adequate fluid management include urine output, blood pressure, and other hemodynamic parameters. Because inhalation injury causes destruction of mucosal barriers that results in tissue damage and increases in pulmonary vascular permeability, increased fluid requirements can cause a worsening of the pulmonary edema. Studies have shown that combined burn and inhalation injuries have an increased fluid requirement compared with burn injuries alone.[69] These factors combine to make fluid management of inhalation injury patients, especially those with burn injury, challenging. The management strategy incorporates providing minimal amounts of fluid to maintain adequate hemodynamic parameters and urine output.[70]

Long-Term Sequelae. Inhalation injury produces changes in pulmonary architecture that have complex long-term consequences. Long-term studies of survivors of inhalation injury may have symptoms similar to asthma such as cough, dyspnea, and symptoms of obstruction. The extent of obstruction is related to the extent of the inhalation injury and the amount of smoke inhaled. Residual inhaled toxins and irritants are thought to underlie continued long-term bronchial obstruction.

Studies have shown a persistence of inflammation in both bronchial lavage fluid as well as serum. Increased levels of cytokines and lymphocytic inflammation continue to persist up to 6 months after the initial injury. In addition, carbonaceous material has been found in alveolar macrophages months after smoke inhalation and may provide the irritants necessary to create increased levels of inflammatory mediators and bronchial hyper-responsiveness.[71,72]

Long-term structural abnormalities from inhalation injury affect about 10% of patients. These include tracheal stenosis, found only in patients who required intubation or tracheostomy. Bronchiectasis, a dilation of the bronchial tree, and bronchiolitis obliterans are both rare occurrences that lead to pulmonary dysfunctions and symptoms of obstruction. Bronchiolitis obliterans has been found after inhalation with toxic chemicals such as chlorine, phosgene, and ammonia and is thought to occur from residual toxins remaining in the lungs.[73]

TREATMENT

Medical Management. A burn injury with an inhalation injury initially necessitates stabilization and resuscitation of the patient. The cornerstones of management include adequate fluid resuscitation, maintenance of airway patency, adequate and effective mechanical ventilation when required, and vigilant surveillance for infectious complications. However, it is often noted that fluid needs may exceed calculated resuscitation in burn injury complicated by inhalation injury by over 50%.

Pulmonary Toilet. Endoscopic intervention has several roles in the evaluation and treatment of inhalation injury. In the initial injury period airway edema and mucosal sloughing can present in the first 12 to 24 hours. Laryngoscopy and bronchoscopy are used in this period to evaluate the extent of injury to tracheobronchial mucosa and provide predictive indicators for airway patency and collapse. During the clinical

course of treatment, bronchoscopy is used for removal of debris and casts as well as surveillance for infectious events.[74] Other aspects of pulmonary toilet such as frequent endotracheal suctioning and chest physiotherapy are useful adjuncts in the prevention of pneumonia during treatment of inhalation injury.[75]

Antibiotics. Inhalation injury, especially with concomitant burn injury, predisposes the patient to nosocomial infections by opportunistic organisms. In an effort to reduce the rate of these infections prophylactic antibiotic coverage has been studied and has shown no benefit and may lead to increased antimicrobial resistance by these organisms. Currently, broad-spectrum antibiotics are used when infections or sepsis is suspected; they are not initiated prophylactically.[42] Once an infectious agent is identified by culture or Gram stain, the antibiotic therapy is directed at that source.[76]

Steroid Therapy. In burn injury complicated by inhalation injury, systemic corticosteroid therapy is detrimental except for the treatment of severe bronchospasm. However, with isolated inhalation injury corticosteroid therapy may be useful.[12] The use of corticosteroids early in the course of lung injury has shown confounding results and often results in deleterious outcomes. These studies have shown no improvement in outcome or mortality rates compared with control groups, and in some cases corticosteroid treatment leads to worse outcomes and complications. One meta-analysis of corticosteroid therapy for lung injury has shown that use of systemic corticosteroids should be considered only in patients with persistent ARDS who have no septic or infectious complications.[78,79]

Ventilator Management. The hallmark of ventilator management during the treatment of inhalation injury is to minimize further damage and inflammation to lung tissue and provide adequate ventilation and oxygenation.[80] This management strategy has led to several schemes of mechanical ventilation incorporating reduced barotrauma and improved pulmonary gas exchange.[55]

Positive End-Expiratory Pressure. During inhalation injury, injury to the lung increases the capillary permeability and results in influx of inflammatory mediators and edema. This causes an increase in the hydrostatic pressure across the alveolar regions of the lung, resulting in collapse. This coupled with changes in surfactant due to lung injury results in increased opening alveolar pressures and extensive atelectasis. Studies have shown that increasing positive end-expiratory pressure (PEEP) above that of the hydrostatic pressures can prevent collapse of these regions.[81] However, because hydrostatic pressures are not evenly distributed and atelectasis tends to occur in dependent lung regions, increasing PEEP to overcome the collapse in these regions could lead to overdistention of other regions, resulting in barotraumas.[82]

Inverse Ratio Ventilation. With severe lung injury, mechanical ventilation leads to increase in shear forces and changes in pulmonary blood flow. This coupled with a reduction in elasticity, which results in decreased lung compliance, leads to further injury to the lung and ventilation-perfusion mismatches.[83,84] One way of counteracting the mechanical ventilation–induced damage to lung parenchyma and reducing the shearing forces is to change the inspiratory to expiratory ratio.[85] By reversing the ratio from increased expiratory time to an increased inspiratory time, the peak inspiratory pressure of the lung is reduced and oxygenation is improved.[86] This is possibly a result of the prolonged inspiratory phase of ventilation that dissipates the shearing forces on the lung, increases distal alveolar pressure as well as delivered tidal volume, and results in less damage from mechanical ventilation. In addition, owing to the shortened expiratory time, intrinsic PEEP increases, thus preventing alveolar collapse and increasing lung reruitment.[87] Despite the theoretical advantages of inverse ratio ventilation, studies have yet to consistently show an advantage over conventional ventilation.[88]

High-Frequency Ventilation. The high-frequency mode of ventilation uses rapid respiratory rates and small tidal volumes to achieve adequate oxygenation and ventilation while minimizing barotrauma.[89] There are three major types: high-frequency positive-pressure ventilation (HFPPV), high-frequency jet ventilation (HFJV), and high-frequency oscillation (HFOV). HFPPV and HFJV are the oldest forms of high-frequency ventilation and incorporate passive expiration dependent on chest wall elastic recoil. HFPPV delivers small tidal volumes (4 mL/kg) at high flow rates (250 L/min) and frequency (100 breaths/min). Because expiration within this mode is passive, there is an increased risk of air trapping and overdistention. HFJV also delivers small tidal volumes and high respiratory rates. The volume is determined by the jet velocity and duration of flow. Like HFPPV, tidal volumes are difficult to measure and manipulate with HFJV, and thus ventilation is adjusted empirically.[90] Also like HFPPV, expiration is passive and can result in air trapping. HFOV maintains open lung volumes by applying a constant airway pressure but does not allow for patient-triggered inspiratory flow. Thus, inspiration and expiration are active processes and air trapping is reduced. Oxygenation is maintained by increasing the mean airway pressure until an adequate oxygen level is reached. Ventilation is achieved by oscillating the airway pressure through electromagnetically driven pistons that deliver cyclic tidal volumes and facilitate ventilation. The oscillatory frequency determines the piston displacement, and thus reduced frequency increases tidal volume delivery and improves ventilation.[91] The therapeutic advantage of HFOV is due to the maintenance of mean airway pressure that reduces the opening and closing of alveolar spaces at low lung volumes and thus reduces the trauma due to the shearing forces created by the decreased compliance. In addition, the reduced tidal volumes and the high frequency of ventilation results in increased end-expiratory volumes, increasing recruitment of atelectatic segments and reducing lung injury due to overdistention and shearing forces.

Many of the recent studies investigating the usefulness of high-frequency ventilation have focused on HFOV because of this mode's theoretical protective advantage.[92] Several trials of HFOV in patients with acute lung injury and ARDS have shown improvements in oxygenation and ventilation. However, sample sizes for these studies have not been large enough to show a significant survival benefit.[93,94] In addition, more information is needed to refine algorithms for the use of HFOV in these settings.

Extracorporeal Membrane Oxygenation. Extracorporeal membrane oxygenation (ECMO) is used in situations in which mechanical ventilation fails to provide adequate oxygenation or elimination of carbon dioxide. The use of ECMO has shown variable results, and a few studies have shown some improvement of survival.[95] However, large trials on the use of ECMO are lacking.[96,97] As the ECMO technology improves, this alternative to mechanical ventilation in patients in pulmonary failure who do not respond to conventional interventions may become more widespread.

FUTURE DIRECTIONS

Burn and inhalation injuries pose difficult challenges for clinicians. In particular, interventions such as mechanical ventilation aimed at treating pulmonary failure from lung injury often cause further injury. Future avenues of investigation should include a larger assessment of different ventilation modes (inverse ratio ventilation, high-frequency ventilation) that reduce the damage inflicted on the lungs by mechanical ventilation. In addition, therapeutic interventions (surfactant replacement, antithrombolytic therapy) that are designed to attenuate the inflammatory response, which is responsible for much of the damage, also need further investigation.

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Chapter 88
DROWNING

David Szpilman • James P. Orlowski • Joost Bierens

KEY POINTS

1. Each year, **drowning is responsible for an estimated 500,000 deaths around the world.** The exact number is unknown because many deaths go unreported.
2. **Among those aged 5 to 14 years,** drowning is the leading cause of death worldwide for males and the fifth leading cause for females.
3. **Drowning is a process that begins when the airway goes below a liquid surface (usually water) and, if uninterrupted, may lead to death.** A patient can be rescued at any time during the process and given appropriate resuscitative measures.
4. Despite some pathophysiologic differences in experimental models, from a clinical and therapeutic view, **there are no important differences in humans between drowning in fresh water and drowning in salt water.**
5. **Prevention is the most powerful intervention.**
6. Hypoxia caused by submersion results first in cessation of breathing, leading to cardiac arrest in a short time if not corrected. **In-water resuscitation (ventilation only) provides the victim a 3.15 times better chance of surviving without sequelae.**
7. During resuscitation, **attempts at active drainage by placing the victim's head down increase the risk of vomiting more than fivefold** and lead to a small but significant increase in mortality (19%) when compared with keeping the victim in a horizontal position.
8. **Bringing the medical equipment to the victim (rather than vice versa) saves precious time.**
9. **Once a victim is intubated, oxygenation and ventilation can be achieved, even through copious pulmonary edema fluid.**
10. **In severe cases (grades 4 to 6), hospital care is feasible only if adequate and prompt prehospital care was given.** If this is not the case, the appropriate approach is to step back and follow accident site protocols.
11. **Pools and beaches usually do not have sufficient bacterial colonies to cause pneumonia immediately after the incident.** If the victim needs mechanical respiratory assistance, the incidence of secondary pneumonia increases from 34% to 52% in the third or fourth day of hospitalization, when pulmonary edema is almost resolved.
12. Rarely, drowning victims who seem healthy on assessment in the emergency department, including having normal chest radiographs, can develop **fulminant pulmonary edema as long as 12 hours after the incident.**
13. **Grade 3 to 6 drownings have the potential to cause multisystem organ failure. With advances in intensive care therapy, prognosis is based primarily on neurologic outcome.** Grade 1 to 5 drowning victims return home without sequelae in 95% of cases.

Drowning is usually related to leisure situations that take a dramatically dangerous turn. Parents, friends, relatives, baby-sitters, or guardians may feel not only profound loss and grief but also guilt for failing to fulfill their responsibilities, or intense anger at others who did not provide adequate supervision or medical care. Drowning is a neglected public health problem.[1] Each year, drowning is responsible for an estimated 500,000 deaths around the world. The exact number is unknown because many deaths go unreported.[2] Age, gender, alcohol use, socioeconomic status (as measured by income or education), and lack of supervision are key risk factors for drowning. Considering all ages, males die five times more often from drowning than females do. An estimated 40% to 45% of drowning deaths happen during swimming.[3] Young children, teenagers, and older adults are at highest risk of drowning.[4] In those aged 5 to 14 years, drowning is the leading cause of death worldwide among males and the fifth leading cause among females.[4] The patterns of drowning are highly dependent on geographic factors. In the United States, drowning is the third most common cause of death related to unintentional injury for all ages, and it ranks second for people aged 5 to 44 years.[5] Considering all deaths from drowning in the United States (4390 in 1993), 53% drowned in swimming pools[3]; each year, 50,000 new pools are built, in addition to the 2.2 million residential pools and 2.3 million nonresidential pools already in existence. In Brazil, drowning is the second leading cause of death for those aged 5 to 14 years and the third leading cause of injury-associated death for all ages. Brazil has an average of 7210 deaths per year due to drowning (5.2 per 100,000 inhabitants).[6] Ironically, 90% of all drowning deaths occur within 10 meters of safety.[2] On Rio de Janeiro beaches, precipitant causes are discernible in 13% of all cases; the most

common are alcohol (37%), convulsion (18%), trauma (including boating accidents; 16.3%), cardiopulmonary disease (14.1%), skin diving and scuba diving (3.7%), diving resulting in head or spinal cord injury, and others (e.g., homicide, suicide, syncope, cramps, immersion syndrome; 11.6%). It is important to recognize the cause to drowning, because it might guide specific approaches to rescue and resuscitation. In Brazil, freshwater drowning happens more commonly in rivers, lakes, and dams, accounting for half of the deaths by drowning.[7]

In contrast to the United States and Brazil, in the Netherlands, there are many more drowning deaths secondary to suicide than from accidental causes, a demonstration of geographic and cultural differences. In the Netherlands, children are most at risk, but less than 6% of all drownings occur at beaches. Each year in the Netherlands, some 300 persons die from drowning, and 450 are admitted to hospitals. The average hospital stay is 11 days, but 33% of patients are discharged within 48 hours; 10% die.

NEW DEFINITION

The lack of information about the impact of drowning on public health is partly due to a paucity of sound epidemiologic data in this field. Data collection has been hampered by the absence of a uniform and internationally accepted definition that includes both fatal and nonfatal cases. This lack of consensus is evident by the different definitions and terminology used by various water safety and health organizations, experts in the field, papers in the scientific medical literature, and laypersons.[8]

Within the framework of the first World Congress on Drowning, a definition was developed to provide a common basis for future epidemiologic studies worldwide. The Task Force on Epidemiology of Drowning was established in 1998, and in 1999, one task force member (David Szpilman) was invited to write a discussion paper on the definition of drowning and other water-related injuries. This was released on the World Congress's web site in 2000 and provoked a lively electronic discussion, with contributions from many experts around the world. Based on this discussion, the task force released a revised discussion paper on the web site at the beginning of 2002. At the task force's 2002 meeting, the following definition was adopted: "Drowning is the process of experiencing respiratory impairment from submersion or immersion in liquid." The drowning process is a continuum that begins when a person's airway goes below the surface of a liquid, usually water; if this process is uninterrupted, it can lead to death. A person can be rescued at any time during the process and given appropriate resuscitative measures, in which case the process is interrupted. Any submersion or immersion incident without evidence of liquid aspiration should be considered a water rescue (i.e., no respiratory impairment is evident, regardless of the presence of other injury or hypothermia). The term "near-drowning" has been abandoned, and confusing terms such as dry drowning and secondary drowning (delayed onset of respiratory distress) have been eliminated. The final and complete discussion of this new definition can be reviewed at www.drowning.nl.[9]

PATHOPHYSIOLOGY

Despite some pathophysiologic differences in experimental models between drowning in fresh water and drowning in salt water, from a clinical and therapeutic view, there are no important differences in humans. The most significant pathophysiologic alteration is hypoxia.[10] When there is no way to keep the airways out of water, breath holding is the first automatic response when there is no hypoxia and consciousness is preserved. Water in the mouth is spit out or actively swallowed. The initial involuntary aspiration of water produces coughing or, rarely, laryngospasm, leading to hypoxia. If laryngospasm occurs, it is short-lived, owing to worsening hypoxia. As more water is aspirated into the lungs, hypoxemia worsens, and consciousness is lost or deteriorates; progressive hypoxemia leads to irreversible apnea and then asystole (death). Respiratory disturbances depend less on water composition and more on the amount of water aspirated. The aspiration of either fresh or salt water produces surfactant destruction, alveolitis, and noncardiogenic pulmonary edema, resulting in an increased intrapulmonary shunt and hypoxia.[11] In animal research, aspiration of 2.2 mL of water per kilogram of body weight decreases the arterial partial pressure of oxygen (PaO_2) to approximately 60 mm Hg within 3 minutes.[12] In humans, aspiration of as little as 1 to 3 mL/kg of water produces profound alterations in pulmonary gas exchange and decreases pulmonary compliance by 10% to 40%.[11] Humans rarely aspirate sufficient water to cause significant electrolyte disturbances, and victims need no initial electrolyte correction.[13] Ventricular fibrillation in humans is related to hypoxia and acidosis, not hemolysis and hyperkalemia. Hypoxia produces a well-established sequence of cardiac deterioration: tachycardia, bradycardia, a pulseless phase of ineffective cardiac contractions (pulseless electrical activity), and finally complete loss of cardiac rhythm and electrical activity (asystole). Decreased cardiac output, arterial hypotension, and increased pulmonary arterial pressure and pulmonary vascular resistance are the results of hypoxia.[11] Also common is intense peripheral vasoconstriction caused by hypoxia, epinephrine release, and hypothermia.

A victim can be rescued at any time during the drowning process and may not require any intervention at all or may need appropriate resuscitative measures, in which case the drowning process is interrupted. The victim may recover after only the initial resuscitation or may need subsequent therapy aimed at eliminating hypoxia, hypercarbia, and acidosis and restoring normal organ function. In drowning, apnea occurs first, and if the victim is not ventilated soon enough, circulatory arrest will ensue and, in the absence of effective resuscitative efforts, death will result. It should be noted that the heart and brain are the two organs at greatest risk for permanent, detrimental changes from relatively brief periods of hypoxia. The development of posthypoxic encephalopathy, with or without cerebral edema, is the most common cause of death and morbidity in hospitalized drowning victims.

DROWNING CHAIN OF SURVIVAL: PREVENTION TO HOSPITAL

In 1996, the United States Lifesaving Association reported 62,747 rescues on the shores of U.S. beaches and estimated that there were eight cases of drowning for each reported death. On Rio de Janeiro beaches, approximately 290 rescues occurred for each reported death (0.34%), and there was 1 death for every 10 victims admitted for medical care at the Drowning Resuscitation Center. In 31 years of work, the lifeguards of the Rescue Service of Rio de Janeiro have made

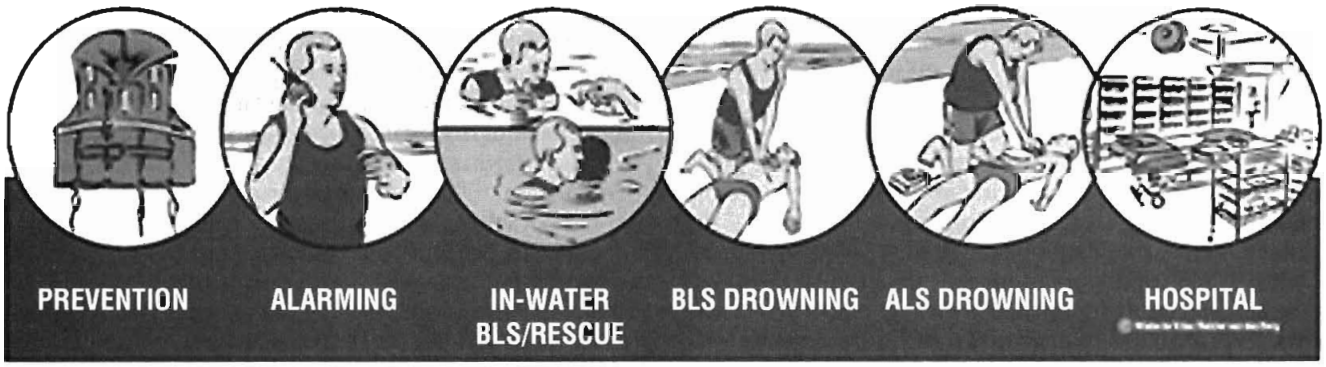

FIGURE 88–1. Drowning chain of survival. ALS, advanced life support; BLS, basic life support. (From Szpilman D, Morizot-Leite L, Vries W, et al: First aid courses for the aquatic environment. In Handbook of Drowning. Netherlands, in press.)

approximately 166,000 rescues on beaches, and 8500 victims needed medical attention in the Drowning Resuscitation Center.[14] Rescue is an essential component of keeping the patient alive, and the first-aid evaluation is made in a hostile environment (water). It is essential for physicians to be aware of the complete drowning chain of survival,[15] from the prehospital to the hospital setting (Fig. 88-1).[15]

PREVENTION

Despite the emphasis on immediate treatment, the best approach to drowning is prevention (Table 88-1). Prevention could have been effective in more than 85% of drownings.

RECOGNITION OF THE DROWNING INCIDENT

Any attempt at rescue must be preceded by the recognition that someone is drowning. Contrary to popular belief, the victim does not wave or call for help.[16] The victim is typically in an upright posture with arms extended laterally, thrashing and slapping the water. Individuals close by may not recognize that the victim is struggling and may assume that the victim is just playing and splashing in the water. The victim may submerge and surface his or her head several times during this struggling activity. Children can struggle for only 10 to 20 seconds before final submersion, and adults can struggle for up to 60 seconds.[16] Because efforts at breathing take precedence, the drowning victim is usually unable to cry for help.

IN-WATER BASIC LIFE SUPPORT AND RESCUE

For non-lifeguards, the priority is to avoid becoming a second victim. If possible, potential rescuers should follow the advice to "throw before you go and reach (with long objects) before you assist." They can also advise the victim how to get out of the situation (e.g., choose a better way to escape, swim, float) and provide reassurance that assistance is coming.

The decision when to do basic water life support[15] is based on the victim's level of consciousness. If the victim is conscious, rescue to land without any further medical care is the protocol.[17] A panicked and struggling victim can be dangerous to a would-be rescuer. For this reason, it is always best to approach a struggling victim with an intermediary

TABLE 88–1. DROWNING: PREVENTIVE MEASURES

General

Watch children carefully; 84% of drownings occur because of inadequate adult supervision.
Begin swimming lessons beginning when children are 2 years old.
Avoid inflatable swimming aids such as "floaties"; they can give a false sense of security. Use a lifejacket!
Never try to rescue someone if you are not sure you can do it. Many people have died trying to save someone else.
Avoid drinking alcohol and eating heavily before swimming.
Do not dive in shallow water—cervical spine injury could occur.

Beaches	Pools and Similar Places
Always swim in a lifeguard-supervised area.	More than 65% of deaths occur in fresh water, even on the coast.
Ask the lifeguard to point out safe places to swim or play.	Fence off your pool, and include a gate. Fencing can decrease the chance of drowning by 50% to 70%.
Read and follow warning signs posted on the beach.	Whenever infants or toddlers are in or around water, be within arm's length, providing "touch supervision."
Do not overestimate your swimming capability—46.6% of drowning victims thought they knew how to swim.	Use portable phones in pool areas, so you are not called away to answer.
Swim away from piers, rocks, and stakes.	Do not hyperventilate to increase submersion time.
Take lost children to the nearest lifeguard tower.	Learn CPR. More than 42% of pool owners are not aware of first-aid techniques.
More than 80% of drowning events occur in rip currents (the rip is usually the most falsely calm place between two sandbars). If caught in a rip, swim transversely to the sandbar, or let it take you away without fighting and wave for help.	
If you are fishing on rocks, be cautious about waves that may sweep you into the ocean.	
Keep away from marine animals.	

object. Lifeguards use rescue or torpedo buoys for this purpose that can double as thorax and face flotation devices to keep the victim's head out of the water and the airways free.[16]

For an unconscious victim, the most important step is the immediate institution of resuscitative measures. Hypoxia caused by submersion results first in cessation of breathing, followed by cardiac arrest within a short time if not corrected. In-water resuscitation (ventilation only) provides the victim a 3.15 times better chance of surviving without sequelae. Rescuers should check ventilation and, if possible and if indicated, attempt to provide mouth-to-mouth ventilation while still in the water. Unfortunately, external cardiac compressions cannot be performed effectively in the water, so assessment for a pulse and chest compressions must be delayed until the victim is out of the water.[17]

A few studies have been done to determine how often in-water cervical spine injury occurs. In one study of sandy beaches, 46,060 water rescues were evaluated retrospectively, and it was determined that the incidence of cervical spine injury in this setting is very low (0.009%).[18] In another retrospective survey of more than 2400 drownings, only 11 patients (<0.5%) had cervical spine injuries, and all had a history of obvious trauma from diving, falling from height, or a motor vehicle accident.[19] Other water locations may have different rates of cervical spine injury, depending on a wide variety of factors. Any time spent immobilizing the cervical spine in an unconscious victim with no signs of trauma could lead to cardiopulmonary deterioration and even death; thus, routine cervical spine immobilization in water rescues is not recommended.[18,19] If a spinal cord injury is suspected, rescuers should float the victim supine into a horizontal position, allowing the airways to be out of the water, and check for spontaneous breathing. If there is no spontaneous breathing, protocols for in-water (mouth-to-mouth) resuscitation should be followed while maintaining the head in as neutral a position as possible. The jaw thrust without a head tilt or chin lift can be used to open the airway. If there is spontaneous breathing, rescuers should keep floating the victim, using their hands to stabilize his or her neck in a neutral position. If possible, a back support device should be used to move the victim to a dry place, maintaining the neck in a neutral position. The head, neck, chest, and body should be aligned and supported if the victim must be moved or turned.[10]

ON-LAND BASIC DROWNING LIFE SUPPORT

Level of consciousness determines how the victim is removed from the water, but a vertical position is preferred to avoid vomiting and further compromise of the airways.[20] If the victim is exhausted, confused, or unconscious, however, transport should be accomplished in a position as near horizontal possible, but with the head maintained above body level (keep the body horizontal in cases of prolonged immersion or cold water drowning).[20] Airways must be kept open at all times. The first procedure on land is to place the victim in a position parallel to the waterline,[20] as horizontal as possible and lying supine, far enough away from the water to avoid incoming waves. If the victim is conscious, reposition him or her supine with the head up. If the victim is breathing, use the recovery (lateral decubitus) position.[20]

In a 10-year study in Australia, vomiting occurred in more than 65% of victims who needed ventilatory support during the rescue period and in 86% of those who required both ventilatory support and chest compressions.[21] Even in victims who required no intervention after water rescue, vomiting occurred in 50% once they reached shore. The presence of vomit in the airway can result in further aspiration and impairment of oxygenation by obstructing the airways; it can also discourage rescuers from attempting mouth-to-mouth resuscitation.[21] The abdominal thrust (Heimlich) maneuver should never be used as a means of expelling water from the lungs—it is ineffective and carries significant risks. During resuscitation, attempts at active drainage by placing the victim head down increase the risk of vomiting more than fivefold and lead to a small but significant increase in mortality (19%) when compared with keeping the victim in a horizontal position.[20] If vomiting occurs, turn the victim's mouth to the side and remove the vomitus with a finger sweep, a cloth, or suction.

One of the most difficult medical decisions a lifeguard or an emergency medical technician must make is how to treat a drowning victim appropriately. Cardiopulmonary or isolated respiratory arrest is present in approximately 0.5% of all rescues. The most basic questions are whether the rescuer should administer oxygen, call an ambulance, transport the person to a hospital, or observe on site. Even hospital emergency physicians may be unsure of the appropriate treatment modalities, because the severity of injury varies in drowning victims. To address these issues, a classification system was developed in Rio de Janeiro in 1972 and updated in 1997 to assist lifeguards, ambulance personnel, and physicians who treat drowning victims.[22] It was based on an analysis of 41,279 rescues, of which 2304 (5.6%) needed medical attention. It was revalidated in 2001 by a 10-year study of 46,080 rescues.[23] This classification system (Fig. 88-2) covers support from the site of the accident to the hospital, recommends treatment, and predicts the likelihood of death based on injury severity. The severity can easily be assessed by an on-scene rescuer, emergency medical technician, or physician using only clinical variables.[22]

ADVANCED DROWNING LIFE SUPPORT ON SITE

Bringing medical equipment to the victim instead of carrying the victim to the ambulance saves precious time. Advanced medical treatment is given according to the drowning classification, described here from most to least severe.

Dead Body. Victim with submersion time greater than 1 hour or with obvious physical evidence of death (rigor mortis, putrefaction, dependent lividity). Do *not* start resuscitation—follow to the morgue.

Grade 6—Cardiopulmonary Arrest. Resuscitation started by a layperson or a lifeguard at the scene must be continued by advanced life support personnel until successful. If there is no way to warm the victim appropriately at the scene, the patient should be transported while receiving resuscitation to a hospital, where advanced warming measure can be accomplished. The first priority is adequate oxygenation and ventilation. Medical staff should continue cardiac compressions while starting artificial ventilation using a bag and facemask with 15 L of oxygen until an orotracheal tube can be inserted. Suctioning the airways to intubate is usually necessary. Once intubated, victims can be oxygenated and ventilated effectively, even though there may be copious pulmonary edema fluid. The Sellick maneuver should be used, if possible, during intubation to prevent

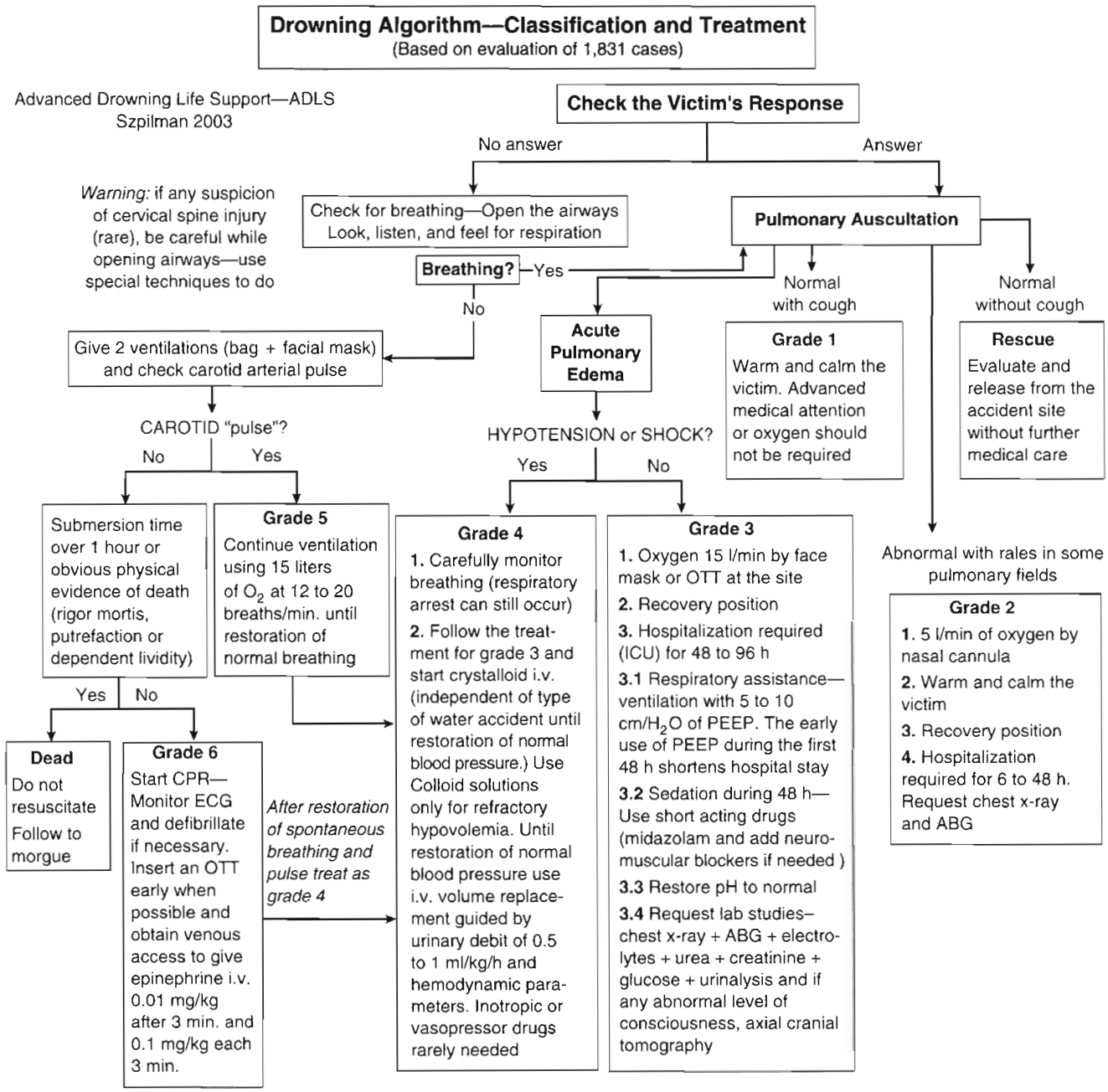

FIGURE 88–2. Do not spend time trying to drain the water from lungs; this will only increase the occurrence of vomiting and complications. Do not enthusiastically aspirate foam while ventilating. Do not use diuretics or water restriction to treat pulmonary edema. Do not use antibiotics before 48 h except if the accident occurred in an area of high water bacterial colonization (CFU $>10^{20}$). Do not use steroids except in case of refractory bronchospasm. Always treat hypothermia. Do not stop CPR until body temperature rises to 34°C. There is no difference in ADLS support between different kinds of water. Drowning classification algorithm—advanced drowning life support (ADLS). ABG, arterial blood gas; CPR, cardiopulmonary resuscitation; ECG, electrocardiogram; ICU, intensive care unit; OTT, oro-tracheal tube; PEEP, positive end-expiratory pressure. (From Szpilman D: Near-drowning and drowning classification: A proposal to stratify mortality based on the analysis of 1831 cases. Chest 1997;112:660-665.)

regurgitation and aspiration. The orotracheal tube should be aspirated only when fluid interferes with effective ventilation.

External defibrillation patches may have a role in monitoring the cardiac rhythm. If the patient is pulseless and hypothermic (<34°C), cardiopulmonary resuscitation (CPR) must continue. Although ventricular fibrillation is uncommon, especially in pediatric victims, some adults may develop it, possibly as a consequence of coronary artery disease or the therapies administered, such as epinephrine. Peripheral venous access is the preferred route for drugs. Although some drugs can be administered endotracheally, despite copious fluid, the drug dosage and rate of absorption are unclear.[16] The dose of epinephrine for resuscitation in drowning victims is controversial; in these patients, the time elapsed before initiation of resuscitation can be much longer and the outcome much different from that in other situations. Both beneficial and toxic physiologic effects of epinephrine administration during CPR have been shown in animal and human studies. Initial or escalating high-dose epinephrine occasionally results in the return of spontaneous circulation and early survival; however, higher doses of epinephrine do not improve long-term survival or neurologic outcome in nondrowning cardiac arrest when used as initial therapy. Therefore, high-dose epinephrine is not recommended for routine use, but it can be considered if 1-mg doses fail.[24] Nevertheless, in some studies, high doses of epinephrine in

drowning victims have increased the rate of successful resuscitation.[22,25] Our recommendation is to use a first dose of 0.01 mg/kg i.v. after 3 to 5 minutes of CPR[26]; if no response occurs, increase to 0.1 mg/kg after each 3 to 5 minutes of CPR.[10]

Grade 5—Respiratory Arrest. Respiratory arrest is usually reversed by the time advanced life support personnel arrive at the scene. An apneic victim requires mechanical ventilatory support. Oxygenation and ventilation protocols for grade 6 should be followed until spontaneous breathing is restored; then follow protocols for grade 4.

Grade 4—Acute Pulmonary Edema with Hypotension. Oxygen with mechanical ventilatory support is first-line therapy. Initially, oxygen should be administered by facemask at 15 L/minute until an orotracheal tube can be inserted. In grade 4 drownings, early intubation is needed in 100% of cases, with provision of positive airway pressure. Mechanical ventilation is indicated by an arterial oxygen saturation (SaO_2) of less than 90%, an arterial partial pressure of carbon dioxide ($PaCO_2$) of more than 45 mm Hg, or an abnormally high respiratory rate or effort to maintain adequate arterial blood gases, such that the patient is consuming large amounts of energy breathing and is likely to tire.[16] Patients should be given sedatives, analgesics, and muscular blockers as needed to tolerate intubation and artificial mechanical ventilation with a tidal volume of at least 5 mL/kg body weight. The inspired oxygen fraction (FiO_2) can start at 1.0 but should be reduced to 0.45 or less as soon as possible to avoid adding oxygen toxicity to pulmonary injury. Positive end-expiratory pressure (PEEP) should be added initially at a level of 5 cm H_2O and then increased by increments of 2 to 3 cm H_2O until an intrapulmonary shunt of 20% or less or a PaO_2/FiO_2 of 250 or more is achieved. If low blood pressure is not corrected by oxygen, a rapid crystalloid infusion should be used before trying to reduce PEEP.[11,27]

Grade 3—Acute Pulmonary Edema without Hypotension. Victims with an SaO_2 greater than 90% with the use of 15 L of oxygen by facemask can tolerate noninvasive ventilatory support in only 27.6% of cases. The rest need intubation and mechanical ventilation, which should be instituted using the same protocols as for grade 4.

Grade 2—Abnormal Auscultation with Rales in Some Pulmonary Fields. Victims need oxygen by nasal cannula in 93.2% of cases; the rest need no oxygen assistance.

Grade 1—Coughing with Normal Lung Auscultation. Victims do not need any oxygen or respiratory assistance.

Rescue—No Coughing, Foamy Secretions, or Difficulty Breathing. The victim can be evaluated and released from the accident site without further medical care.

HOSPITAL

Hospital care is recommended for grades 2 to 6. Decision-making in the emergency department about admission to an ICU or hospital bed versus observation in the emergency department or discharge home should involve a thorough history of the accident and previous illnesses, a physical examination, and diagnostic studies, including chest radiographs and arterial blood gas measurements. Electrolytes, blood urea nitrogen, creatinine, and hemoglobin should be assessed serially, although perturbations in these laboratory tests are unusual. In some cases, a toxicologic screen for suspected alcohol or drug ingestion might be warranted. Patients classified as grades 3 to 6 should be admitted to an ICU for close observation and therapy. Grade 2 patients can be observed in the emergency room for 6 to 24 hours, and grade 1 and rescue cases with no complaints or associated illnesses can be released home. Table 88-2 shows the need for hospital admission and overall and hospital mortality rates for each grade of severity.

Except in rare situations, grade 4 to 6 patients arrive at the hospital mechanically ventilated with acceptable oxygenation. If not, the emergency physician should follow grade 4 ventilation protocols. Once the desired oxygenation is achieved at a given level of positive airway pressure, that level of PEEP should be maintained unchanged for 48 hours to permit adequate surfactant regeneration. During that time, if the level of consciousness allows the patient to breathe spontaneously, it is reasonable to use continuous positive airway pressure (CPAP) plus pressure support ventilation. In selected cases, CPAP may be provided by mask (e.g., in cooperative adolescents) or nasal cannula (e.g., in infants who are obligate nasal breathers). A clinical picture similar to that of acute respiratory distress syndrome (ARDS) is common after significant drowning episodes (grades 3 to 6), but with a more rapid recovery. Ventilatory management is similar to that of other patients with ARDS, including efforts to minimize volutrauma and barotrauma. However, permissive hypercapnia probably is not suitable for grade 6 drowning victims with significant hypoxic-ischemic brain injury. Instead, mild to moderate hyperventilation, aiming for a $PaCO_2$ in the

TABLE 88–2. RATES OF MORTALITY AND HOSPITAL ADMISSION FOR DROWNING, BY GRADE

Grade	No. of Patients	Overall Mortality (%)	Admitted to Hospital (%)	Hospital Mortality (%)
Rescued	38,976	0 (0)	0 (0)	0 (0)
1	1,189	0 (0)	35 (2.9)	0 (0)
2	338	2 (0.6)	50 (14.8)	2 (4.0)
3	58	3 (5.2)	26 (44.8)	3 (11.5)
4	36	7 (19.4)	32 (88.9)	7 (19.4)
5	25	11 (44)	21 (84)*	7 (33.3)
6	185	172 (93)	23 (12.4)†	10 (43.5)
Total	1,831‡	195 (10.6%) $P < 0.0001$	187 (10.2%)	29 (15.5%)

*Not included are 4 patients who were pronounced dead and taken directly to the morgue.
†Not included are162 patients who were pronounced dead and taken directly to the morgue.
‡Excluding the rescues cases.
From Szpilman D: Near-drowning classification: A proposal to stratify mortality based on the analysis is of 1831 cases. Chest 1997;112:660-665.

range of 30 to 35 mm Hg, is indicated, together with other therapeutic measures to control cerebral edema.

Despite aggressive management, neurologic injury and sequelae, including persistent vegetative state, can complicate the management of grade 6 drowning victims. In those who are hemodynamically unstable or have severe pulmonary dysfunction (grades 4 to 6), pulmonary artery catheterization may improve the ability to assess and treat the patient. No evidence exists to support the routine administration of hypertonic solutions and transfusions for freshwater drowning or hypotonic solutions for saltwater drowning.[11,27] Echocardiography to assess cardiac function and ejection fraction may help the clinician decide whether to use inotropic agents, vasopressors, or both if the patient remains hypotensive after volume resuscitation. Some studies have shown that cardiac dysfunction, with low cardiac output, is common in the period immediately after severe drowning (grades 4 to 6).[11] Supportive measures include Foley catheter placement to monitor urine output.

Metabolic acidosis is present in 70% of severe drowning patients when they arrive at the hospital.[13] Acidosis should be corrected when the pH is lower than 7.2 or the bicarbonate is less than 12 mEq/L, if the victim has adequate ventilatory support.[27] Significant depletion of bicarbonate is rarely present in the first 10 to 15 minutes of CPR, contraindicating bicarbonate replacement in the early resuscitative phase.[26]

Usually, pools and beaches do not have sufficient bacteria to cause pneumonia during the immediate postdrowning period.[28] If the patient needs mechanical respiratory assistance, the incidence of secondary pneumonia increases from 34% to 52% by the fourth day of hospitalization.[29] Prophylactic antibiotics are of doubtful value in the initial management of drowning victims and tend to select out more resistant and aggressive organisms. An altered chest radiograph should not be interpreted as pneumonia, because it is usually the result of pulmonary edema and aspirated water in the alveoli and bronchi. A preferable approach is daily monitoring of tracheal aspirates with Gram stain, culture, and sensitivity. At the first sign (usually after the first 48 to 72 hours of ICU care) of pulmonary infection—gauged by prolonged fever, sustained leukocytosis, persistent or new pulmonary infiltrates, and leukocytosis in the tracheal aspirate—antibiotic therapy should be selected based on the predominant organism and pattern of sensitivity. Fiber-optic bronchoscopy may be useful for obtaining quantitative cultures, for determining the extent and severity of airway injury in cases of solid aspiration, and, rarely, for therapeutic clearing of sand, gravel, and other solids. Corticosteroids are of doubtful value in pulmonary injury and should not be used, except for bronchospasm.

The clinician must be aware of and vigilant for potential complications of ventilatory therapy, such as volutrauma and barotrauma.[28] Spontaneous pneumothoraces are common (10%), secondary to positive-pressure ventilation and local areas of hyperinflation. Any sudden change in hemodynamic stability during mechanical ventilation should be evaluated to rule out pneumothorax or other barotrauma. Nasogastric tube placement reduces gastric distention and prevents further aspiration. Rarely, drowning victims who seem healthy on assessment in the emergency department, including having normal chest radiographs, develop fulminant pulmonary edema as long as 12 hours after the incident. Whether this late-onset pulmonary edema is delayed ARDS or neurogenic pulmonary edema secondary to hypoxia is unclear, but it is extremely unusual.

Renal insufficiency or renal failure is rare in drowning victims but can occur secondary to anoxia, shock, or hemoglobinuria.

Besides the reversible pulmonary injury, the most important complication is the anoxic-ischemic cerebral insult that may be present after resuscitation. Most late deaths and long-term sequelae of drowning are neurologic in origin.[28] Although the highest priority is restoration of spontaneous circulation, in the early stages after rescue, every effort should be made to resuscitate the brain and prevent further neurologic damage. These steps include the provision of adequate oxygenation (SaO_2 >92%) and cerebral perfusion (mean arterial pressure around 100 mm Hg). Any victim who remains comatose and unresponsive after successful CPR or deteriorates neurologically should be evaluated for the development of cerebral edema.

Continuous monitoring of core and brain (tympanic) temperature is mandatory in the emergency department and ICU (and in the prehospital setting, if possible). Drowning victims in whom adequate spontaneous circulation has been restored but who remain comatose should not be actively rewarmed to temperatures greater than 32°C to 34°C. If the core temperature exceeds 34°C in a comatose patient, hypothermia (32°C to 34°C) should be achieved as soon as possible and sustained for 12 to 24 hours. Hyperthermia should be prevented at all times in the acute recovery period.

Although there is insufficient evidence to support a specific target $PaCO_2$ or oxygen saturation during and after resuscitation, hypoxemia should be avoided. In select cases, the induction of barbiturate coma can control cerebral edema and intracranial hypertension when other therapies are unsuccessful. Unfortunately, studies evaluating the results of cerebral resuscitation measures in drowning victims failed to demonstrate that therapies directed at controlling intracranial hypertension and maintaining cerebral perfusion pressure improve outcome. These studies showed poor outcomes (i.e., death or moderate to profound neurologic sequelae) when the intracranial pressure was 20 mm Hg or more and the cerebral perfusion pressure was 60 mm Hg or less, even when therapies directed at controlling and improving these pressures were used.

New therapeutic interventions for drowning victims, such as extracorporeal membrane oxygenation, artificial surfactant, nitric oxide, and liquid lung ventilation, are still in the investigational stage.

OUTCOME AND SCORING SYSTEMS

Grade 3 to 6 drownings have the potential to cause multisystem organ failure.[16] Grade 1 to 5 drowning victims return home without sequelae in 95% of cases.[22] A major concern among researchers is grade 6 drowning. Several questions need to be answered: How do we know when to make the effort to resuscitate? How long we should continue? How different should the treatment be? What will the patient's quality of life be after successful resuscitation?[11] Both at the rescue site and in the hospital, no one indicator is reliable in predicting the outcome in grade 6 patients.[30] Based on the longest documented submersion time in cold water (66 minutes) with complete recovery,[16] resuscitation should be started without delay in every victim without a palpable carotid pulse who has been submerged for less than 1 hour or does not have obvious physical evidence of death (rigor mortis, putrefaction, dependent lividity).

TABLE 88–3. PROBABILITY OF DEATH OR SEVERE NEUROLOGIC IMPAIRMENT, BASED ON DURATION OF SUBMERSION

Duration of Submersion (min)	Probability of Death or Severe Neurologic Impairment (%)
0 to <5	10
5 to <10*	56
10 to <25	88
>25	100

*Note that the 5 additional minutes of submersion increases mortality almost 6 times.

From Cummins RO, Szpilman D: Submersion. In Cummins RO, Field JM, Hazinski MF (eds): ACLS—The Reference Textbook, vol 2, ACLS for Experienced Providers. Dallas, American Heart Association, 2003, pp 97-107.

Some clinical series claim that successful resuscitation after prolonged submersion is possible only in cold or icy water; however, there are anecdotal cases of prolonged warm water drowning and survival without sequelae.[22,31,32] Multiple studies have established that outcome is determined almost solely by one factor—duration of submersion (Table 88-3).[17,21,22,28,31-35] Based on a report of a drowning victim who was successfully resuscitated after 2 hours of CPR,[28] efforts should stop only if asystole persists after rewarming the victim above 34°C.

After successful CPR, it is crucial to stratify the severity of neurologic deficits, which allows the comparison of different therapeutic approaches. Various prognostic scoring systems have been developed to predict which patients will do well with standard therapy and which are likely to have significant cerebral anoxic encephalopathy requiring aggressive measures to protect the brain. One of the best measures is the Glasgow coma scale score in the period immediately (during the first hour) after resuscitation (Conn and Modell neurologic classification).[28,36] Because of the typical 2- to 6-hour delay between rescue and transfer from an outlying emergency facility to an ICU, many patients with severe anoxic-ischemic cerebral insults and coma have had multiple determinations of neurologic status before definitive therapy is begun. Data suggest that patients who remain profoundly comatose (i.e., decorticate, decerebrate, or flaccid) 2 to 6 hours after the drowning accident are brain dead or will have moderate to severe neurologic impairment. Patients who are improving but remain unresponsive have a 50% likelihood of a good outcome. Patients who are definitely improving and alert or are stuporous or obtunded but respond to stimuli 2 to 6 hours after the incident are likely to have normal or near-normal neurologic outcomes. These prognostic variables are important in counseling family members in the early stages after the accident and in deciding which patients are likely to have a good outcome with standard supportive therapy and which victims are candidates for experimental cerebral resuscitation therapies.[33]

ANNOTATED REFERENCES

Bierens JJLM, Velde EA, Berkel M, Zanten JJ: Submersion in the Netherlands: Prognostic indicators and results of resuscitation. Ann Emerg Med 1990;19:1390-1395.

This retrospective study revealed some important prognostic indicators and found that submersion time is the most important one. However, no one indicator can predict the final outcome of drowning.

Cummins RO, Szpilman D: Submersion. In Cummins RO, Field JM, Hazinski MF (eds): ACLS—The Reference Textbook, vol 2, ACLS for Experienced Providers. Dallas, American Heart Association, 2003, pp 97-107.

An excellent review article that highlights important issues such as in-water resuscitation, cervical trauma, and prognostic indicators in the prehospital setting.

Orlowski JP, Szpilman D: Drowning—rescue, resuscitation, and reanimation: Pediatric critical care: A new millennium. Pediatr Clin North Am 2001;48:627-646.

A very good review article that highlights issues such as prevention, physiopathology, basic life support, and treatment.

Special resuscitation situations: Guidelines for cardiopulmonary resuscitation and emergency cardiac care (ECC). Circulation 2000;102:122-153.

These guidelines deal with many different aspects of drowning, including modification of definitions, classification, and new approaches in advanced life support.

Szpilman D: Near-drowning and drowning classification: A proposal to stratify mortality based on the analysis of 1831 cases. Chest 1997;112:122-153.

This retrospective study reviewed 41,279 water rescues to establish a classification system for drowning according to severity, based on mortality rates. Using clinical parameters ranging from first-aid observations, presence of breathing, arterial pulse, pulmonary auscultation, and arterial blood pressure, six grades were developed, representing different mortality rates and treatment.

Chapter 89

ACUTE PARENCHYMAL DISEASE IN INFANTS AND CHILDREN

Kathleen M. Ventre • John H. Arnold

KEY POINTS

1. Whereas **inhaled bronchodilators and systemic corticosteroids are of proven benefit** in the management of asthma-induced bronchospasm, symptomatic medical therapies have not been shown to alter outcomes in critically ill children with airways obstruction due to bronchiolitis.
2. **In critically ill patients with lower airways disease,** noninvasive positive-pressure ventilation may be a feasible strategy to avoid intubation in select pediatric patients. Noninvasive respiratory support has been used successfully in the management of asthma and bronchiolitis.
3. **Noninvasive mechanical ventilatory support** may also obviate the need for intubation in pediatric patients with alveolar disease. This technique has been applied with success in a variety of alveolar diseases in pediatric patients.
4. A great deal of experimental data support the use of **lung-protective ventilation in pediatric alveolar disease.** Lung-protective ventilation involves the preservation of end-expiratory lung volume by judicious use of positive end-expiratory pressure (PEEP) and/or recruitment maneuvers, minimizing cyclic stretch, and avoidance of parenchymal overdistention at end inspiration by limiting tidal volume and transpulmonary pressure.
5. **High-frequency oscillatory ventilation** has theoretical advantage in providing a lung-protective strategy of ventilation by maintaining maximal recruitment throughout the respiratory cycle and achieving ventilation through use of very small phasic changes in pressure and volume.
6. **In pediatric patients, interstitial lung disease may develop** as a result of either congenital abnormalities of the alveolar-capillary unit or acquired pulmonary conditions. The potential causes for interstitial lung disease in children differ from those in adult patients.
7. **Bronchopulmonary dysplasia, or acquired chronic lung disease of infancy,** is believed to develop as a result of inflammatory response to lung injury. A strategy involving promotion and maintenance of alveolar recruitment and minimizing cyclic changes in lung volume is likely to limit excess lung injury in neonates.
8. Recent experience with the **supportive care of infants with congenital diaphragmatic hernia** seems to favor delaying surgical repair until physiologic stability is achieved as well as the judicious titration of mechanical ventilatory support to limit excess lung injury.
9. **Successfully separating the pediatric patient from mechanical ventilatory support** requires timely recognition of acceptable respiratory mechanics and gas exchange. A protocol for gradual weaning of mechanical ventilatory support may not be important for the majority of pediatric patients.

Pulmonary parenchymal processes in children whom the intensive care clinician may encounter include common and uncommon diseases of the lower airways, alveoli, and pulmonary interstitium. Among the more challenging conditions to manage in the ICU are those that include disease or dysfunction of all three of these components, such as bronchopulmonary dysplasia (BPD) and congenital diaphragmatic hernia (CDH). In this chapter we discuss the pathophysiology and management principles pertinent to each disease category, with emphasis given to common examples and conditions that are unique to the pediatric patient.

DISEASES OF THE AIRWAYS

STATUS ASTHMATICUS

Although unusual anatomic conditions of the lower airways can occur in pediatric patients (Table 89-1), status asthmaticus and bronchiolitis are probably the most common causes of lower airways disease in the pediatric ICU. Severe exacerbations of asthma in children present a common management challenge for the critical care clinician. Asthma is common in the industrialized world. Annual rates of hospitalization for the disease in infants and children up to 14 years of age have increased dramatically over the past decade, and pediatric patients continue to have the highest hospitalization rate of any age group.[1,2] Mortality rates for American children age 5 to 14 years with asthma seemed to peak in the early 1990s and have declined slightly since then.[1,2] Status asthmaticus is characterized by acute, severe airway obstruction due to bronchoconstriction that is refractory to initial management

TABLE 89–1. ANATOMIC CAUSES OF LOWER AIRWAYS DYSFUNCTION

Tracheomalacia, bronchomalacia
Vascular anomaly
Tracheoesophageal fistula
Idiopathic
Bronchiectasis
Congenital lobar emphysema
Cystic adenomatoid malformation
Pulmonary sequestration
Bronchogenic cyst

with supplemental oxygen, inhaled bronchodilators, and corticosteroids. The pathophysiology of the condition begins with a precipitant that triggers contraction of hyperresponsive bronchial smooth muscle, mucus secretion, and mucosal edema, which result in obstruction of large and small airways. Hyperinflation from premature closure of lower airways in expiration leads to an increased functional residual capacity[3] and an increased respiratory workload that ultimately leads to alveolar hypoventilation and hypoxemia. An abrupt and profound acidosis can occur when respiratory compensation for accumulated inorganic acids no longer occurs (Fig. 89-1).[3] On physical examination, the child with status asthmaticus will often appear anxious or lethargic, will often demonstrate accessory muscle use, and, depending on the quality of air entry, can demonstrate either cough with profound inspiratory and/or expiratory wheezing and prolongation of audible expiration, or a silent chest. Pulsus paradoxus, far in excess of normal, can often be demonstrated, reflecting the profoundly negative intrapleural pressures generated by these patients during spontaneous respiration.

Therapy

Supportive care in status asthmaticus begins with maintaining the airway, monitoring the quality of respirations, and maintenance of euvolemia. Standard medical therapies for these patients include bronchodilators and corticosteroids, and several adjunctive therapies have been investigated as possible rescue agents in difficult cases (Table 89-2). Short-acting beta-agonist agents, targeted to mediate airway smooth muscle relaxation via local $beta_2$ receptors,[3] are the most commonly used bronchodilators for status asthmaticus. Among these agents, albuterol is the most widely used. Unlike epinephrine and isoproterenol, it is relatively $beta_2$ selective[3] and it is most commonly administered by nebulization. It is typically given at 0.15 mg/kg/dose up to 5 mg on a frequent intermittent

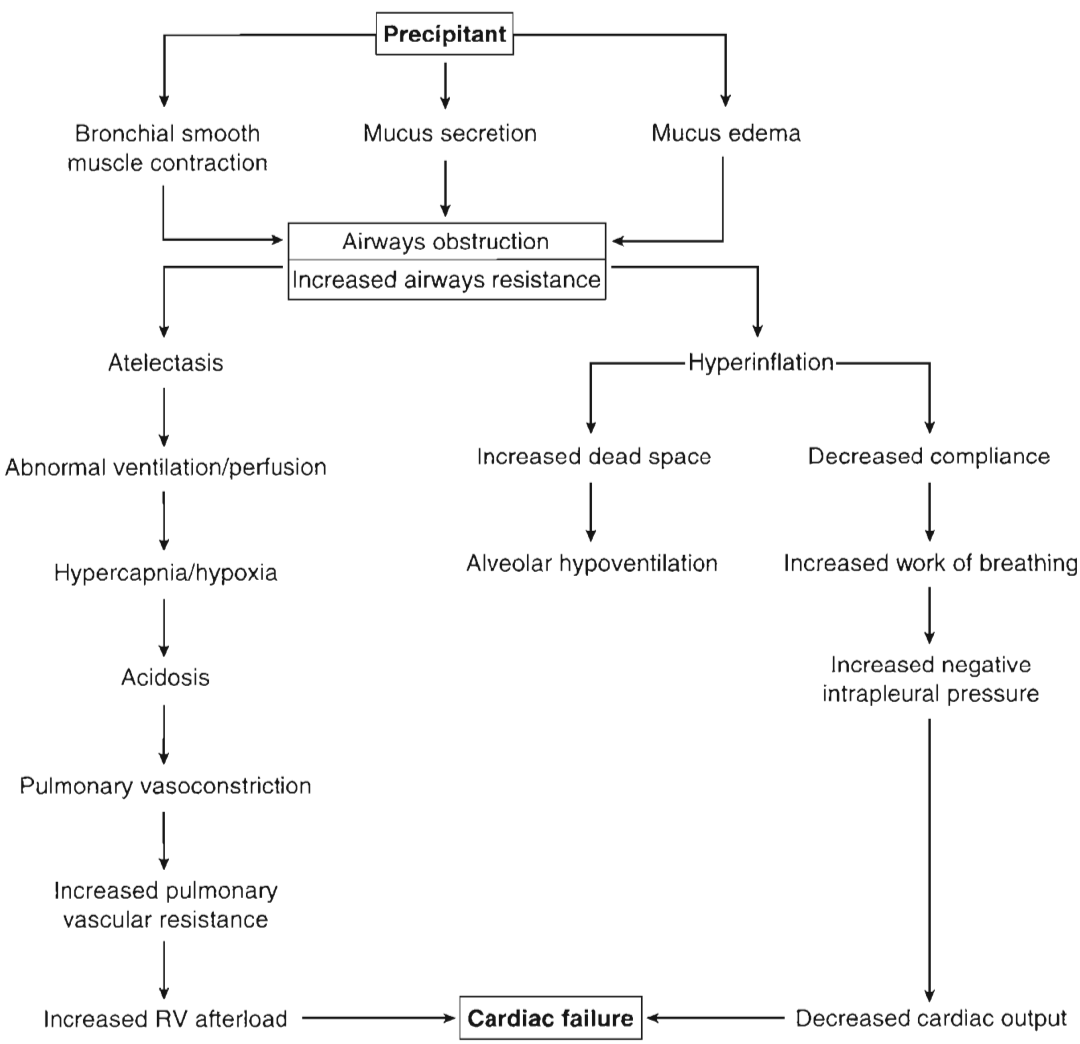

FIGURE 89–1. Pathophysiology in status asthmaticus. (Modified from Helfaer M, Nichols D, Rogers M: Lower airway disease: Bronchiolitis and asthma. In Rogers M [ed]: Textbook of Pediatric Intensive Care, 3rd ed. Baltimore, Williams & Wilkins, 1996, p 141.)

TABLE 89–2. SELECTED PHARMACOTHERAPIES FOR STATUS ASTHMATICUS

Nebulized Therapies
Albuterol (0.5%), 0.15 mg/kg/dose (0.03 mL/kg/dose) inhaled q1-6 h prn. Continuous inhalation 0.5 mg/kg/h
Ipratropium, 0.25-0.5 mg inhaled q4-6h
Racemic epinephrine (2.25%), 0.25-0.5 mL inhaled qh prn
Subcutaneous Therapies
Epinephrine (1:1000), 0.01 mg/kg/dose (0.01 mL/kg/dose) s.c. (max: 0.5 mL/dose)
Intravenous Therapies
Terbutaline, 10 μg/kg i.v. × 1, followed by 0.4-6 μg/kg/min i.v. infusion
Magnesium sulfate 25-50 mg/kg IV over 20 minutes (max 2 g/dose)
Methylprednisolone, 1 mg/kg/dose i.v. q6h

basis, but only a small fraction of the nebulized dose may actually be delivered to the lung, particularly in critically ill infants and children who are intubated with small endotracheal tubes.[4-6] Several studies have demonstrated that small doses of nebulized beta agonist given in rapid sequential fashion produce sustained improvements in forced expiratory volume more often than when larger doses are given less frequently,[7,8] and there is also evidence to suggest that continuous nebulization of the drug may actually lead to more rapid and sustained clinical improvement.[9]

A preparation of the therapeutically active isomer of albuterol (levalbuterol) has been proved effective when administered to children with stable asthma.[10] There are no controlled trials presently available to evaluate its use in children with acute exacerbations of the disease. Inhaled anticholinergic agents such as ipratropium also have a role in the management of severe bronchospasm in children with asthma. Addition of inhaled ipratropium to inhaled beta agonists has been demonstrated to result in significant patient improvement and pulmonary function, especially in children with severe asthma.[11,12] In the patient who does not respond to inhaled bronchodilators, it is possible to administer beta-agonist therapy by the parenteral route. In some countries, the intravenous preparation of albuterol is available, which allows for the parenteral administration of this $beta_2$-selective agent. In the United States where this agent is not available, terbutaline, which has some $beta_2$ selectivity, can be administered intravenously. Although terbutaline has not been associated with clinically significant cardiac toxicity in most pediatric patients,[3,13] it is advisable to monitor the electrocardiogram and serum troponin level during its administration.

The inflammatory basis for asthma has long been recognized, and corticosteroids have had an important role in the management of status asthmaticus. The use of corticosteroids has been demonstrated to significantly improve airways obstruction in patients with severe acute asthma.[14] The parenteral route is the method of choice for administering these agents to the critically ill child, and it is important to realize that fatal anaphylaxis to these drugs has been reported.[15,16] Methylprednisolone is one of the most commonly used agents for acute severe asthma. Because of its half life, steady-state levels can be achieved relatively quickly; and although dosing regimens vary, it is probably most appropriate to dose the drug every 6 hours. There does not seem to be any advantage to administering massive doses of glucocorticoids in status asthmaticus.[17] If methylprednisolone is not available, equipotent doses of another glucocorticoid may be used.

Magnesium has been investigated for use in status asthmaticus because of its potential to augment the effects of bronchodilators by causing relaxation of airway smooth muscle. A recent randomized controlled trial in adults demonstrated that intravenous administration of 2 g of magnesium sulfate improves pulmonary function when administered as an adjunct to nebulized beta agonists and intravenously administered corticosteroids in patients with especially low FEV_1 (<20% of predicted).[18] Although magnesium is occasionally added to standard therapy in pediatric status asthmaticus, the evidence supporting its use in this population is limited.[19]

Enthusiasm for the use of methylxanthines (theophylline, aminophylline) in pediatric asthma has fluctuated over time. These drugs are primarily phosphodiesterase inhibitors, but the mechanism of their effects in asthma is not well understood. A recent randomized controlled trial investigated the effects of aminophylline on 163 children in status asthmaticus to whom the drug was administered as an adjunct to nebulized beta agonists, nebulized anticholinergics, and parenteral corticosteroids.[20] Aminophylline appeared to improve pulmonary function and may have averted intubation in a portion of those patients who received it.[20] Although it may have a role as adjunct therapy in the treatment of severe status asthmaticus, its widespread use is limited by a narrow range of therapeutic serum levels that overlaps with levels that are associated with systemic toxicity.[3]

BRONCHIOLITIS

Bronchiolitis involves invasion of the large and small airway respiratory epithelium by inflammatory cells in the setting of acute respiratory illness. The primary cause of bronchiolitis is respiratory syncytial virus (RSV), which is responsible for 45% to 75% of cases, although parainfluenza viruses, rhinoviruses, adenoviruses, influenza viruses, enteroviruses, and *Mycoplasma pneumoniae* can produce the clinical syndrome as well. RSV dependably produces yearly epidemics, which occur during the winter and spring months. Infection with RSV is nearly universal among infants and children by age 2 years, but only 1% require hospitalization.[21] Among all hospitalized children, the percentage requiring intensive care has been reported as 7% to 9% among patients without comorbidity and as high as 20% to 37% in those with preceding cardiac disease, chronic lung disease, prematurity, age younger than 6 weeks, and immunocompromise.[22] These patients are also at increased risk of mortality from RSV[23] and have been identified as candidates to receive monthly prophylaxis with an RSV antigen-specific monoclonal antibody (palivizumab) each month during RSV season.

The mode of transmission may be either through direct contact with contagious secretions or by exposure to aerosolized particles from the respiratory mucosa.[21] The incubation period varies from 2 to 8 days,[21] symptoms tend to escalate over 3 to 5 days, and convalescence can be prolonged (up to several weeks in the most vulnerable small infants). On histologic examination, reappearance of ciliated respiratory epithelium commonly takes more than 2 weeks.[21] Viral shedding from the respiratory tract typically occurs over 3 to 8 days but may also continue for up to 4 to 6 weeks

in small infants. Symptoms typically begin with signs of upper respiratory illness, including fever, coryza, and, possibly, otitis media. Small infants commonly present with lethargy and central apnea[24] early in the course of illness. Cough and tachypnea soon develop as the illness progresses to the lower airways, usually 1 to 3 days after incubation.[21] Wheezing, produced by flow limitation in peripheral airways, is a nearly universal finding and may be attributable in large part to intermittent obstruction of large and small airways with necrotic epithelial debris, edema, and mucus,[21] rather than to the bronchospasm more commonly seen in asthma. Radiographic findings are often nonspecific but commonly include hyperinflation, peribronchial thickening, subsegmental consolidation, and multiple areas of atelectasis or infiltration, involving most frequently the right middle and right upper lobes. A large prospective study of RSV-infected hospitalized children found that secondary bacterial infection occurred in only 1.2% of the study cohort, establishing that risk of bacterial disease is low in RSV bronchiolitis, despite potentially suggestive radiographic findings and the widespread use of broad-spectrum antimicrobial agents in these patients.[25]

Therapy

Treatment of the infant or child with bronchiolitis is primarily supportive. Many years of clinical experience with empirical use of symptomatic medical therapies have failed to determine a clear role for any of these agents in the management of this disease. Data on the use of medical therapies in critically ill children with bronchiolitis is especially scant. Aerosolized ribavirin, a synthetic guanosine analogue with broad-spectrum antiviral activity, is currently the only specific therapy approved for hospitalized infants with RSV bronchiolitis.[21] In general, it has been shown to improve oxygenation and clinical status scores and to reduce inflammatory mediators associated with ongoing wheezing in patients with RSV.[21] A meta-analysis of three studies on the use of ribavirin in ventilated patients showed a small but significant decrease in ventilator days associated with the use of this agent.[26] Nonetheless, prospects for widespread administration of this agent or even additional large-scale trials to further evaluate its role are limited by the technical challenges, cost, and occupational hazards associated with its use.[27-29]

Widespread use of bronchodilators and corticosteroids for the management of bronchiolitis is common despite the absence of evidence for improved clinical outcomes in critically ill children.[26] There are presently no randomized, controlled trials evaluating the effect of bronchodilators in critically ill children with bronchiolitis.[26] A recent large, randomized controlled trial[30] as well as a systematic review[31] have failed to establish that any bronchodilator produces a significant improvement in relevant outcome measures in less severely ill hospitalized children with bronchiolitis. A few small studies have associated some short-term physiologic benefit with the use of corticosteroids, immune globulin, and surfactant in critically ill infants and children with bronchiolitis, but effectiveness of these therapies in altering outcomes in this population has not been established.[26] Because future prospects for providing lasting immunity to RSV remain doubtful,[21] there is an ongoing need for large, multicenter studies to identify therapies that may benefit critically ill children with this disease.

Meanwhile, supportive care of the patient with bronchiolitis consists of an ongoing assessment of airway patency, the adequacy of respirations, and maintenance of adequate circulating volume. Supplemental oxygen is often required to reverse hypoxemia, and the clinician should be attentive to a change in neurologic status, which often heralds impending respiratory failure.

MECHANICAL VENTILATION

The need for mechanical ventilation in the patient with lower airways disease arises commonly from failure of ventilation and resulting hypercapnia. Hypoxemia and recurrent apnea, which are common in young infants with bronchiolitis, also frequently precipitate the institution of ventilatory support. Assuming adequate airway protection, oxygenation, and respiratory drive, it is probably best to avoid intubation in the patient with lower airways disease unless the overall clinical status of the child warrants the risk of augmenting airway hyperreactivity.[32] To this end, there are several adjunctive therapies that may obviate the need for intubation when added to aggressively applied conventional therapies. An inspired mixture of helium and oxygen (heliox) has been used to alleviate airway obstruction in pediatric patients. Because of its low density and reduced Reynolds number, helium is able to convert turbulent gas flow to laminar flow in airways, and its clinical effect is generally immediate. Because it is an inert gas, it can potentially lower airways resistance without toxicity. When given as 60% to 80% of the total inspired gas mixture, helium can produce more efficient delivery of oxygen as well as nebulized drugs.[33] In general, use of heliox in patients with lower airways disease has produced inconsistent results. A small randomized controlled trial in spontaneously breathing children with status asthmaticus demonstrated that administration of heliox improves respiratory mechanics by lowering the pulsus paradoxus, increasing peak flow, and decreasing the dyspnea index, which may decrease the need for mechanical ventilation.[34] In another small series, a 60:40 heliox mixture administered to 7 intubated patients resulted in a 15% to 50% reduction in peak inspiratory pressure and a 30% to 60% reduction in $PaCO_2$.[35] A recent literature review on the use of heliox in patients of all ages with acute asthma concluded that it may be useful in the short-term management of these patients but that clinical advantage attributable to its use diminishes over time.[36] There is little evidence available on the use of heliox in critically ill patients with bronchiolitis. This issue was prospectively investigated in a nonrandomized study of 38 nonintubated infants with RSV bronchiolitis admitted to an ICU.[37] The investigators were able to demonstrate favorable changes in respiratory status through the first 4 hours of heliox administration and a significant decrease in ICU length of stay among infants who received heliox therapy.[37] In a small randomized, crossover study of RSV-positive, nonintubated patients, clinical indicators of respiratory status improved during heliox administration, particularly among children with more severe disease.[38] However, many of the patients required another form of respiratory support and the study was not designed to evaluate outcomes such as ICU length of stay.[38]

The application of noninvasive forms of mechanical support such as continuous positive airway pressure (CPAP) or bilevel positive pressure using either a nasal or full

facemask has potential advantage in the patient with adequate respiratory drive. Careful titration of applied CPAP (or PEEP) noninvasively may prevent premature airways closure during expiration and decrease gas trapping. The patient who develops high levels of intrinsic PEEP due to hyperinflation manifests an increased work of breathing and, ultimately, respiratory muscle fatigue that may precipitate dramatic and rapid clinical deterioration. Noninvasive respiratory support may allow unloading of the muscles of respiration without adding to airway reactivity and has been used with success in managing asthma as well as bronchiolitis.[39-41]

In the patient with respiratory failure for whom noninvasive mechanical support is not feasible, intubation and mechanical ventilation is warranted. Once tracheal intubation is performed in the patient with airways disease, the clinician should be watchful for complications of the transition to positive-pressure ventilation. In the spontaneously breathing child with severe airways obstruction, profoundly negative intrathoracic pressures develop to generate lung inflation. These conditions produce maximal venous return as right atrial pressure remains subatmospheric.[42] The transition to positive-pressure ventilation in this setting increases juxtacardiac pressures and right ventricular afterload, resulting in decreased venous return, decreased left ventricular end-diastolic volume, and decreased left ventricular compliance,[42] with risk of air leak, hypotension, and cardiac arrest.[3] Initial ventilator settings can be guided by auscultation, careful ventilator waveform analysis, and attention to inspiratory plateau pressure. It is generally preferable to allow the patient to breathe in a spontaneous ventilator mode, using a strategy of permissive hypercapnia. If controlled ventilation is necessary, it is preferable to apply the lowest minute ventilation that provides adequate gas exchange.[43] High-frequency oscillatory ventilation (see later) has been used to rescue a limited number of pediatric patients with asthma and bronchiolitis who demonstrate respiratory failure refractory to management with conventional ventilation.[44] One report recommends the use of high distending pressures to decrease airways resistance, low frequencies, longer expiratory times, and muscle relaxation to minimize gas trapping.[45,46]

Sedation and muscle relaxation to ensure compliance with the ventilator strategy may be necessary if the patient exhibits significant distress and dyssynchrony with the ventilator. Ketamine, a dissociative anesthetic with sympathomimetic and bronchodilatory properties, is often used for sedation in the intubated asthmatic child.[47] The inhalational anesthetic isoflurane may be a useful adjunct to the management of severe status asthmaticus in the intubated child who is difficult to sedate or who is unresponsive to other therapies because of its favorable effects on airways reactivity. The mechanism underlying its bronchodilatory properties is not well understood.[48] Although isoflurane has a better safety profile than halothane when used for this purpose, periodic monitoring of renal function may be advisable in the child who requires prolonged therapy with this agent.[48]

DISEASES OF THE ALVEOLI

PNEUMONIA

Defined as acute respiratory symptoms accompanied by parenchymal infiltrates on a chest radiograph, pneumonia is a common syndrome in children that may be caused by viral or bacterial pathogens.[49] Important viral pathogens responsible for pneumonia in infants and children include RSV, influenza, parainfluenza, and adenovirus. As previously discussed, each of these is agents is also capable of producing the clinical syndrome of "bronchiolitis" in infants and children. The precise infectious etiology may be suggested by the physical examination, the age of the patient, and seasonal incidence patterns. Virologic or bacteriologic confirmation by microbiologic analysis is generally sought to enhance therapeutic decisions as well as cohorting of similarly affected patients. RSV is the most common viral cause of lower respiratory tract infection in infancy,[50] although, as discussed earlier, RSV infection involves primarily the small airways. Influenza is another very important cause of pediatric pneumonia. Infection rates in healthy children are estimated at 10% to 40% each year, and approximately 1% of these children require hospitalization.[50] The course of up to 25% of infected children is complicated by lower respiratory tract disease.[50] Neonates and children up to 5 years of age, especially those with underlying lung disease, congenital heart disease, immunocompromise, and other chronic conditions, seem to be at special risk for influenza pneumonia.[50] Neonates are at risk for especially severe influenza syndromes, which may also include apnea and sepsis.[50] Infants and children older than 6 months of age, especially those in high-risk categories, are candidates for annual vaccination against influenza.[51] Antiviral therapy for A and B strains of influenza are now available and can be considered for patients of appropriate age who are at high risk of complicated or severe disease.[50] When administered within 48 hours of disease onset, amantadine, which is approved for use in children older than age 1 year, may decrease the severity of influenza A disease, but data in young patients are limited.[50] Oseltamivir, a neuraminidase inhibitor active against both A and B strains of influenza, has been demonstrated to decrease symptom duration when administered early in disease and is approved for use in children older than 1 year of age.[52] Unlike RSV, secondary bacterial pneumonia is common in influenza infection and is typically caused by *Streptococcus pneumoniae* or *Staphylococcus aureus,* making it especially important to consider appropriate empirical antimicrobial therapy in certain cases.[53,54] Parainfluenza viruses are also responsible for causing pneumonia in children, and seasonal epidemics commonly occur in autumn.[50] Primary infection tends to occur in young children 2 to 6 years of age, and recurrent infection is generally less severe, except perhaps in the immunocompromised.[50] Finally, adenoviruses have been reported to cause up to 20% of pneumonias in children younger than age 5 years and the mortality rate attributable to the disease in this population has been reported as high as 20%.[55] In neonates, adenovirus can produce an especially severe syndrome of disseminated disease and sepsis, which can present in the first 10 days of life.[55] The incubation period is generally 2 to 14 days,[50] and the virus can produce a profound and destructive lower respiratory process. Necrotizing bronchitis, purulent exudative alveolitis, and hyaline membrane formation have been identified on autopsy specimens of affected patients.[55] Survivors of severe adenoviral infections commonly demonstrate chronic sequelae, such as recurrent wheezing and bronchiolitis obliterans.[55]

Most commonly, bacterial presence is established in the lower respiratory tract as a result of oropharyngeal overgrowth

of environmentally acquired pathogens and subsequent introduction of these secretions into the lower airways. Children with aspiration syndromes, immunodeficiencies, and malformations of the respiratory tract are at increased risk of bacterial lower respiratory infection.[56] Bacterial pathogens remain an important cause of potentially lethal pediatric pneumonias in the developing world, and they are the most important cause of severe and complex pneumonia in Europe and North America.[49] It is challenging to establish a causal role for specific bacteria when these agents are normally found in the upper airway secretions, which are most commonly obtained for diagnosis in children. The best data regarding etiology comes from lung puncture studies, which reveal that *Streptococcus pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus* are among the important causes of bacterial pneumonia in children.[49] In neonates and young infants up to about 3 months of age, group B *Streptococcus* (GBS), *Listeria monocytogenes,* and gram-negative enteric organisms are the major causes of pneumonia and sepsis.[50,56] Widespread maternal intrapartum antibiotic prophylaxis has influenced the incidence of perinatal GBS infection as well as its antimicrobial resistance patterns.[57] Incidence of GBS sepsis has declined among very low birth weight infants in the era of ampicillin prophylaxis, whereas the incidence of *Escherichia coli* sepsis (largely resistant to ampicillin) has increased in the same time period.[57] Perinatally acquired *Chlamydia trachomatis* is another important cause of lower respiratory tract infection in infants up to age 12 weeks.[56] Although uncommon, periodic epidemics of infection with *Bordetella pertussis* occur among incompletely immunized infants and children.[56] Apnea and intermittent cyanosis, which frequently accompany acute *B. pertussis* infection in young children, may warrant intensive care.

Since the introduction of a conjugate vaccine against *H. influenzae* type B (Hib) in 1988, the incidence of invasive disease in infants and young children attributable to this organism has declined by 99%.[50] Other serotypes of the organism, including nonencapsulated strains, may also cause pneumonia.[50] In recent years, the heptavalent pneumococcal conjugate vaccine has also become available, which has made it possible to provide immunity to relevant strains of *S. pneumoniae* in infants and young children, a subset of the pediatric population most susceptible to infection with this organism. Children with congenital or acquired immunodeficiency syndromes, absent or deficient splenic function, as well as African Americans and some Native American populations may be especially susceptible to infection with encapsulated organisms and stand to benefit considerably from aggressive immunization efforts.[50]

Therapy

In the clinical arena one is often faced with having to select empirical antimicrobial therapy before definitive viral or bacterial diagnosis. The presence of a focal alveolar process on chest radiographs, especially if accompanied by significant parapneumonic effusion, evidence of parenchymal necrosis and/or abnormal peripheral blood cell counts, and C-reactive protein, adds considerably to the predictive value for the presence of bacterial disease.[49] Before demonstrating evidence of localized infection, neonates and young infants may demonstrate nonspecific but potentially ominous signs of lethargy, hypothermia, and apnea. Infants younger than 3 months of age should be treated with both ampicillin and gentamicin, and consideration should be given to adding a third-generation cephalosporin in severe cases.[49] Investigation and empirical coverage for infection with *B. pertussis* should also be considered in infants with severe respiratory disease that features profound peripheral lymphocytosis, paroxysmal cough, and/or apnea.

For the critically ill child with community-acquired bacterial pneumonia, reasonable coverage may be obtained with a third-generation cephalosporin.[49,56] A macrolide agent can be added in cases in which infection with atypical agents such as *M. pneumoniae* and *Chlamydia pneumoniae* is possible, particularly in patients with sickle cell disease.[49,58] Although emerging resistance to penicillins in *S. pneumoniae* is well known, high doses of cephalosporins are still appropriate in the majority of nonsusceptible strains if meningitis is not also suspected, but the addition of vancomycin may be warranted in some cases.[49,59] If infection with *S. aureus* is possible, an antistaphylococcal penicillin such as oxacillin should be added, unless local resistance patterns warrant the use of vancomycin.[49] In patients at risk for aspiration pneumonia and in immunocompromised children, special consideration should be given to administration of two antibiotics effective against gram-negative organisms (e.g., *Pseudomonas*) and to optimizing coverage for anaerobic organisms.

Management of pleural effusion is another important consideration in the care of the patient with bacterial pneumonia. Although drainage of parapneumonic effusions is indicated under certain circumstances, satisfactory recovery may occur in many cases without intervention.[60] Recently, an evidence-based clinical practice guideline was developed for the medical and surgical treatment of parapneumonic effusions in adults.[61] The panel issued management suggestions according to the underlying risk of poor clinical outcome based on effusion size and loculation, as well as on microbiologic and chemical analysis of the pleural fluid.[61] Pleural fluid drainage was recommended for large effusions occupying more than 50% of the hemithorax, whether or not loculation or pleural thickening is present. Drainage was also recommended for purulent effusions, those with positive culture or Gram stain, or those with pH less than 7.20 as measured by a blood gas analyzer.[61] In situations in which drainage is indicated, more complex or invasive options such as thoracoscopic or "open" procedures are likely to be necessary for sufficient control of the effusion.[61] Although much has been published on the management of parapneumonic effusion, there are few randomized, controlled trials in adult patients. It must be emphasized that the consensus panel's recommendations are based primarily on case series, historical controls, and expert opinion.[61]

The literature on parapneumonic effusion in children also does not presently provide robust evidence on which to base clinical intervention. The data do suggest that *S. pneumoniae* is a very important cause of pediatric pneumonia that is complicated by necrosis and/or effusion. In a recent review of 368 hospitalized children with pneumococcal pneumonia, there was an increased incidence of complications associated with the disease over the 6.5-year course of the study, and pneumococcal serotypes associated with these events tended to be ones not covered by the conjugate vaccine.[62] The effect of image-guided needle aspiration versus percutaneous pigtail catheter drainage was also examined in a 5-year retrospective study of pediatric parapneumonic effusions.[63] When comparing outcomes in

the two groups, the authors found no difference in length of stay but did report a significant decrease in the need for second intervention in patients who received a chest drain.[63] Other independent predictors for second intervention in their study population included loculation of pleural fluid and pH less than 7.2. A combination of low glucose and low pH in the pleural fluid specimen was especially predictive of the need for re-intervention.[63]

The decision to perform thoracostomy drainage in pediatric patients with parapneumonic effusion may depend on the clinical context in which it occurs. In a small series of children with necrotizing pneumonia or lung abscess, bronchopleural fistula was associated with placement of chest drains in five of nine patients with necrotizing pneumonia,[64] whereas clinical experience with this disease in children suggests that complete resolution often takes place without the need for invasive procedures.[64,65] Other potentially promising therapies in children with parapneumonic effusions include video-assisted thoracic surgery (VATS)[66] and intrapleural thrombolysis.[67]

In summary, it is certainly important to drain large parapneumonic effusions when they are suspected of causing hemodynamic instability in the critically ill child. Pleural drainage may also be useful to relieve respiratory embarrassment that may contribute to respiratory failure or ongoing ventilator dependence. The best opportunity to achieve sufficient drainage is probably in the first 48 to 72 hours of disease, before organization of the effusion begins to take place. A randomized, controlled trial is necessary to resolve the issue of which pediatric patients with parapneumonic effusion would benefit from aggressive pleural drainage.

ACUTE RESPIRATORY DISTRESS SYNDROME

What was once known as the adult respiratory distress syndrome is now called the acute respiratory distress syndrome (ARDS) in an effort to acknowledge its prevalence in the pediatric population. A syndrome of lung injury featuring exudative pulmonary edema that leads to hypoxic respiratory failure had been described in adults for many years, but consensus criteria for the diagnosis of the syndrome did not enter the scientific literature until 1994. Acute lung injury, which often precedes ARDS, may arise as a consequence of primary pulmonary disease or as a feature of systemic pathophysiology that is nonpulmonary in origin. The incidence of the syndrome in children is believed to be similar to that in adults, and pediatric ARDS most commonly occurs in the setting of sepsis.[68] Among patients with the sepsis syndrome who go on to develop ARDS, the most frequent primary sources of infection are the bloodstream and the abdomen.[68] Pneumonia arising from infectious causes and noninfectious causes (e.g., aspiration events and thermal injury) as well as head trauma, chest trauma, and post-resuscitation syndromes are other important causes of ARDS in children.[68-71] On the basis of a series of small studies, mortality rate in pediatric ARDS averages 52% and has been reported to range from 28.5% to 90%.[68,71] Although consensus diagnostic criteria have been derived for adults,[72] accurate mortality prediction in the pediatric population remains problematic. At present, there are several multicenter efforts designed to investigate therapeutic interventions in pediatric ARDS, including prone positioning and surfactant administration. At this time, these trials have not been completed and preliminary results have not been published.

MECHANICAL VENTILATION

Mechanical ventilatory support of the patient with acute lung injury and ARDS is often necessary to provide adequate oxygenation. In relatively stable patients, noninvasive ventilation may be effective when instituted early in the disease process. This method has been used with success in the management of alveolar disease in immunocompromised adult patients and reduced rates of intubation and mortality.[73] Data on the use of noninvasive positive-pressure ventilation in pediatric patients are limited, but several case series report success with the application of this technique in children with alveolar disease.[74-76] In a recent investigation, noninvasive bilevel positive airway pressure was used to support pediatric patients with pneumonia, acute chest syndrome and sickle-cell disease, underlying chronic hypoventilation syndromes, and postoperative hypoventilation with atelectasis.[76] The authors report favorable changes in respiratory rate, heart rate, and oxygenation among all patients receiving noninvasive support, and 91% of respiratory failure episodes in their study were reversed without the need for intubation.[76]

When noninvasive techniques are not appropriate or have failed, endotracheal intubation is warranted. It has been well established in a number of animal and human studies that ventilatory strategy may have a profound influence on the course of disease and ultimately on clinical outcome.[77-81] In pediatric ARDS, in which duration of mechanical ventilation may commonly exceed 3 weeks,[68] it is especially important to maximize lung protective ventilatory strategies. Lung protective ventilation involves (1) preservation of end-expiratory lung volume by judicious use of PEEP and/or recruitment maneuvers to minimize atelectrauma; (2) minimization of cyclic stretch; and (3) avoidance of parenchymal overdistention at end inspiration by limiting tidal volume and transpulmonary pressure.[77-81]

When oxygenation failure is refractory to conventional ventilation, high-frequency oscillatory ventilation (HFOV) is a modality that is well established in the pediatric population. During HFOV, lung recruitment is maintained by application of a relatively high mean airway pressure with superimposed pressure oscillations at a frequency of 3 to 15 Hz.[80] Because maximal recruitment is maintained throughout the respiratory cycle and ventilation is achieved using very small phasic changes in pressure and volume, this technique allows the lung to be ventilated above the critical opening pressure of injured lung units while avoiding end-inspiratory overdistention of more compliant lung units (Fig. 89-2).[44,82,83] Such an "open lung" strategy of mechanical ventilation can capitalize on pulmonary hysteresis to achieve satisfactory gas exchange at lower alveolar pressures (Fig. 89-3). In 1994, a prospective multicenter, randomized clinical study compared HFOV and conventional mechanical ventilation in pediatric patients with diffuse alveolar disease or air leak syndromes.[84] Patients in the HFOV arm showed rapid and sustained improvements in oxygenation without suffering adverse effects on ventilation.[84] Ultimately these patients showed a decrease in barotrauma as evidenced by a decreased need for supplemental oxygen at 30 days and demonstrated improved outcomes compared with their cohorts in the conventional arm, particularly when HFOV was instituted within 72 hours of intubation.[84] The "oxygenation index" (OI), defined as $(MAP \times FiO_2 \times 100)/PaO_2$, used often in the pediatric literature to quantify oxygenation

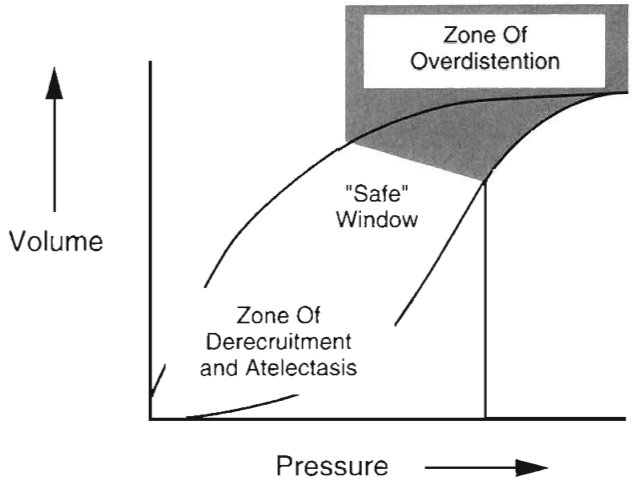

FIGURE 89–2. Pressure-volume relationships in acute lung injury. High end-expiratory pressures and small tidal volumes minimize the potential for derecruitment *(lower left)* and overdistention *(upper right)*. (From Froese AB: High-frequency oscillatory ventilation for adult respiratory distress syndrome: Let's get it right this time! Crit Care Med 1997;25:906-908.)

failure, was shown to discriminate between survivors and nonsurvivors in the first 72 hours of therapy.[84] Furthermore, the time at which changes in the OI were found to occur seemed to influence the likelihood of survival: an OI = 42 at 24 hours predicted mortality with an odds ratio of 20.8, a sensitivity of 62%, and a specificity of 93%.[84] The OI may prove to be a time-sensitive predictor of survival in patients with hypoxic respiratory failure. Such an indicator would facilitate development of a stepwise approach to the mechanical support of these patients.[85]

Inhaled nitric oxide (iNO) has been credited with significantly decreasing the need for extracorporeal membrane oxygenation (ECMO) in neonates with hypoxic respiratory failure, especially when used in combination with HFOV in patients who have failed either therapy alone.[86,87] The idea that improved pulmonary recruitment offered by HFOV might enhance the effect of iNO seems to be applicable to older children as well.[88] However, as has been well established in a number of adult studies,[89-91] iNO produces short-term physiologic improvements in oxygenation without sustained clinical benefit or improvement in outcome in pediatric patients.[88,92,93] Risk of rebound pulmonary hypertension and profound deterioration of oxygenating efficiency after abrupt discontinuation of iNO warrants careful weaning of the dose when the drug is used in managing the neonate with pulmonary hypertension.[94]

DISEASES OF THE INTERSTITIUM

The interstitial lung diseases (ILD) in children are a diverse group of rare conditions that involve alteration of the alveolar wall, infiltration and fibrosis of the pulmonary interstitium, and loss of functional alveolar-capillary units.[95] The major clinical findings include abnormal gas exchange and both restrictive and obstructive pulmonary physiology. There are numerous potential causes, ranging from primary congenital abnormalities of the alveolar-capillary unit that present in early infancy to acquired syndromes of chronic interstitial disease referable to infection, recurrent aspiration, or symptomatic cardiovascular disease (Table 89-3).[95] In children, as in adults, the morbidity and mortality of these diseases are high[96,97] but the frequency distribution of specific causes may be very different in the two populations. For example, a recent descriptive, prospective evaluation of 51 pediatric patients with ILD reported no cases of idiopathic pulmonary fibrosis or desquamative interstitial pneumonitis (DIP), and only one case of lymphocytic interstitial pneumonitis (LIP).[96] The rarity of these conditions among pediatric patients has been previously described.[97] Usual interstitial pneumonitis (UIP) is believed to be particularly rare in children.[98] In contrast, infectious causes may be much more common in the pediatric population, accounting for perhaps 20% of pediatric ILD in some series.[95,96] Given the wide variety of potential causes in ILD, a systematic approach to the diagnostic workup has been suggested.[96] Although history and physical examination may not be helpful in the majority of instances, noninvasive tests such as serologic studies, cultures, chest radiographs, chest computed tomography, barium swallow, pH studies, and echocardiograms will more often allow the clinician to arrive at a specific diagnosis.[96] In those children in whom an etiology still cannot be determined, invasive testing such as bronchoalveolar lavage, cardiac catheterization, and lung biopsy should be considered.[96] Results of biopsy specimens may be particularly important to guide decision making in critically ill children who are not responding to therapy.

Therapy

Because many of the causes for pediatric ILD may begin with an inflammatory response to lung injury, treatment of children with this condition commonly involves the use of anti-inflammatory agents such as corticosteroids. A favorable response to corticosteroids among children with ILD may be evident in only 40% of cases,[99] and this variability may reflect the diverse potential causes of the disease. Because of its anti-inflammatory properties, hydroxychloroquine has also been used in the management of pediatric ILD but it is associated with the development of hepatic toxicity and retinopathy in children who receive it.[99] Ultimately, identifying and controlling underlying causes and contributing issues are very important, when this is possible.

COMPLEX PARENCHYMAL DISEASES

BRONCHOPULMONARY DYSPLASIA

Bronchopulmonary dysplasia is a term that describes histopathologic changes in the lungs of infants who require mechanical ventilation in the neonatal period and who demonstrate radiologic abnormalities and supplemental oxygen dependence at 28 days of life.[100] These changes include heterogeneous alveolar consolidation, squamous metaplasia of airway epithelium, hyperplasia of mucous glands, peribronchial fibrosis, airway smooth muscle hypertrophy, and vascular lesions of pulmonary hypertension.[101,102] Clinically, the syndrome is associated with airway hyperreactivity and intermittent obstruction, leading to increased work of breathing, recurrent wheezing, chronic abnormalities of gas exchange, and pulmonary hypertension in some cases.[102] Focal airway collapse consistent with tracheomalacia and/or bronchomalacia (see Table 89-1) has also been documented in these infants,[103] and their pathogenesis in this context is not known. BPD is most likely to develop in premature infants with birth weight less than 1000 g.[101,102] These infants

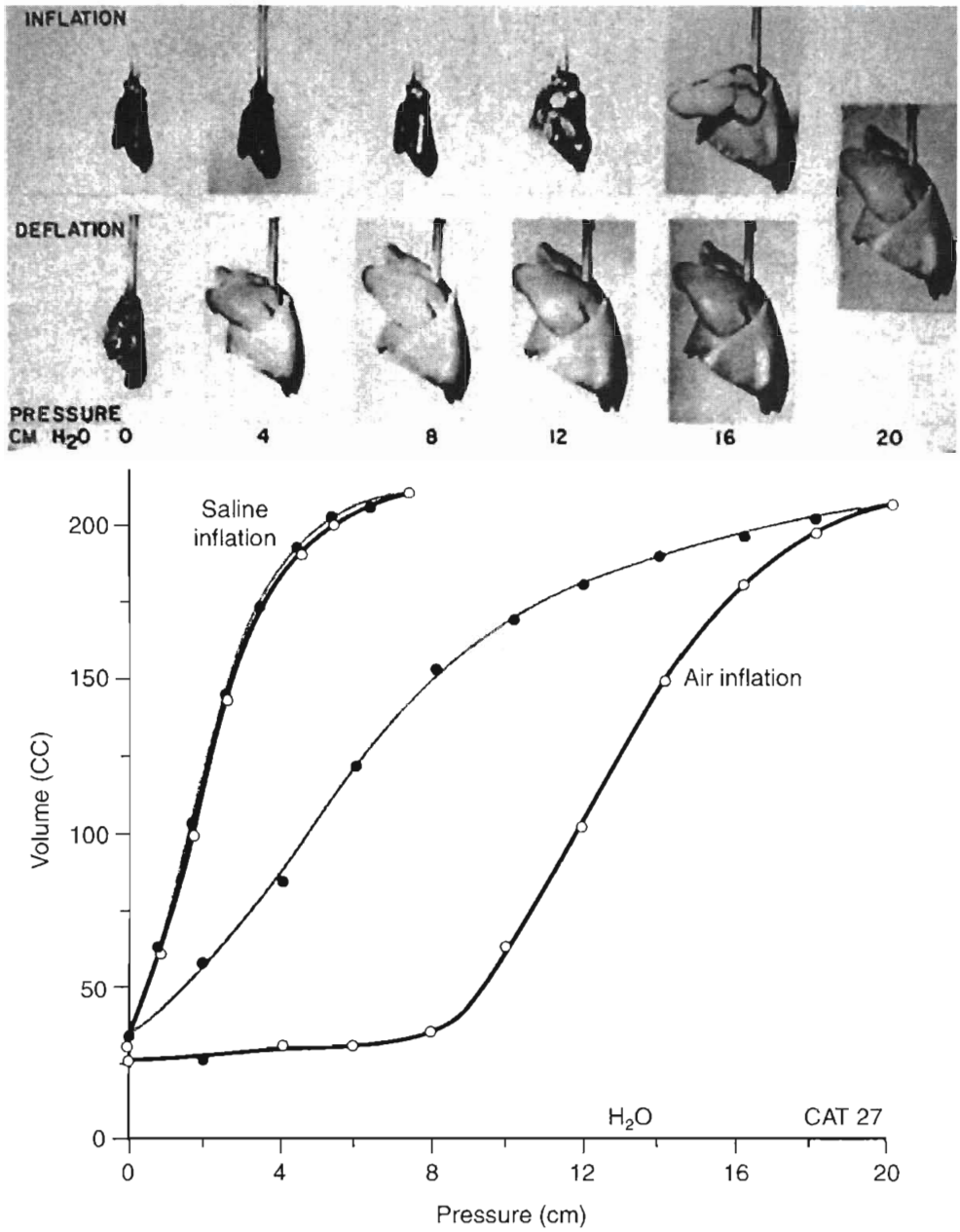

FIGURE 89–3. Static hysteresis. Pulmonary volume-pressure curve obtained by air inflation of excised cat lungs. As pressure is increased above 8 cm H_2O, volume recruitment occurs up to approximately 20 cm H_2O. During deflation (expiration), higher lung volumes are maintained at lower corresponding pressures. (Modified from Radford E: Static mechanical properties of mammalian lungs. In Fenn W, Rahn H [eds]: Handbook of Physiology: A Critical, Comprehensive Presentation of Physiological Knowledge and Concepts. Washington, DC, American Physiological Society, 1964, vol I, pp 434-435.)

may be born at a gestational age (24 to 26 weeks) at which alveolar development is not yet complete, so lung injury acquired at this time can result in structural derangement of the alveoli as well as enduring alveolar hypoplasia.[101]

The spectrum of pathology is believed to derive from an inflammatory response to lung injury, because numerous investigations have identified mediators of inflammation in the BAL fluid of infants with chronic lung disease.[104] The present understanding of the pathogenesis of lung injury in the neonate mirrors what has been learned from laboratory and clinical investigations of this process in adults. Neonates and young infants with respiratory failure, however, may be especially susceptible to ventilator-associated lung injury because surfactant deficiency, high chest wall compliance, and a dynamic functional residual capacity that is near closing capacity in this age group may potentiate a cycle of de-recruitment and re-inflation, which has been shown to promote lung injury in animal models and humans (including surfactant-deficient preterm animals).[77-79,105,106] Mechanical ventilatory techniques targeted to promote alveolar recruitment and maintain lung volume have in fact decreased the incidence of ventilator-associated lung injury in neonates. Numerous large prospective, randomized, controlled trials have found favorable outcomes among high-risk infants supported with HFOV compared with cohorts who are supported with conventional phasic ventilation, with no apparent increase in the development of intracranial hemorrhage or other significant morbidities.[107-109]

Pulmonary edema from cardiogenic and noncardiogenic causes, infectious issues, and exposure to high concentrations of supplemental oxygen are other factors important in the pathogenesis of BPD. Premature infants may be at special risk from exposure to high concentrations of supplemental oxygen because they are deficient in antiproteases and antioxidant enzymes, which are necessary to limit lung injury from reactive oxygen species.[100] Improvements in neonatal supportive care, including the availability of surfactant therapy, have dramatically improved survival rates among premature infants, but chronic lung disease among survivors of prematurity remains an important clinical issue.[100]

TABLE 89–3. CAUSES OF INTERSTITIAL LUNG DISEASE IN PEDIATRICS

Known Etiology
Infection
Viral
Bacterial
Fungal
Parasitic
Opportunistic
Bronchopulmonary dysplasia
Environmental/drug exposure
Lipid storage diseases
Aspiration syndromes
Gastroesophageal reflux
Swallowing disorders
Unknown Etiology
Usual interstitial pneumonitis
Desquamative interstitial pneumonitis
Lymphocytic interstitial pneumonitis
Pulmonary hemosiderosis
Pulmonary infiltrates with eosinophilia
Pulmonary vascular disorders
Alveolar capillary dysplasia
Hemangiomatosis
Veno-occlusive disease
Telangiectasia
Lymphangiomatosis
Lymphangiectasis
Bronchiolitis obliterans
Bronchiolitis obliterans with organizing pneumonia
Surfactant protein deficiency
Cellular interstitial pneumonitis
Etiologies Associated with Systemic Disease
Connective tissue disorders
Histiocytosis X
Metastatic malignancy
Neurocutaneous syndromes
Sarcoidosis

Adapted from Howenstine MS, Eigen H: Current concepts on interstitial lung disease in children. Curr Opin Pediatr 1999;11:200-204 and Fan LL, Langston C: Chronic interstitial lung disease in children. Pediatr Pulmonol 1993;16:184-196.

TABLE 89–4. PHARMACOTHERAPIES COMMONLY USED IN MANAGEMENT OF INFANTS WITH BRONCHOPULMONARY DYSPLASIA

Inhaled Therapies
Albuterol (0.5%), 0.15 mg/kg/dose inhaled q1-6h prn. Continuous nebulization 0.5 mg/kg/h
Ipratropium, 0.25-0.5 mg/dose inhaled q4-6h
Fluticasone, 44-88 µg bid (maintenance therapy) (max: 440 µg/day)
Diuretic Therapies
Furosemide, 1-2 mg/kg/dose i.v./p.o q6h
Chlorothiazide, 10-20 mg/kg/day i.v. divided q12h (max 1000 mg/day)
< 6 months: 20-40 mg/kg/day p.o. divided q12h
≥ 6 months: 20 mg/kg/day p.o. divided q12h
Spironolactone, 1.5 mg/kg/dose p.o. q12h
Gastrointestinal Therapies
Metoclopramide, 0.1-0.2 mg/kg/dose i.v./p.o. q6h (max: 10 mg/dose)
Ranitidine, 1 mg/kg/dose i.v. q8h; 2-3 mg/kg/dose p.o. q12h

Therapy

Lower respiratory tract infection is one of the most common reasons for hospital readmission in the first year of life for infants with BPD and accounts for a significant fraction of these pulmonary exacerbations.[101] Other potential causes include aspiration syndromes, worsening pulmonary hypertension, and the evolution of clinically important systemic-to-pulmonary collateral vessels.[102] Therefore, the diagnostic approach to the infant with BPD who demonstrates unexplained deterioration may include dynamic airway studies as well as echocardiography and, in certain cases, cardiac catheterization.[102] Treatment of these episodes is supportive and often includes empirical antibiotic coverage for potential infectious causes. Among the medications that may be useful in producing short-term improvements in pulmonary mechanics are bronchodilators, corticosteroids, and diuretics (Table 89-4).[100,102,110] Aerosolized beta agonists may be useful in the management of smooth muscle–mediated bronchospasm in the infant with chronic lung disease, but the consequent decrease in airway smooth muscle tone may aggravate airway collapse in the infant with tracheomalacia or bronchomalacia.[103] Diuretics may be especially helpful in the management of these infants because many demonstrate a tendency to accumulate fluid in the pulmonary interstitium on the basis of alterations in pulmonary vascular resistance, plasma oncotic pressure, and capillary permeability, as well as impaired lymphatic drainage.[104] Judicious use of diuretics can also facilitate the delivery of adequate nutrition to the infant with chronic lung disease.[104] iNO has also been studied for its potential role in treating refractory hypoxemia in infants with chronic lung disease. Case series have documented improvements in oxygenation with the use of iNO, including in infants with intercurrent infection, with a sustained response reported in some cases.[111,112]

CONGENITAL DIAPHRAGMATIC HERNIA

Management of the infant with CDH is one of the greatest clinical challenges that the intensive care clinician encounters. The Bochdalek hernia is the most severe form and occurs when herniation of abdominal contents occurs into the thoracic cavity through a posterolateral diaphragmatic defect, usually at around the 10th week of gestation. This phase of gestation concurrently includes the branching of bronchi and pulmonary arteries, and this crucial process may be interrupted by the growing mass of herniated viscera.[113] On the other hand, the discovery that administering the teratogen nitrogen to rats in mid-gestation results in diaphragmatic defects in the developing fetus as well as a spectrum of anomalies in other organ systems similar to that seen in humans with CDH suggests that the pathogenesis of this syndrome may originate from fetal exposure to an agent that causes generalized maldevelopment from that point forward.[114-117] The complex pathology associated with CDH in humans includes a hypoplastic and abnormally muscularized pulmonary arterial tree.[113] Other congenital anomalies are associated with CDH in up to 39% of cases. Congenital cardiac disease is the most commonly associated feature and most frequently involves some degree of cardiac hypoplasia, although a wide variety of structural cardiac anomalies may be associated with CDH.[118] Genitourinary, gastrointestinal, neurologic, and skeletal defects are also commonly described.[113] Adjunctive medical therapies have not managed to improve the dismal survival statistics of these infants, whose mortality rate is traditionally reported in the range of 50%. Nonetheless, there are experienced centers that have

TABLE 89–5. THERAPEUTIC HISTORY AND OUTCOMES FOR CONGENITAL DIAPHRAGMATIC HERNIA, CHIILDREN'S HOSPITAL, BOSTON

	1981-1984	1984-1987	1987-1991	1991-1994	*P* Value
ECMO	N/A	Postop	Preop	Preop	
Surgery	Immediate	Immediate	Delayed	Delayed	
Ventilation	Hyper	Hyper	Hyper	Permissive hypercapnia	
Paralysis	Yes	Yes	Yes	No	
Analgesia	High-dose fentanyl	High-dose fentanyl	High-dose fentanyl	Epidural	
Monitoring	Postductal	Postductal	Postductal	Preductal	
Survival, Isolated CDH					
ECMO	N/A	50%	48%	71%	NS
CMV	73%	67%	80%	100%	0.02
Overall	73%	61%	57%	84%	0.02

CMV, conventional mechanical ventilation.
From Wilson JM, Lund DP, Lillehei CW, Vacanti JP: Congenital diaphragmatic hernia—a tale of two cities: The Boston experience. J Pediatr Surg 1997;32:401-405.

reported encouraging results in recent years by adopting strategic forms of mechanical support in these patients that incorporate much of what has been learned about minimizing pulmonary and hemodynamic consequences of mechanical ventilation.

Therapy

In infants with CDH, as in those with BPD, intensive care management targets lower airways disease, alveolar disease, and pulmonary vascular dysfunction. Initial medical stabilization of the infant with CDH includes endotracheal intubation and nasogastric decompression. It is preferable to obtain preductal (i.e., right radial) arterial access, when possible. Information from preductal blood gases should guide clinical intervention because it reflects the oxygenation, ventilation, and acid-base status of the cerebral circulation. Initially, echocardiography is suggested to rule out structural cardiac disease, and it may be repeated as necessary throughout the clinical course to determine evidence of ongoing right-to-left shunting as well as estimates of right ventricular pressure and function in response to therapy.[113] iNO has been used in infants with CDH with varying results, and a role for the drug in reducing the need for ECMO or in improving survival among these patients was not established by a large, randomized controlled trial on the use of iNO in neonates with pulmonary hypertension.[119] In general, data supporting the use of iNO in the management of infants with CDH is limited to small case series and individual case studies.[120-122] In CDH, as in BPD, deficient alveolar development may explain the limited potential benefit from iNO.[112] Finally, recommendations for the optimal timing of surgical repair in these infants have evolved over time. It was once considered appropriate to refer infants with CDH for immediate repair. Growing experience with the mechanical support of these patients, along with the observation that pulmonary vascular resistance and reactivity as well as pulmonary compliance could become more favorable for successful repair within days after birth, have since favored delaying surgical repair until a satisfactory level of stability can be achieved.[113,123]

MECHANICAL VENTILATION

Given what is presently known about ventilator-associated lung injury, it is logical to apply lung protective ventilation strategies to infants with chronic lung disease as well as to infants with CDH. Although the technique has not been traditionally applied to neonates, permissive hypercapnia is, in fact, well tolerated by most infants.[124-126] Because of the heterogeneity of airspace involvement in these diseases, regional hyperinflation can easily occur. Therefore, it makes sense to maintain end-expiratory lung volume with a careful titration of PEEP and limit tidal volume to 4 to 6 mL/kg to ventilate at the area of maximal compliance on the pressure-volume curve.[127] While managing these patients, monitoring of tidal volume at the endotracheal tube is important because compressible volume losses in the ventilator circuit can be significant. Judicious use of sedation and the use of spontaneous ventilation (e.g., flow-triggered pressure support) may improve matching of ventilation to perfusion and may allow optimal patient-ventilator synchrony.

A review of all infants with CDH managed at Children's Hospital in Boston revealed a significant increase in survival from 44% to 69% during the period in which permissive hypercapnia was used to manage these infants, with even higher survival rates noted in infants without coexisting heart disease (Table 89-5).[128] Of note, neither the introduction of ECMO nor delaying surgical repair was associated with significant increases in survival in this single-center historical experience.[128] Other case series have also reported favorable results using "kinder, gentler" ventilatory strategies, rather than more aggressive techniques that attempt to control pulmonary vascular resistance.[123,129,130] These observations suggest that ventilator-associated lung injury may greatly contribute to excess mortality in infants with CDH,[123,128] and it is possible that a survival benefit attributable to ECMO may emerge as lung-sparing mechanical ventilation is more widely applied.[128] At least one single-center experience suggests that epidural analgesia in the postoperative period maximizes spontaneous ventilation and may further improve pulmonary outcomes in these infants.[128] In some infants with CDH who develop refractory hypoxemia and hypercarbia, one center has reported successful use of high-frequency oscillatory ventilation.[123]

WEANING THE PEDIATRIC PATIENT FROM MECHANICAL VENTILATION

Although it is clear that it is best to discontinue mechanical ventilatory support as soon as this is feasible, a great deal of controversy surrounds ventilator mode selection, the pace of weaning, and timing of separation from mechanical support in children. In the largest pediatric study presently available in the literature, the use of specific weaning modes and

ventilator weaning protocols was evaluated against standard care (no defined protocol) for mechanically ventilated infants and children.[131] Patients with alveolar disease as well as lower airways disease were included, whereas those older than 2 years of age with status asthmaticus and those with CDH were excluded. In this study, 182 intubated, spontaneously breathing children who met standardized bedside criteria for extubation readiness were randomized to application of pressure support ventilation (PSV), volume support ventilation (VSV), or no protocol.[131] There were no significant differences among the three treatment groups in extubation failure rates, and most children were weaned from the ventilator in 2 days or less.[131] In children who were successfully extubated, the median duration of ventilator weaning did not significantly differ according to mode of ventilation.[131]

Separating the infant or child with complex and/or chronic pulmonary disease from mechanical ventilation is challenging and requires an appreciation of the components of pulmonary dysfunction and timely recognition of acceptable mechanics and gas exchange in the spontaneously breathing patient. For example, the patient with a syndrome of alveolar hypoplasia is expected to be tachypneic at baseline, and this feature precludes the use of commonly applied criteria for extubation readiness. In these cases, weaning from mechanical ventilation can be guided by an ongoing assessment of tidal volume (measured at the endotracheal tube), work of breathing, serum pH, and evidence of appropriate daily weight gain as pressure support is decreased.

CONCLUSION

A fundamental understanding of age-specific diagnostic and treatment considerations is required when caring for the pediatric patient with pulmonary disease. Although the capacity for physiologic compensation in infants and children is remarkably efficient, these individuals are also prone to sudden and profound clinical deterioration, warranting the application of sophisticated supportive measures in the ICU. In recent years, work in the laboratory as well as the clinical arena has brought about an appreciation that in airways disease, alveolar disease, and complex conditions such as BPD and CDH, gentler strategies of mechanical ventilation may have a central role in improving functional outcomes. Thoughtful application of therapies proven to reverse pulmonary pathophysiology while promoting spontaneous ventilation as much as possible is likely to enhance already favorable survival statistics for even the most critically ill pediatric patients.

ANNOTATED REFERENCES

Arnold JH, Hanson JH, Toro-Figuero LO, et al: Prospective, randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. Crit Care Med 1994;22:1530-1539.

This prospective, multicenter, crossover trial showed that high-frequency oscillatory ventilation produced rapid and sustained improvements in oxygenation and decreased need for supplemental oxygen at 30 days when used to support pediatric patients with diffuse alveolar disease or air leak.

Courtney SE, Durand DJ, Asselin JM, et al: High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. N Engl J Med 2002;347:643-652.

Large multicenter, well-controlled trial demonstrating significant benefit of high-frequency oscillatory ventilation compared to conventional ventilation in very low birth weight infants. Infants who received high-frequency oscillatory ventilation were successfully extubated earlier and were more likely to survive without need for supplemental oxygen at 36 weeks post menstrual age. No increase was observed in the occurrence of intracranial hemorrhage or other complications referable to prematurity.

Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. The Neonatal Inhaled Nitric Oxide Study Group (NINOS). Pediatrics 1997;99:838-845.

Multicenter trial in which infants with isolated congenital diaphragmatic hernia and hypoxic respiratory failure were randomized to receive inhaled nitric oxide or 100% oxygen. The study was unable to show a survival benefit or reduction in need for extracorporeal membrane oxygenation among those infants who received nitric oxide.

Randolph AG, Wypij D, Venkataraman ST, et al: Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: A randomized controlled trial. JAMA 2002;288:2561-2568.

Large multicenter trial that evaluated standardized ventilator weaning protocols versus no defined protocol in pediatric patients mechanically ventilated for acute illness. Most of the study population was successfully weaned from the ventilator in 48 hours or less. Use of protocols for the gradual weaning of mechanical ventilatory support had no impact on the duration of mechanical ventilation.

Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342:1301-1308.

Landmark multicenter trial showing that in adult patients with acute lung injury and ARDS (PaO_2/FiO_2 =300), mechanical ventilation limiting tidal volumes to 6 mL/kg ideal body weight and plateau pressure = 30 cm H_2O results in decreased mortality and more ventilator-free days when compared with tidal volumes of 12 mL/kg ideal body weight and plateau pressure =50 cm H_2O.

Chapter 90
PULMONARY EDEMA

Gad Cotter • Edo Kaluski • Zvi Vered

KEY POINTS

1. Under normal circumstances the **alveolar space is maintained free of fluids** mainly due to an active process of fluid clearances mediated by active Na^+ transport of the type II endothelial cells. Therefore, fluid can accumulate in the alveolar space when transudated at an increased rate, either due to physical pressure in-balance (significant increase in pulmonary capillary pressure or rapid shifts in thoracic pressure) or due to increased permeability of the capillary-alveolar barrier.
2. The **diagnosis of pulmonary edema** is based on presentation with acute respiratory distress accompanied by physical findings of diffuse "wet" rales over the lung fields that are most prominent on the bases and decreased peripheral perfusion associated with typical findings on chest radiography.
3. **Pulmonary edema can be divided into cardiovascular- and noncardiovascular-based types mostly on clinical grounds.** However, cardiovascular pulmonary edema is commonly associated with abnormal electrocardiographic findings, large cardiac silhouette on chest radiography, increased plasma levels of brain natriuretic peptide, abnormal echocardiographic findings, and high pulmonary capillary wedge pressure.
4. The **most common type of noncardiovascular pulmonary edema is ARDS,** the final common pathway for many injuries affecting the lung (e.g., infection, shock, and toxic damage).
5. Other causes of noncardiovascular pulmonary edema (postoperative, pregnancy related) are caused by **excessive administration of fluids and large fluid shifts** leading to abrupt increase in wedge pressure, although in other cases inflammatory damage to the alveolar capillary membrane (transfusion-associated pulmonary edema) as well as increased peripheral resistance (neurogenic pulmonary edema) play a pivotal role.
6. This syndrome is caused by a combination of **decreased myocardial contractility** (mostly caused by ischemic damage, valvular diseases, cardiomyopathy, or arrhythmias) combined with **increased systemic vascular resistance** caused by undetermined inflammatory-endothelial activation, leading to a vicious cycle of decreased systemic oxygenation and perfusion, begetting respiratory failure, multiorgan failure, and death.
7. Although only examined in a few studies, reduced oxygen saturation, very high or very low blood pressure, high pulse rate and respiratory rate, and reduced myocardial contractility, evidenced by an increased wedge pressure on right-sided heart catheterization, seem to be **negative early prognostic signs** in patients admitted with pulmonary edema.
8. The **most important step in the treatment of pulmonary edema is the initial stabilization,** which can be achieved by improving systemic oxygenation (high-flow facemask and maybe noninvasive ventilation), administration of nitrovasodilators to patients with systolic blood pressure greater than 120 mm Hg, administration of small doses of furosemide and morphine, arrhythmia control, and mechanical ventilation to nonresponders.
9. Although no firm data exist on effective measures to prevent recurrence, early revascularization in patients with significant acute ischemia and surgical correction of severe valvular lesions are warranted. In the future, new drugs that increase left ventricular contractility without increasing oxygen demand and arrhythmias as well as neurohormonal inflammatory modulators may play a pivotal role in prevention of recurrence.

DEFINITION

Pulmonary edema is a life-threatening syndrome caused by accumulation of fluid within the alveoli leading to disruption of the normal gas exchange process, severe hypoxemia, failure of tissue oxygenation, acidosis, and widespread organ failure; if untreated, it rapidly progresses to death.

PHYSIOLOGIC BACKGROUND

Under normal circumstances the alveolar space is kept free of fluids by an active process of sodium (Na^+) and perhaps chloride (Cl^-) transport. Fluid is regularly transudated from the pulmonary capillaries through the thin gas exchange apparatus, composed of the capillary endothelial and type 1 alveolar cells, into the alveoli. This process is slowed

considerably owing to the tight gap junctions existing between the cells that reduce potential fluid transudation. Some fluid, however, escapes these mechanisms and reaches the alveoli. In the past the common paradigm suggested that this fluid is removed from the alveoli by a simple oncotic pressure gradient. However, 20 years ago Matthay and coworkers[1] demonstrated that alveolar fluid clearance is not affected by the Starling forces but is rather an active process. Na^+ from the alveolar fluid enters the type II alveolar cells through amiloride-sensitive channels as well as cotransport with glucose, H^+, amino acids, phosphorus, and other yet undefined mechanisms and then is extruded at the basal side of the cells by an active process mostly (>90%) controlled by the Na^+,K^+-ATPase. The fluid follows the Na^+ by a simple osmotic mechanism, which is at least partially mediated by aquaporins.[2] Furthermore, some fluid reabsorption occurs also in the airways, although in these regions active Cl^- reabsorption probably plays a role in the overall fluid clearance.[3]

Therefore, fluid can accumulate in the alveolar space only when this protective mechanism fails. This can occur when fluid is transudated into the alveolar space at an increased rate, overwhelming the active reabsorption mechanism, or when active fluid clearance mechanisms become less effective (Fig. 90-1). Increased fluid transudation can be related either to physical pressures in-balance (significant increase in pulmonary capillary pressure or rapid shifts in thoracic pressure) or to increased permeability of the capillary-alveolar barrier.

DIAGNOSIS

Although the clinical syndrome of pulmonary edema might differ slightly because of its diverse etiologic factors, the diagnosis of pulmonary edema is, in most cases, rather easy to make if the clinician is experienced.[4] Patients usually present with acute severe respiratory distress. On inspection the patient is anxious, sometimes cyanotic, tachypneic, diaphoretic, and dyspneic and is sitting up and gasping for air and using accessory respiratory muscles to assist in the work of breathing. The patient often coughs up a pink frothy fluid. On examination the patient's extremities are cold, pale, and sweaty. On auscultation, symmetrical diffuse "wet" rales are heard over the lung fields that are most prominent in the bases.

The most useful ancillary test to establish the presence of pulmonary edema is the chest radiograph (Fig. 90-2).[5] In addition to the milder signs of pulmonary congestion such as "cephalization," that is, redistribution of the blood flow to the upper lung fields, and Kerley-B lines, one may observe predominant interstitial lines, reflecting pulmonary interstitial edema and diffuse small nodular opacities that progressively coalesce in the inner two thirds of the lung field producing the "butterfly" appearance. Differentiation between cardiovascular and noncardiovascular pulmonary edema based on the chest radiographic findings may be difficult. However, increased cardiac silhouette, widened pulmonary arteries, and central distribution of the pulmonary blood flow usually direct toward a cardiovascular etiology.

The differentiation between cardiovascular and noncardiovascular pulmonary edema is mostly based on the clinical circumstances. Patients presenting to the emergency department with acute pulmonary edema usually have cardiovascular pulmonary edema, especially when accompanied by a history of heart failure, valvular or ischemic heart disease in the presence of harsh cardiac murmurs, abnormal electrocardiogram, or a large cardiac silhouette on a chest radiograph. Recently, the measurement of brain natriuretic peptide (BNP) has become a useful immediate ancillary tool for the diagnosis of cardiovascular pulmonary edema. Noncardiovascular pulmonary edema occurs almost exclusively in typical clinical settings, commonly as a complication

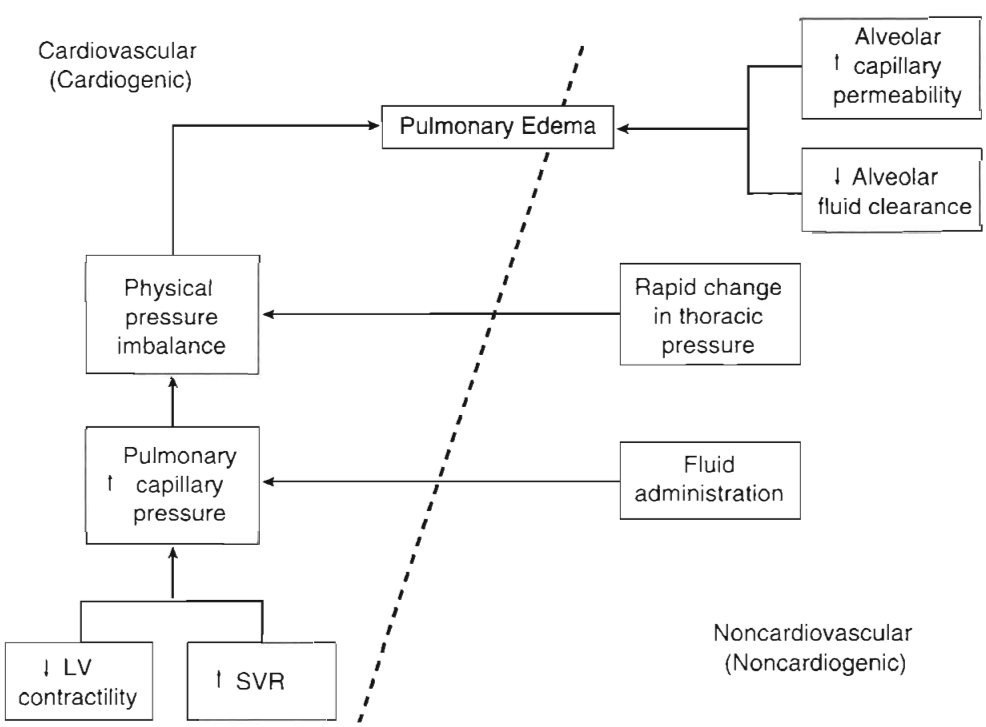

FIGURE 90–1. The pathophysiology of pulmonary edema.

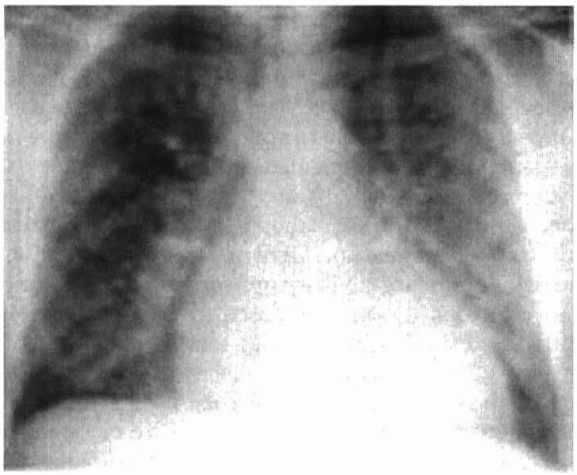

FIGURE 90–2. Chest radiograph of a patient with pulmonary edema.

of an obvious condition such as severe diseases related to acute respiratory distress syndrome (ARDS) or other clinical conditions such as climbing to high altitude, diving in cold water, transfusion-related acute lung injury (TRALI), a major operation, pregnancy, neurogenic events, opiate overdose, radiocontrast use, anticancer treatment, or inhalatory injury.

However, sometimes the differentiation between cardiovascular and noncardiovascular pulmonary edema is difficult based on clinical characteristics. In such cases the measurement of a low pulmonary capillary wedge pressure during right-sided heart catheterization is instrumental in the diagnosis of noncardiovascular edema. Reduced echocardiographic ejection fraction as well as reduced cardiac output during right-sided heart catheterization may occur in both syndromes and hence are not specific enough for differentiation between the two syndromes.

NONCARDIOVASCULAR (NONCARDIOGENIC) PULMONARY EDEMA

The most common cause of noncardiovascular pulmonary edema is ARDS. ARDS is the common final pathway of many injuries affecting the lung, including infections (both pneumonia and systemic infections), other primary systemic inflammatory reactions, various shock syndromes, inhaled toxins (both gaseous and gastric content and foreign materials), disseminated intravascular coagulation, and systemic toxic syndromes. Although damage to the alveolar-endothelial barrier combined with decreased alveolar fluid clearance leads to fluid accumulation within the alveoli, impairing the gas exchange mechanism, the clinical presentation, pathogenesis, and course of ARDS are significantly different from those of pulmonary edema and therefore this syndrome is reviewed in detail elsewhere (see Chapter 75).

In most other syndromes of noncardiovascular pulmonary edema a combination of factors including inflammation, direct damage to the capillary-alveolar membrane, and hypoxia causing leakage of the capillary-alveolar barrier and decreased alveolar fluid clearance are prominent pathogenetic mechanisms of pulmonary edema. However, increased vascular resistance and decreased left ventricular contractility, the main factors contributing to cardiovascular pulmonary edema, may also be present in some of the syndromes that have traditionally been defined as noncardiovascular, whereas increased permeability of the alveolar-capillary membrane as well as decreased alveolar fluid clearance may be observed in cardiovascular pulmonary edema. Hence, it is possible that, in the future, the distinction between cardiovascular and noncardiovascular pulmonary edema will become less important.

The causes of noncardiovascular pulmonary edema are described in Table 90-1, and the most common causes are reviewed in the following sections.

POSTOPERATIVE PULMONARY EDEMA

Postoperative pulmonary edema is a relatively common finding, especially when the surgical procedures are extensive and the patient is elderly and suffers from significant cardiac comorbidities. Although previously reported to be a rare postoperative complication, with an incidence of less than 5%,[6] and in some minor procedures less than 1%,[7] in one study performed in a large hospital,[8] the rate of postoperative pulmonary edema was found to be 7.6%. In 5%, a comorbidity contributing to the pulmonary edema event was identified (e.g., acute myocardial infarction, acute renal failure, acute gastrointestinal bleeding, pneumonia, pulmonary embolism, or hyponatremia). However, pulmonary edema developed in 2.6% of patients without such risk factors. The mortality of postoperative pulmonary edema was 12% overall and 4% in patients with postoperative pulmonary edema without significant predisposing risk factors. The pathogenesis of postoperative pulmonary edema is diverse. Cardiovascular factors are major contributors to pulmonary edema in patients sustaining a postoperative myocardial

TABLE 90–1. ETIOLOGY OF NONCARDIOVASCULAR PULMONARY EDEMA

Increased Alveolar-Capillary Permeability and Reduced Alveolar Fluid Clearance
Acute respiratory distress syndrome
Neurogenic pulmonary edema
Preeclampsia
Drug Substance and Toxic Inhalation Pulmonary Edema
Opiate overdose
Anticancer therapy
Salicylate overdose
Thiazolidinedione-related pulmonary edema
Radiocontrast-related pulmonary edema
Environmental and toxic inhalation pulmonary edema
Other drugs[35]: tricyclic antidepressants, hydrochlorothiazide
Alveolar-Capillary Pressure Imbalance
Perioperative pulmonary edema
Elevated Capillary Pressure: Excessive Fluid Transfusion or Fluid Shifts
Peripartum pulmonary edema
Ovarian hyperstimulation syndrome[13]
Exertional pulmonary edema
Hypoxia-Related Pulmonary Edema
High-altitude pulmonary edema
Rapid Change in Thoracic Pressure
Post upper airways obstruction
Post pneumonectomy
Post evacuation of pleural effusion
Post evacuation of pericardial fluid (rare)

infarction, whereas alveolar capillary leakage and reduced alveolar fluid clearance play a major role in postoperative pulmonary edema related to major infections. In the absence of predisposing risk factors, fluid overload may be the main reason for pulmonary edema. In one study,[8] fatal pulmonary edema was associated with administration of an average of 9 L during 27 hours. Therefore, careful monitoring of perioperative net fluid retention as well as measures to prevent perioperative myocardial infarction, renal failure, bleeding, and infections are important in the prevention of this life-threatening complication.

PREGNANCY-RELATED PULMONARY EDEMA

Pulmonary edema is an uncommon complication of pregnancy. In one large prospective study[9] it was demonstrated that pulmonary edema complicates approximately 0.1% of all pregnancies. It usually occurs in the peripartum period from a combination of factors, including mobilization of fluids and fluid administration, use of tocolytic treatment, and preeclampsia. The diagnosis of pulmonary edema is made during the antepartum period in 47%, the intrapartum period in 14%, and the postpartum period in 39%. Tocolytic treatment use is the most common cause of pregnancy-related pulmonary edema (26%). In most cases, multiple tocolytics that include a beta-mimetic agent are administered, probably inducing a significant increase in systemic vascular resistance. In a further 26%, pulmonary edema is related to a preexisting cardiac disease that is exacerbated during the peripartum period and in combination with the large volume shifts during this period that induce pulmonary edema. Fluid overload per se is the main etiology of pulmonary edema in 22% of patients. In these cases pulmonary edema is related to a large volume transfusion of approximately 6 L over a short period of time. The administration of a large volume of fluids in the peripartum period has become common practice, aiming at reducing preterm delivery. However, such practice should be tempered to prevent this life-threatening complication. Finally, preeclampsia is the main cause of pulmonary edema in 18% of cases. Preeclampsia causes pulmonary edema through a combination of cardiovascular (reduced left ventricular contractility and increased systemic vascular resistance) as well as noncardiovascular factors (endothelial damage leading to increased fluid leak into the alveoli). Increased maternal age, parity, and history of hypertension increase the likelihood of pulmonary edema in patients with preeclampsia.

Although the differential diagnosis of peripartum pulmonary edema is extensive, it is imperative to rule out other possibilities, especially pulmonary emboli, before initiation of treatment. In most cases, interruption of fluid transfusion and tocolytics in combination with diuretics and measures to decrease blood pressure will promptly reverse the clinical symptoms.

Peripartum cardiomyopathy is an important entity causing pulmonary edema but should be listed among the causes of cardiovascular pulmonary edema.

POSTOBSTRUCTIVE PULMONARY EDEMA

This syndrome occurs after the relief of either acute or chronic obstructions of the upper airways.[10] The most common cause is relief of obstruction occurring during anesthesia, although other acute causes of upper airways obstruction such as epiglottitis, croup, foreign bodies, strangulation, tumors, goiter, vocal cord paralysis, and obstruction of endotracheal tubes have been reported. Furthermore, the relief of chronic upper airway obstruction after tonsillectomy or adenoidectomy may also lead to pulmonary edema. Pulmonary edema develops minutes to hours after the relief of obstructions, and its incidence may be up to 10% after relief of acute obstructions and up to 40% after relief of chronic obstruction.[11] The pathophysiology of postobstructive pulmonary edema is not known, but a combination of increased pulmonary capillary pressure owing to significant negative pressure during the obstructive period combined with hypoxia leading to decreased alveolar fluid clearance, increased systemic vascular resistance due to sympathetic overflow, and stress failure of the alveolar-capillary membrane have all been postulated as possible causative mechanisms.[12] The diagnosis is based on usual clinical and chest radiographic findings. Some authorities advocate the use of noninvasive positive-pressure ventilation as the main treatment modality.[10,12]

POSTPNEUMONECTOMY PULMONARY EDEMA

Pulmonary edema develops in 2.5% to 4.5% of patients after pneumonectomy.[13-15] The pathogenesis of this syndrome is unknown. However, a combination of large fluid transfusion, excessive negative pressure in the operated hemithorax due to underwater suction systems, major lymphatic interruption related to extensive surgery, and damage to the alveolar-capillary membrane have been implicated as possible causes. The fatality of this syndrome is significant, up to 85% in one series.[13] Hence, prevention by use of balanced pneumonectomy drainage and judicious fluid transfusions is of great importance. Once it is established, treatment should consist of positive-pressure ventilation and supportive measures.

RE-EXPANSION PULMONARY EDEMA

Pulmonary edema may occur after evacuation of a large pneumothorax or pleural effusion. In one series,[16] its incidence was reported to be 6%, mainly in relation to chronic cases. The pathogenesis is not known, but leaks in the alveolar capillary membrane after prolonged atelectasis and rapid re-expansion were suggested by some authors. The treatment is symptomatic. The prognosis is not known, although in some older series a mortality of up to 20% was described.

NEUROGENIC PULMONARY EDEMA

Neurogenic pulmonary edema is an uncommon complication of various neurologic insults such as head injury, intracranial and subarachnoid hemorrhage, as well as some acute neurologic diseases, including seizures, tumors, hydrocephalus, and neurosurgical procedures. The clinical course is highly variable. The syndrome is often acute and fulminant but may be subclinical and smoldering, manifesting as a mild progressive shortness of breath. The pathogenesis of neurogenic pulmonary edema[17,18] is probably related to a combination of increased sympathetic discharge leading to both increased systemic vascular resistance and decreased left ventricular contractility, as well as increased alveolar-capillary leakage. It is therefore possible that the large variability in clinical presentation is related to the specific contribution of

each of the pathogenic mechanisms involved. The differential diagnosis of neurogenic pulmonary edema is extensive, and careful diagnosis is crucial before institution of treatment. In addition to the measures usually applied in pulmonary edema (see later), some authorities in the neurologic literature advocate the use of alpha-adrenergic blockers such as phentolamine and phenoxybenzamine owing to the possible role of sympathetic overflow in this syndrome. However, these treatment options have never been examined in a prospective, controlled study and hence should be used with caution.[17]

EXERTIONAL AND SWIMMING-INDUCED PULMONARY EDEMA

Pulmonary edema has been reported to occur during and especially after strenuous exercise and diverse sports activities[19,20] and is especially common (up to 60%) after prolonged swimming in cold water.[21] The pathogenesis of this syndrome is unknown. However, stress damage to the alveolar-capillary barrier owing to the dramatic increase in cardiac output as well as peripheral vasoconstriction, especially in cold water swimming, are possible mechanisms. The prognosis is usually benign, and some authorities advocate the use of inhaled beta-mimetics to expedite alveolar fluid reabsorption.[22]

HIGH-ALTITUDE PULMONARY EDEMA

High-altitude pulmonary edema is a syndrome related to climbing to high altitudes. Its exact pathophysiology is unknown, but in a few recent studies it was demonstrated that a combination of hypoxia-induced vasoconstriction leading to increased pulmonary capillary pressure and alveolar fluid transudation[23] together with decreased alveolar fluid clearance[24] leads to alveolar fluid accumulation and edema. The inflammatory changes previously described in these patients are probably secondary to pulmonary edema rather than a primary pathophysiologic event.[25] Important risk factors for high-altitude pulmonary edema include rapid ascent, significant excretion, cold ambience, and individual susceptibility. People who previously sustained an episode of high-altitude pulmonary edema are at an increased risk for repeated episodes when climbing to high altitudes, probably owing to a tendency for more hypoxia-related vasoconstriction or reduced alveolar fluid clearance. The clinical presentation is typical, ranging from cough to full-blown respiratory failure. The treatment includes oxygen administration, rapid descent to lower altitudes or simulated descent by a hyperbaric chamber, and possibly administration of calcium antagonists. Furosemide and dexamethasone are probably not efficacious. Recently, it has been suggested that the use of beta-mimetic drugs (e.g., salmeterol inhalation) by virtue of their effect to increase alveolar fluid clearance may become an effective measure in both the treatment and prevention of high-altitude pulmonary edema.[26]

DRUG-, SUBSTANCE- AND TOXIC INHALATION–INDUCED PULMONARY EDEMA

The most common cause of drug-induced pulmonary edema is the use of cardiodepressants such as beta-adrenergic blockers and some calcium blockers and antiarrhythmics. Even topical administration of beta-adrenergic blockers might provoke pulmonary edema[27]; hence, careful examination of all drug treatments and especially new drugs that have been administered is imperative when admitting a patient with pulmonary edema.

Pulmonary edema has been associated with the intake or toxicities of drugs that provoke edema through different mechanisms.

Opiate Overdose Pulmonary Edema

This type of pulmonary edema is observed with all opiate derivatives, including opium (as described in 1880 by William Osler),[28] heroin,[29] and methadone. Recently, opiate-related pulmonary edema is most commonly the result of heroin overdose. Its prevalence is unknown; however, in one retrospective study it has been reported to occur in approximately 10% of patients admitted with heroin overdose, related to a more severe respiratory depression but not co-intoxication with alcohol or cocaine ("speed ball"). In the past it had been suggested that opiate-related pulmonary edema is associated with the impurities of the intravenous preparation. However, more recent studies have suggested that opiates by themselves induce damage to the alveolar-capillary membrane, causing fluid transudation into the alveoli combined with depressed alveolar fluid clearance induced by the overdose-related hypoxia. Opiate-related pulmonary edema is rarely life threatening and is easily manageable by medical treatment. However, sometimes this complication occurs up to 36 hours after resolution of the heroin overdose; hence a period of observation is warranted in all patients admitted with such an overdose.

Anti-Cancer Therapy–Related Pulmonary Edema

Pulmonary edema has been described as a complication of anti-cancer therapies. Its incidence is unknown, and most reports in the literature are sporadic case reports. In one review,[30] Briasoulis and Pavlidis relate pulmonary edema to treatment with interleukin-2; granulocyte and granulocyte-macrophage colony-stimulating factors; cytotoxic drugs such as cytarabine, gemcitabine, docetaxel, vinblastine, methotrexate, and 5-fluorouracil; bone marrow transplantation; and the vitamin-A derivative ATRA. Although the pathogenesis of anti-cancer therapy–related pulmonary edema is unknown, and likely to be different for the different agents implicated, increased alveolar-capillary membrane permeability due to direct toxicity (by cytotoxic drugs) and inflammatory activation (by interleukin-2, bone marrow transplantation, and ATRA) are possible mechanisms. The prognosis is usually related to the underlying condition.

Salicylate Overdose

Although there are scattered reports of an association between pulmonary edema and nonsteroidal anti-inflammatory agents as a group, pulmonary edema has been mainly reported to complicate salicylate overdose.[31] It occurs in 10% to 60% of patients sustaining a salicylate overdose and exclusively in patients with blood levels greater than 30 mg/dL, but its incidence is not related to the exact blood levels. It is more common in older and sicker patients, especially when the intoxication is chronic. Treatment is symptomatic and includes all measures to treat salicylate toxicity per se. Importantly, pH should be maintained as close to normal as possible. In a few cases hemodialysis has been used, especially when blood

levels were greater than 100 mg/dL; however, the reports on its efficacy are limited.

Thiazolidinedione-Related Pulmonary Edema

The thiazolidinediones currently include troglitazone, rosiglitazone, and pioglitazone. They are known to promote fluid retention and possibly diuretic resistance and have been reported to cause pulmonary edema.[32]

Radiocontrast-Related Pulmonary Edema

Pulmonary edema is a rare complication of radiocontrast administration with an unknown incidence. The pathophysiology is related to an increased leakage of the alveolar-capillary membrane owing to both direct toxic effects of the radiocontrast media and complement-mediated inflammatory activation.[33] The treatment is conventional (see later), and the prognosis is usually favorable.

Environmental and Toxic Inhalation Pulmonary Edema

Pulmonary edema is one of the more serious complications of inhalation of toxic gases and irritants.[34] The list of possible inhalatory causes of pulmonary edema is vast[34]; however, the most common causes include gases such as chlorine, hydrogen sulfite, fluorine, methyl isocyanate, paraquat, pesticides, insecticides, and fumigants. Other common causes include particulated fat emboli, low-dose irradiation particles, environmental air pollution ("metal fume fever" due to manganese), and, last, inhalation of recreational drugs such as cocaine and crack cocaine. The treatment is usually symptomatic. Both morbidity and mortality from this condition are high; hence, prevention of accidental exposure is of utmost importance.

TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)

TRALI is a syndrome of sudden-onset noncardiovascular pulmonary edema occurring during or a few hours after transfusion of a blood product.[35,35a] The incidence is 1 to 5 in 10,000 transfusions, and it usually occurs after administration of products containing large amounts of plasma, although it has been reported to occur after administration of as little as 50 mL of whole blood or any plasma containing blood products including intravenous immunoglobulins. The pathogenesis is unknown; however, it has been suggested that leukocyte activation due to antibodies in donor plasma to antigens of recipient white blood cells or reactive lipids in aged cellular blood components are important contributing factors. Although host factors such as infection, cytokine administration, lung disease, and recent surgery may contribute to the incidence and severity of TRALI, the syndrome was also reported in healthy volunteers receiving blood products. Activated leukocytes are sequestered in the lungs and cause damage to the capillary-alveolar membrane leading to congestion, hypoxia, pulmonary edema, hypovolemia, hypotension, and fever. Laboratory findings include hemoconcentration, hypoalbuminemia, and neutropenia or neutrophilia. Differential diagnosis includes ARDS, other forms of pulmonary edema, and pneumonia. Early diagnosis is important to prevent administration of diuretics that may be detrimental in TRALI. Treatment includes oxygen administration and sometimes mechanical ventilation (required in approximately 68% of cases). Corticosteroids have been advocated by some authors, although their use has never been examined in a controlled prospective study. In contrast to ARDS the clinical course in TRALI is often benign, with improvement starting after 24 to 48 hours; if the patient survives, no sequela are observed. However, mortality remains high, at about 5%, and TRALI is the third cause of transfusion-related mortality. Prevention is the most important measure including avoiding unnecessary transfusions, increased use of red cells containing less plasma, and possibly avoiding the use of products containing large amounts of plasma derived from multiparous women, who often are autoimmunized against leukocyte antigens during pregnancy.

CARDIOVASCULAR (CARDIOGENIC) PULMONARY EDEMA

DEFINITION AND INCIDENCE

Cardiogenic pulmonary edema is the extreme form of acute heart failure. Although a standard definition of this syndrome does not exist we have previously defined cardiogenic pulmonary edema as an episode of acute heart failure accompanied by severe respiratory distress and oxygen saturation less than 90% on room air before treatment.[36] The incidence of cardiogenic pulmonary edema is not known. Although there are approximately 1 million annual hospital admissions due to heart failure in the United States,[37] the exact fraction of acute heart failure and pulmonary edema is not known.

PATHOGENESIS

Initiation Phase

Cardiogenic pulmonary edema is caused by a failure of the cardiovascular system, leading to an increase in left ventricular pressures transmitted backward to the pulmonary veins, inducing an increase in pulmonary capillary pressure and transudation of fluid from the capillaries to the pulmonary interstitium and alveoli, overwhelming the reabsorption ability of the alveolar cells.[3] The cardiovascular failure that causes pulmonary edema is the end product of a combination of reduced left ventricular contractility and increased systemic vascular resistance (Fig. 90-3), leading to a vicious cycle.[36] First, the decrease in left ventricular contractility induces a significant neurohormonal (sympathetic, renin-angiotensin, and endothelin) and inflammatory (interleukin-6–mediated) activation,[38] leading to peripheral vasoconstriction and increased systemic vascular resistance. Second, increased systemic vascular resistance imposes a significant afterload mismatch, further reducing left ventricular contractility. This vicious cycle causes a decrease in cardiac output and peripheral perfusion and also an increase in left ventricular pressure that leads to the pulmonary edema syndrome.

Amplification Phase

This vicious cycle is amplified by four distinct mechanisms (Fig. 90-4):

1. *Myocardial ischemia:* In many patients pulmonary edema coexists with significant coronary artery disease. In such patients the hypoxia, acidosis, and reduced cardiac output present during pulmonary edema may induce myocardial ischemia, thus further reducing left ventricular contractility, increasing left ventricular pressures, and further worsening the pulmonary edema syndrome.

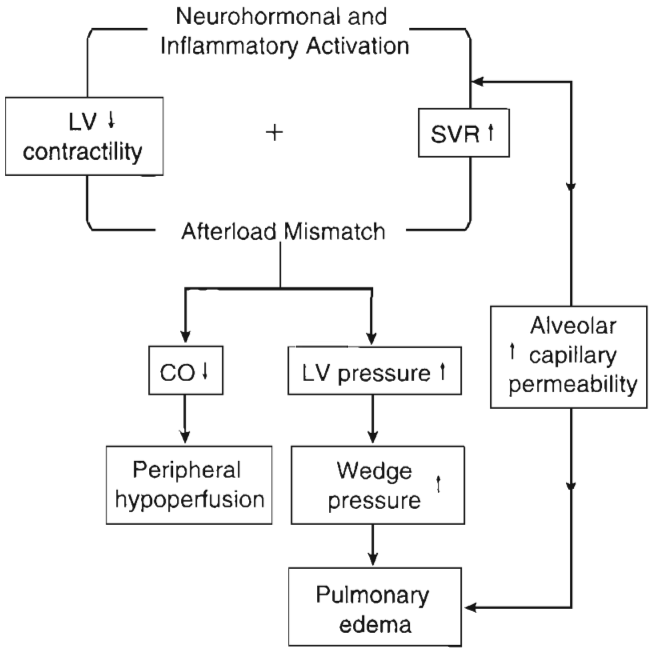

FIGURE 90–3. The initiation phase of pulmonary edema.

2. *Right ventricular failure:* The increased fluid content in the lungs and decreased oxygen saturation induce pulmonary vasoconstriction. This is translated into an increase in right ventricular pressure, again compromising left ventricular function through the ventricular interaction mechanism.[39]
3. *Respiratory failure:* The decreased oxygenation, acidemia, and reduced cardiac output may lead to depressed central respiratory drive and failure of the respiratory muscles, leading to respiratory failure superimposed on cardiovascular failure.
4. *Leakage of the alveolar-capillary membrane and decreased alveolar fluid clearance:* Although debated during recent years, it seems that in cardiovascular pulmonary edema the acute inflammatory reaction leads to prolonged leakage of the alveolar-capillary membrane. This process may contribute to the initial event as well as to the known tendency of patients admitted with cardiovascular pulmonary edema to develop recurrent events during the days after the initial event.[40] Furthermore, the significant hypoxia present during the initiation of the acute heart failure event may depress the rate of alveolar fluid clearance, further enhancing pulmonary edema.[3]

Common Final Pathway

As the cycle leading to pulmonary edema progressively amplifies, the patient's condition deteriorates into a state of severe cardiovascular failure with low cardiac output, reduced oxygenation, significantly activated neurohormonal and inflammatory modulators, increased systemic vascular resistance, decreased peripheral perfusion, myocardial ischemia, respiratory failure, and, if untreated, death.

ETIOLOGY

As previously stated, in most cases cardiogenic pulmonary edema is caused by a combination of decreased left ventricular contractility and increased systemic vascular resistance. These two mechanisms exist to a certain degree in most forms of cardiogenic pulmonary edema. For example, in patients who sustain pulmonary edema due to severe acute ischemia, some increase in systemic vascular resistance is commonly observed owing to sympathetic activation, whereas in patients presenting with "flush" hypertensive pulmonary edema, left ventricular contractility by invasive hemodynamic measurements is at least to some extent decreased. Often, however, the etiologic factor is primarily related to either an acute decrease of left ventricular contractility or an increase in systemic vascular resistance (Table 90-2).

Although severe myocardial ischemia is a common etiology of cardiogenic pulmonary edema, minor ischemia, as evident

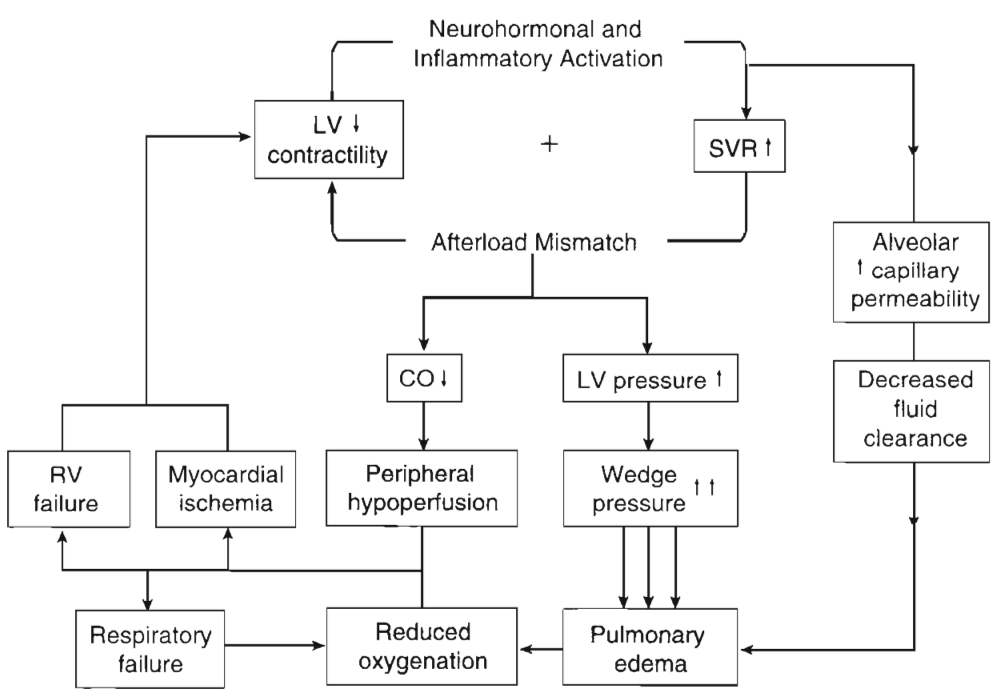

FIGURE 90–4. The amplification phase of pulmonary edema.

TABLE 90–2. ETIOLOGIC FACTORS OF CARDIOVASCULAR PULMONARY EDEMA

Reduced Left Ventricular Contractility
Severe acute myocardial ischemia
Valvular or mechanical factors (see Table 90-7)
Cardiomyopathies (dilated, hypertrophic, restrictive)
Myocarditis
Cardiodepressant drugs (beta-adrenergic blockers, calcium channel blockers, antiarrhythmics)
Severe arrhythmias
Increased Systemic Vascular Resistance
"Flush" hypertensive pulmonary edema
Renal artery stenosis
Pheochromocytoma, hypertensive crisis
Neurogenic pulmonary edema?
Cold immersion pulmonary edema?

TABLE 90–3. INITIAL EVALUATION OF PATIENTS WITH SUSPECTED CARDIOVASCULAR PULMONARY EDEMA

Immediate Work-Up
History of heart failure or regular intake of loop diuretics, previous myocardial infarction, or known significant valvular disease
Physical examination: check blood pressure, temperature, signs of peripheral edema, and cardiac and pulmonary physical findings
Arrhythmia monitoring
Pulse oximetry
12-Lead electrocardiogram
Chest radiograph
Advanced Work-Up
Complete blood gas analysis
Laboratory evaluation (complete blood cell count, electrolytes, urea/creatinine, creatine kinase, troponin)
Brain natriuretic peptide measurement (if available)
Echocardiographic evaluation
Right-sided heart catheterization

by minor electrocardiographic changes and mild increase in plasma markers (creatine kinase [CK], troponin), is part of the common final pathway of cardiogenic pulmonary edema. Hence, careful evaluation of these symptoms and signs should be implemented on an individual basis, because routine revascularization procedures in these patients are sometimes related to significant complications and restoring coronary flow to nonviable myocardial segments may not reduce recurrent heart failure events.[41] Furthermore, in recent years it has become apparent that the etiology of the cardiogenic pulmonary edema is often associated with a hypertensive event related to echocardiographic signs of diastolic dysfunction, increased endothelin levels, and sustained inflammatory activation at recovery.[38,42] This novel syndrome is related to older age, relatively preserved left ventricular ejection fraction, higher prevalence of female sex, and history of hypertension and is probably one of the more common causes of cardiovascular pulmonary edema.[42,43]

DIAGNOSIS AND INITIAL EVALUATION

Although immediate treatment is imperative to avert cardiovascular and respiratory failure and death, it is important in parallel to treatment administration that an initial evaluation is performed in patients admitted with pulmonary edema (Table 90-3). This evaluation has important goals:

1. *Establish the diagnosis of pulmonary edema.* Although the diagnosis can often be made with high certainty based on symptoms and clinical signs, further evaluation is essential to rule out other acute diseases leading to respiratory failure and/or hemodynamic insufficiency (Table 90-4). In patients with a known history of heart failure, significant ischemic heart disease, or valvular lesions, the classic symptoms and signs combined with typical chest radiographic findings (see earlier) are sufficient for diagnosis and initiation of treatment. Also, in patients without such history, typical symptoms and signs accompanied by chest radiographic findings in the presence of fever less than 38°C, reduced echocardiographic left ventricular ejection fraction, or elevated BNP or Pro NT-BNP are usually diagnostic of pulmonary edema. In some cases, however, the diagnosis remains uncertain and right-sided heart catheterization may be required to establish the exact diagnosis. During right-sided heart catheterization findings of increased pulmonary capillary wedge pressure, reduced cardiac index, and cardiac power (the product of mean arterial blood pressure and cardiac output measured simultaneously) and increased systemic vascular resistance are usually indicative of pulmonary edema. Although no exact cutoff point exists regarding these hemodynamic variables for the diagnosis of cardiovascular pulmonary edema, if right-sided heart catheterization is performed while the patient is still in pulmonary edema, systemic vascular resistance of more than 3000 dynes is usually measured.[44]
2. *Determine whether pulmonary edema is the result of severe acute ischemia.* As previously stated, this distinction may be difficult to establish. However, patients with significant dynamic ST-segment elevation or depression or deep T-wave inversion on electrocardiography, especially if these changes are in the anterior wall (precordial leads) and not accompanied by pathologic Q waves or bundle branch block and accompanied by significant CK-MB or troponin elevation, should be regarded as suffering from pulmonary edema owing to severe acute ischemia and treated as such (see later).
3. *Determine the severity of pulmonary edema.* Although the data on the risk stratification of patients with cardiovascular pulmonary edema are limited, the following measures

TABLE 90–4. DIFFERENTIAL DIAGNOSIS OF CARDIOVASCULAR PULMONARY EDEMA

Conditions Leading to Respiratory Failure
Exacerbation of obstructive lung disease
Respiratory infections or pneumonia
Acute respiratory distress syndrome
Conditions Leading to Both Respiratory and Cardiovascular Failure
Pulmonary emboli
Sepsis
Cardiogenic shock

of disease severity have been established in patients with acute heart failure and cardiogenic pulmonary edema:

a. *Baseline characteristics:* Older age, male sex, lower weight, hyponatremia, and reduced hemoglobin and renal function have been correlated with worse outcome. No exact cutoff points have been determined for these measures, although age older than 65 years, weight less than 78 kg, sodium less than 135 mEq/L, hemoglobin less than 11 g/dL, and blood urea nitrogen greater than 45 mg/dL have been proposed as such.[45-47]
b. *Findings on admission:* As previously stated, oxygen saturation less than 90% is required for the diagnosis of pulmonary edema. However, as arterial oxygen saturation decreases, the chances of respiratory failure increase and the patient's prognosis becomes worse.[48] Admission blood pressure is also an important sign of disease severity; however, its correlation with outcome is "U"-shaped. Higher admission blood pressure is usually correlated with higher vascular resistance and, hence, worse outcome.[48] On the other hand, low blood pressure (<120 mm Hg systolic) on admission is correlated with decreased left ventricular contractility and is a negative prognostic sign.[44] Finally, higher pulse rate and respiratory rate at admission were correlated with increased rate of adverse events in patients admitted with pulmonary edema.[48]
c. *Cardiac contractility:* Cardiac power[49] is the product of simultaneously measured cardiac output (cardiovascular flow) and mean arterial blood pressure (MAP, cardiovascular pressure). Cardiac power output is calculated as Cpo = CO • MAP • 0.022, and its units are watts. In recent studies cardiac power output was demonstrated to be the strongest predictor of outcome in patients with chronic heart failure[36] and cardiogenic shock[50] as well as acute heart failure. Typically, cardiac power output of less than 0.5 to 0.6 watt on admission is associated with increased rate of recurrent heart failure events. However, the calculation of Cpo requires right-sided heart catheterization, which is currently performed less often. Reduced echocardiographic ejection fraction can be used as a measure of left ventricular contractility.[48]
d. *Measures of neurohormonal activation:* In patients with chronic heart failure, neurohormonal and inflammatory measures have been shown to be correlated with disease severity and outcome. The data on such measures in patients with acute heart failure and pulmonary edema are limited. However, it has been suggested that higher admission endothelin level is the mediator associated with worst outcome, whereas admission BNP is of limited value.[51-53] Currently, endothelin measurements are done only by specialized laboratories and hence cannot be used for immediate risk stratification.

4. *Determine whether the patient suffers from chronic heart failure that has deteriorated due to aggravating factors.* Cardiovascular pulmonary edema may occur owing to an acute aggravation of significant chronic heart failure (Table 90-5). The determination of existing chronic heart failure is important because in these patients acute pulmonary edema may occur as a result of an aggravating factor (Table 90-6) that may be easily manageable, hence improving our ability to treat the acute event and prevent early recurrence. On the other hand, in patients without a history of significant chronic heart failure symptoms, "flash" hypertensive pulmonary edema with relatively preserved left ventricular ejection fraction is a common cause of cardiogenic pulmonary edema, which may be associated with better prognosis.
5. *Determine whether pulmonary edema is related to preserved echocardiographic ejection fraction (HFnEF) or low ejection fraction (HF↓EF).* The distinction between HFnEF and HF↓EF was set by most investigators at EF equals 40%. Patients with HFnEF tend to be older, to be female, and to have a history of hypertension; their pulmonary edema is more often of the "flash" hypertensive type. On Doppler echocardiography they tend to demonstrate signs of diastolic dysfunction, in particular, shorter transmitral E-wave deceleration time and lower E/A-wave ratio; and their prognosis may be better. On the other hand, in patients with HF↓EF, acute ischemia is often a leading cause of pulmonary edema; and their prognosis is worse.[38]
6. *Rule out significant valvular and mechanical cardiac causes of pulmonary edema.* This evaluation underscores the role of early echocardiographic evaluation in patients with suspected cardiovascular pulmonary edema. The echocardiographic evaluation is especially indicated when a significant cardiac murmur is present and the patient's condition does not resolve immediately with conventional medical treatment. Table 90-7 depicts the main mechanical cardiac causes of pulmonary edema. If such a significant valvular or mechanical lesion is detected, the patient may require prompt surgical treatment.

TABLE 90–5. CLINICAL SYMPTOMS AND SIGNS OF DETERIORATED CHRONIC HEART FAILURE VERSUS "TRANSIENT" PULMONARY EDEMA

	"Transient" Pulmonary Edema	Acute Decompensation of Chronic Heart Failure
Chronic heart failure symptoms (dyspnea/fatigue)	+	++++
Treatment with loop diuretics	+	+++
Peripheral edema	+	+++
Gain in body weight	+	+++
Reduced ejection fraction (echo)	+	+++
Neurohormonal activation (endothelin)	+++	++
Aggravating factor	+	+++

TABLE 90–6. COMMON AGGRAVATING FACTORS LEADING TO DECOMPENSATION OF CHRONIC HEART FAILURE

Acute fluid and/or salt intake (diet noncompliance)
Medical treatment noncompliance
Acute ischemia or myocardial infarction
Sepsis or other infections (mostly upper respiratory tract)
Significant arrhythmias (atrial tachycardia, fibrillation or flutter, ventricular tachycardias, bradyarrhythmias)
Pulmonary embolism
Anemia
Hyperkalemia
Acute renal failure

TABLE 90–7. COMMON VALVULAR AND/OR MECHANICAL LESIONS THAT MAY LEAD TO PULMONARY EDEMA

Significant aortic stenosis or regurgitation
Significant mitral stenosis or regurgitation
Mechanical valve malfunction (thrombosis or pannus formation or leakage)
Acquired ventricular septal defect (associated with myocardial infarction)
Infective endocarditis
Aortic dissection

TREATMENT

Immediate Stabilization

Untreated pulmonary edema is a life-threatening situation. The progressive decrease in left ventricular contractility and increase in systemic vascular resistance culminate into a progressive decrease in organ perfusion and oxygenation, progressive acidemia, multi-organ failure, respiratory failure, and death. Accordingly, the immediate goals in the treatment of pulmonary edema are termination of the main aggravating vicious cycles leading to progressive heart failure, that is, improving systemic oxygenation and inducing rapid vasodilatation of both veins and arteries, thus decreasing vascular resistance, alleviating afterload mismatch, and reducing the preload of both the left and right ventricles.

Improving Systemic Oxygenation

This is usually achieved by positioning the patient in a sitting position and administering oxygen by a high-flow facemask. It has been suggested that noninvasive positive-pressure ventilation could further improve oxygenation.[54] However, this treatment might increase intrathoracic pressure, impairing cardiac function, and hence aggravate rather than improve congestion. Indeed, in a single study performed in patients with frank pulmonary edema, bilevel positive airway pressure (BiPAP) ventilation was found to be related to unfavorable outcome.[55] Therefore, the use of noninvasive ventilation in cardiovascular pulmonary edema should be regarded, at least for the time being, as optional and may be applied in patients with milder forms of acute heart failure or patients not responding to conventional oxygen supply and drug therapy.

Arrhythmia Control

In parallel to attempting to improve oxygenation, the patient should be connected to a rhythm monitor and malignant arrhythmias such as ventricular tachycardia, severe bradyarrhythmias, or significant atrial arrhythmias such as rapid atrial fibrillation should be immediately treated.

Intravenous Furosemide and Morphine

First-line treatment should be administered intravenously; hence, intravenous access should be established as soon as possible. Treatment should consist of intravenously administered furosemide at a dose of 40 to 80 mg given as a bolus and intravenously administered morphine up to 3 mg. This treatment combination induces mild diuresis and preload reduction and assists in reducing patient anxiety. Higher doses of furosemide are usually not recommended because such doses may lead to intravascular depletion and prerenal azotemia and are related to significant neurohormonal activation,[56] which can be deleterious in patients with cardiogenic pulmonary edema. Higher doses of morphine may induce respiratory depression and enhance respiratory failure[57] and thus should be avoided.

Intravenous Nitrates

Intravenous nitrates should be administered to all patients with cardiogenic pulmonary edema with a systolic blood pressure of greater than 120 mm Hg on admission. Intravenous nitrates are the only treatment modality that has been shown in a prospective randomized study to improve the outcome of patients admitted with pulmonary edema by averting respiratory failure and reducing the need for mechanical ventilation.[58] These agents can be administered as repeated boluses of 3 mg while monitoring blood pressure and oxygen saturation until either arterial oxygen saturation increases to greater than 90% or systolic blood pressure is reduced to less than 120 mm Hg. Nitrates can also be administered as a continuous drip, but the efficacy of such treatment has not been demonstrated in a prospective study.

Mechanical Ventilation

If the patient develops respiratory failure or pulmonary edema accompanied by significant hypotension, he or she should be classified as having cardiogenic shock and should be treated with mechanical ventilation. Patients not responding to medical treatment within 10 to 20 minutes, as evident by an increase in arterial oxygen saturation to more than 90%, accompanied by decreased tachypnea and blood pressure, are suffering from refractory pulmonary edema[48] and should be treated by mechanical ventilation. Tracheal intubation in patients with pulmonary edema may be difficult because the patient is hypoxic, anxious, and often uncooperative. Thus, tracheal intubation should be performed by the most skilled person available.

First 24 Hours

After the initial stabilization, as vascular resistance decreases toward normal values, cardiac index increases, and wedge pressure decreases, the main goals of treatment shift from rapid arterial and venous dilatation to preventing recurrence. Because decreased left ventricular contractility and increased systemic vascular resistance are important in the pathogenesis of pulmonary edema, traditional treatments employed during this time period are directed toward rapid increase in left ventricular contractility, prevention of recurrent vasoconstriction, and enhancement of diuresis. However, although some of the treatments are efficacious in accelerating symptom relief through their hemodynamic effects (increased left ventricular contractility or vasodilatation leading to reduced wedge pressure), their effect on outcome, as measured by prevention of recurrent events of pulmonary edema and death, when compared with placebo is limited.[59,60] Moreover, in some cases it has been suggested that some of these treatments might actually be associated with adverse outcomes. Therefore, all treatments should be administered with caution and only to patients with refractory symptoms of heart failure after the initial stabilization period.

Increasing Left Ventricular Contractility

Repair of Significant Valvular and Mechanical Lesions. Early echocardiography is warranted to evaluate global and regional cardiac function and detect any mechanical problem such as severe valvular lesion or septal rupture leading to pulmonary edema (see Table 90-7). If such a significant

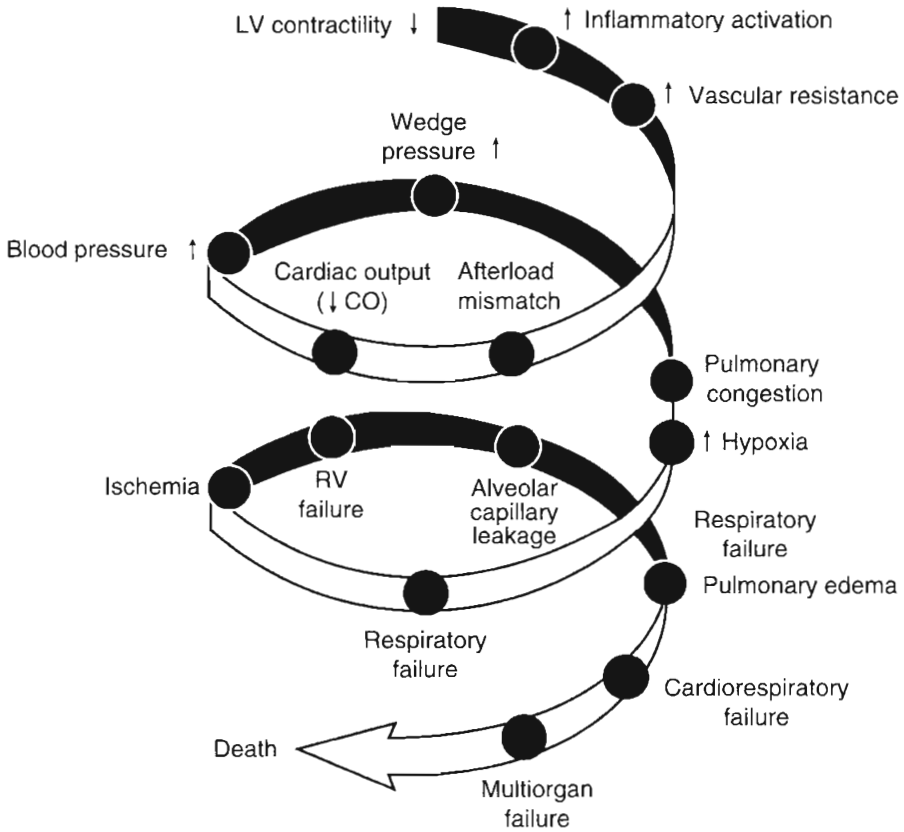

FIGURE 90–5. The common final pathway of cardiovascular pulmonary edema.

mechanical problem is encountered and the patient's condition cannot be stabilized by medical treatment, all efforts should be directed to immediate surgical repair.

Treatment of Severe Acute Ischemia. If severe acute ischemia is considered to be the main etiologic factor leading to pulmonary edema, immediate efforts should be undertaken to relieve ischemia. In patients with acute ST segment elevation due to myocardial infarction, thrombolytic therapy or primary percutaneous coronary intervention should be executed promptly. In patients with a non–ST segment elevation ischemic event, maximal anti-ischemic treatment should be initiated followed by percutaneous coronary intervention if the ischemia or heart failure is refractory to medical treatment.[61] The intra-aortic balloon pump (IABP) as a tool of both immediate ischemia control and a way to improve effective cardiac power output may be efficacious in the treatment of acute heart failure complicating refractory ischemia or a mechanical complication.[62] Even if a patient sustaining pulmonary edema during an acute ischemic event is medically stabilized, the combination of these two syndromes has a grave prognosis. Therefore, after initial stabilization, these patients should be scheduled for immediate coronary angiography, followed by revascularization. Although in most cases, owing to significant stunning, this will not improve cardiac function immediately, it may improve left ventricular contractility over time, hence gradually decreasing the likelihood of recurrent episodes of acute heart failure.

Positive Inotropes. Positive inotropes aimed at improving cardiac systolic function, mostly sympathomimetic amines (i.e., dopamine, dobutamine, and phosphodiesterase inhibitors), are commonly used for the early treatment of pulmonary edema. These agents, although effective in the short term in relieving dyspnea and normalizing hemodynamic measurements,[63] may not be effective in the long-term outcome of patients with acute heart failure or may even be harmful.[59,64] Thus, the administration of these agents should be reserved for refractory cases of primary pump failure (refractory heart failure accompanied by low ejection fraction or low cardiac power output) in which recurrent episodes of heart failure exacerbation cannot be prevented by conventional therapy. Lately, a new class of drugs has been developed that are aimed at improving cardiac systolic function in patients with heart failure. The first drug of this class to be reported, levosimendan, was examined in patients with acute heart failure.[65,66] When administered intravenously for 24 hours it improved subjective dyspnea and prevented recurrent episodes of heart failure exacerbation, as compared with dobutamine. No long-term follow-up data are available.

Preventing Recurrent Vasoconstriction. This goal has been traditionally achieved by the administration of vasodilators. This class of drugs currently includes nitrates and nitroprusside. The main obstacle in the use of such agents for a prolonged period of time is the rapid development of tolerance, limiting their effectiveness to 16 to 24 hours only. Moreover, these drugs have a "U"-shaped dose-response curve.[47] If given in suboptimal dose, vasodilators may have a limited effect in preventing pulmonary edema. However, administration of high doses may also reduce their effectiveness. In some cases vasodilators are given at doses aimed at achieving the maximal possible vasodilatation, leading to the largest increase in cardiac index and decrease in pulmonary wedge pressure achievable. However, in patients with heart failure with reduced left ventricular contractility, inappropriate vasodilatation may result in further decrease in blood pressure and cause hemodynamic instability, ischemia, renal failure, and even frank shock. Therefore, the administration of these drugs should

be carried out under careful blood pressure monitoring, titrating the dose administered against blood pressure decrease. We recommend decreasing the dose of these drugs if systolic blood pressure decreases below 120 mm Hg and discontinue them permanently if blood pressure drops farther. Hence, during the first 24 hours the vasodilator dose should be progressively lowered, aiming at preventing recurrent episodes of inappropriate vasoconstriction instead of inducing true vasodilatation. Natriuretic peptides have been introduced for the treatment of acute heart failure owing to their vasodilatory and diuretic properties. The first drug of this class examined in a clinical study is nisiritide.[67] This drug was shown to be efficacious in improving subjective dyspnea score as well as inducing significant vasodilatation. However, in one analysis, concerns were raised regarding its safety.[60]

Diuretics. The third group of drugs used during the early period after initial stabilization of patients with pulmonary edema is diuretics, of which high-dose loop diuretics and especially furosemide are most commonly employed. However, studies examining the effect of high-dose furosemide administration have demonstrated that such treatment is associated with neurohormonal activation, increased renal failure, and other adverse events.[56,68-70] Therefore, the dose of furosemide administered to patients with acute heart failure should be restricted to the lowest possible dose achieving palliation of the congestive symptoms.

Treatment After the First 24 Hours

As a patient's condition stabilizes, long-term medical treatment should be established. First, as previously stated, in patients with obvious ischemia, coronary angiography and revascularization should be performed as soon as possible. Patients without clinical evidence of ischemia should be scheduled for a noninvasive test to assess the presence of ischemia and viability, either by radionuclide techniques or by dobutamine stress echo. In patients in whom significant ischemia and/or viability is demonstrated, in particular those demonstrating improved function of hypokinetic or akinetic segments during low-dose dobutamine and deterioration during high-dose dobutamine, coronary angiography should be considered. Concomitantly, oral medical treatment aimed at preventing repeated episodes of vasoconstriction should be administered. These drugs should be initiated at low doses and gradually titrated upward to achieve maximal effect while preventing excessive vasodilatation and hypotension. At present, only angiotensin-converting enzyme (ACE) inhibitors have been shown to be effective in this respect. However, even those drugs were examined only in patients with HF↓EF. ACE inhibitors can be substituted by angiotensin receptor I antagonists if side effects such as cough occur. Finally, beta-adrenergic blockers, which are extremely beneficial in the long-term treatment of heart failure, should not be administered to patients with acute heart failure until the patient's condition has stabilized.

It is important to emphasize that no study has examined the long-term treatment of patients with HFnEF; thus the administration of ACE inhibitors and beta-adrenergic blockers in these patients, although recommended by most authorities, remains unproven.

Outcome

As previously stated, the outcome of patients with cardiovascular pulmonary edema is strongly related to factors measured on admission, such as age, hemoglobin, creatinine, oxygen saturation, blood pressure, pulse, left ventricular contractility, and existence of significant ischemia as the main cause of the pulmonary edema. However, it has been demonstrated that a patient's response to treatment is also correlated with outcome.[47] Specifically, if oxygen saturation after 15 to 30 minutes of treatment remains below 95%, the patient is considered to have refractory pulmonary edema, which is correlated with a higher incidence of adverse outcome. Furthermore, significant blood pressure decrease at 15 to 30 minutes is also a predictor of outcome.

To date, the outcomes of patients with acute cardiovascular pulmonary edema have been described in only a few well-controlled prospective studies.[48,58] In these studies, the rate of early mechanical ventilation was approximately 20%, of which about half the patients required mechanical ventilation on admission and the rest required mechanical ventilation owing to early treatment failure (refractory pulmonary edema). Approximately 10% of patients sustained a myocardial infarction, and in 10% there was a further event of recurrent acute heart failure within 24 hours after admission. Cardiogenic shock was diagnosed in 2.5%. At 30 days, 38% of patients sustained a recurrent event of acute heart failure and the mortality was 5%.

DIFFERENCE BETWEEN PULMONARY EDEMA AND CARDIOGENIC SHOCK

Acute heart failure and cardiogenic shock are the two main syndromes of acute cardiovascular decompensation. In both, the main clinical manifestations are a combination of decreased peripheral perfusion and pulmonary congestion. Hemodynamically, the cardiac index is low and wedge pressure is high in both conditions. In one prospective study,[44] the cardiac index was similar in patients with cardiogenic shock and in patients with pulmonary edema.

Yet, the pathogenesis of these two syndromes is different, as is their treatment. In pulmonary edema the main hemodynamic finding is an increase in vascular resistance superimposed on impaired left ventricular contractility, whereas in cardiogenic shock the main findings include extreme pump failure expressed by a low cardiac power output and only a modest increase in vascular resistance. Therefore, vasodilators are very effective in the treatment of pulmonary edema while usually contraindicated for cardiogenic shock.

Accordingly, this distinction should be made early by clinical, echocardiographic, and hemodynamic evaluation. As a rule, vasodilator treatment should not be administered to patients with acute heart failure and systolic blood pressure less than 100 mm Hg. In these patients the initial treatment should be based on the SHOCK study[71] and include increasing doses of intravenous inotropes, intra-aortic balloon counterpulsation, mechanical ventilation, and elimination of precipitating factors. When signs of myocardial ischemia are detected, coronary angiography followed by coronary revascularization should be attempted. Preliminary data suggest that patients not responding to these measures may benefit from administration of L-NMMA (a nitric oxide synthase inhibitor).[72,73] A large, prospective, nonrandomized study is underway to investigate this novel treatment option.

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Section V

CARDIOVASCULAR DISORDERS

Chapter 91
HEMODYNAMIC MONITORING

A. Rhodes • R. M. Grounds • E. D. Bennett

KEY POINTS

1. Hemodynamic monitoring now plays a major role in assessing and managing critically ill patients.
2. Arterial lines provide not only a continuous systemic pressure display but also provide easy access for blood gas analysis and other laboratory tests.
3. Central venous lines provide useful information from careful interpretation of waveforms. This information is usually used to guide fluid therapy. Unfortunately there is no threshold value of central venous pressure that can differentiate patients who will respond to a fluid challenge from those who will not.
4. The pulmonary artery flotation catheter is able to measure the cardiac output, pressures in the right atrium and pulmonary arteries, and the mixed venous oxygen saturation. Modern catheters perform all of these functions on a semicontinuous basis and can also provide information about right ventricular volumes and ejection fraction.
5. Transesophageal Doppler is a relatively noninvasive technique for the rapid beat-to-beat estimation of stroke volume and cardiac output. This can generally only be used in sedated and ventilated patients.
6. Pulse contour analysis of arterial waveforms provides beat-by-beat measurement and variability of stroke volume and cardiac output. There are a variety of proprietary monitors utilizing this technology. They all need calibration against an independent and accurate method of determining cardiac output.
7. The noninvasive methods of NICO and electrical bioimpedance are not widely used, and their accuracy is still unproven.
8. All of these techniques can be used to measure cardiac output and tissue oxygenation. Their therapeutic utility depends on correct training in their use and appropriate interpretation of the data they provide. Therapeutic decisions based on data obtained from hemodynamic monitors must also take into account information obtained from physical examination and laboratory results.
9. The use of a particular method of monitoring should be adapted to the type of patient and is largely dependent on available technical expertise, cost effectiveness, and individual preference in each unit.
10. Despite widespread use of these technologies there are limited data showing clinical benefit and thus their use should be weighed against their potential disadvantages and cost.

Hemodynamic monitoring is the intermittent or continuous observation of normal or altered physiologic parameters pertaining to the circulatory system with a view to early detection of need for therapeutic intervention. It also consists in observing how the cardiovascular system responds to illness, injury, and therapeutic intervention. Invasive hemodynamic monitoring has traditionally been within the realm of the ICU or operating theater, but attempts are now being made to improve noninvasive techniques and validate their use in other clinical settings.

The techniques of hemodynamic monitoring are evolving quickly, particularly over the past few years, and will undoubtedly continue to do so in the next decade. Consequently there are a number of different types of equipment utilizing a variety of different physical principles available for use in the ICU. The use of a particular method of monitoring should be adapted to the type of patient and is largely dependent on available technical expertise, cost effectiveness, and individual preference in each unit.

The primary objective of hemodynamic monitoring is to ensure that the patient is achieving an optimal tissue perfusion and oxygen delivery while maintaining adequate mean arterial pressures. Ideally targeting such goals should lead to significant reduction in morbidity and mortality. There is now evidence to show that such interventions can lead to reduced morbidity and mortality in some critically ill patients.[1-3]

ARTERIAL PRESSURE MONITORING

Noninvasive measurement of blood pressure is one of the most widely undertaken procedures in clinical medicine. Invasive techniques are more commonly employed in intensive care patients for several reasons. Most importantly, the accuracy provided by intra-arterial lines is vital in achieving optimal mean arterial pressure in critically ill patients when they are hemodynamically unstable. In addition, continuous surveillance of arterial pressure is of paramount importance when vasoactive agents are used. Furthermore, frequent noninvasive arterial pressure monitoring adds to the discomfort of the patient. Finally, an arterial line also permits frequent blood gas measurements.

Historically, it has been relatively easy to measure pressure in the major peripheral arteries. Reliance has therefore

been put on the maintenance of systemic pressure under the assumption that adequate pressure will also provide adequate flow and thus adequate tissue perfusion.

Studies in intensive care patients where the focus has been the maintenance of blood pressure have not been particularly fruitful.[1,2,4] Hypotension is usually defined as a systolic pressure less than 90 mm Hg or a mean pressure less than 65 mm Hg.[5] Most intensivists accept that pressure needs to be kept at a level that allows adequate tissue perfusion particularly of the major organs and that the maintenance of flow is paramount.

Interpretation of the changes seen in the arterial waveform in relation to changes in intrathoracic pressure can now also give information about whether the patient is likely to respond to a fluid challenge.[6-9] A greater than 10% or 12% variability of systolic pressure and/or pulse pressure caused by the positive pressure associated with peak inspiration indicates that the patient is probably hypovolemic and is likely to respond to fluid resuscitation. This is an important technologic development because occult hypovolemia is probably not uncommon in critically ill patients and if unrecognized is likely to contribute to an increase in both morbidity and mortality.

CENTRAL VENOUS PRESSURE

Central venous pressure (CVP) is the intravascular pressure in the great thoracic veins, measured relative to atmospheric pressure. It is conventionally measured at the junction of the superior vena cava and the right atrium and provides an estimate of the right atrial pressure. The CVP is normally used as a marker of volemic status or preload.

The CVP is influenced by the volume of blood in the central venous compartment and also the compliance of that compartment (Table 91-1). Starling demonstrated the relationships between CVP and cardiac output and also between the venous return and CVP.[10] By plotting the two relationships on the same set of axes it can be seen that the "ventricular function curve" and the "venous return curve" intersect at only one point, demonstrating that if all other factors remain constant, that is, if nothing happens to alter the shape of either of the two curves, a given CVP can, at equilibrium, be associated with only one possible cardiac output and, similarly, a given cardiac output (or venous return) will, at equilibrium, be associated with a specific CVP (Fig. 91-1). Both curves can of course be affected by a number of factors: total blood volume and the distribution of that blood volume between the different vascular compartments (determined by vascular tone) will affect the venous return curve. The inotropic state of the right ventricle will affect the shape of the ventricular function curve. When any one of these factors is altered there will be an imbalance between cardiac output and venous return that will persist for a short time until a new equilibrium is reached at a new central venous blood volume and/or an altered central venous vascular tone.

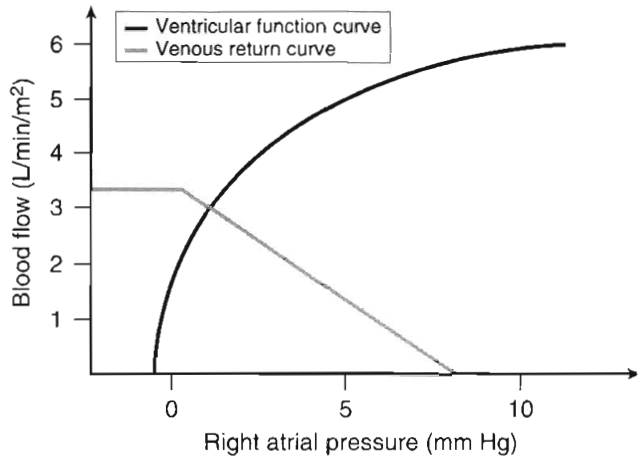


FIGURE 91–1. Ventricular function and venous return curves.

The normal CVP exhibits a complex waveform as illustrated in Figure 91-2. The a wave corresponds to atrial contraction and the x descent to atrial relaxation. The c wave that punctuates the x descent is caused by the closure of the tricuspid valve at the start of ventricular systole and the bulging of its leaflets back into the atrium. The v wave is due to continued venous return in the presence of a closed tricuspid valve. The y descent occurs at the end of ventricular systole when the tricuspid valve opens and blood once again flows from the atrium into the ventricle. This normal CVP

TABLE 91–1. FACTORS AFFECTING THE MEASURED CENTRAL VENOUS PRESSURE

- Central venous blood volume
  - Venous return/cardiac output
  - Total blood volume
  - Regional vascular tone
- Compliance of central compartment
  - Vascular tone
  - Right ventricular compliance
    - Myocardial disease
    - Pericardial disease
    - Tamponade
- Tricuspid valve disease
  - Stenosis
  - Regurgitation
- Cardiac rhythm
  - Junctional rhythm
  - Atrial fibrillation
  - Atrioventricular dissociation
- Reference level of transducer
  - Positioning of patient
- Intrathoracic pressure
  - Respiration
  - Intermittent positive-pressure ventilation
  - Positive end-expiratory pressure
  - Tension pneumothorax

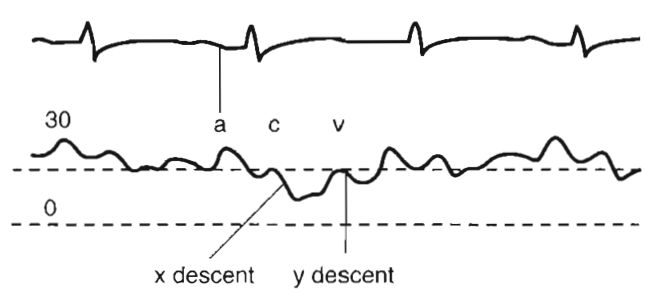


FIGURE 91–2. Central venous pressure waveform. Central venous pressure waveform from a ventilated patient *(bottom)* with time-synchronized electrocardiogram (ECG) trace *(top)*. The a wave represents atrial contraction and occurs immediately after atrial depolarization as represented by the p wave on the ECG. The c wave represents bulging of the tricuspid valve in early ventricular systole and is followed by the v wave, caused by atrial filling during ventricular systole.

TABLE 91–2. DISEASE STATES THAT MODIFY THE CENTRAL VENOUS PRESSURE WAVEFORM

- In atrial fibrillation the a wave is lost and the c wave may become more prominent.
- In the presence of atrioventricular dissociation or junctional rhythm when atrial contraction may occur during ventricular systole, extremely tall cannon a waves occur due to atrial contraction against a closed tricuspid valve.
- In tricuspid regurgitation blood is ejected backward during ventricular systole from the right ventricle into the right atrium. This produces a large fused c-v wave on the central venous pressure trace.
- In tricuspid stenosis, forward movement of blood from the right atrium into the ventricle occurs against a greater than normal resistance leading to an accentuated a wave and an attenuated y descent.
- Similarly, if right ventricular compliance is decreased by either myocardial or pericardial disease the a wave will be accentuated.
- With pericardial constriction a short steep y descent will also be seen that allows differentiation from cardiac tamponade where the central venous pressure will be monophasic with a single x descent.

waveform may be modified by a number of pathologic processes (Table 91-2).

If the CVP is to be used as an index of cardiac preload, the end-diastolic pressure at end expiration must be identified. The c wave marks the closure of the tricuspid valve at the beginning of ventricular systole, and immediately before its onset the measured pressure should be equivalent to the right ventricular end-diastolic pressure (except in the case of tricuspid stenosis in which a pressure gradient will always exist between the two chambers). Where no c wave is clearly visible it is conventional to take the average pressure during the a wave. Where no a wave is visible (e.g., in atrial fibrillation) the pressure at the Z point (that point on the CVP waveform that corresponds with the end of the QRS complex on the electrocardiogram) should be used.

Taking all these factors into account, it is perhaps not surprising that the CVP will not provide a reliable estimate of preload in critically ill patients. The CVP correlates poorly with overall volemic status, right ventricular end-diastolic volume, stroke index, or an individual patient's response to a fluid challenge.[11] It is perhaps best used in non–critically ill patients when it can provide an estimate of the components to right ventricular filling and venous return and therefore can be used to guide fluid challenges by following the trend changes in the variable.

THE PULMONARY ARTERY CATHETER

Continuous, reliable, and accurate pressure and flow monitoring of cardiac performance helps in the early initiation of appropriate therapy toward precise hemodynamic goals. The pulmonary artery catheter with its measured and derived parameters (Tables 91-3 and 91-4) helps to direct therapy in the critically ill who balance their physiology precariously. The first double-lumen, balloon-tipped, flow-directed catheter was designed by Swan and Ganz in 1970.[12] Thereafter, there have been several modifications to the pulmonary artery catheter, which now enables the continuous monitoring of cardiac output from a thermodilution technique, of intravascular pressures, and of mixed venous oxygen saturation.

The pulmonary artery catheter is used to gain a comprehensive overview of the circulation. Information can be

TABLE 91–3. PARAMETERS MEASURED USING THE PULMONARY ARTERY CATHETER

- Pulmonary artery pressure
- Central venous pressure
- Cardiac output
- Pulmonary artery saturation
- Mixed venous oxygen saturation
- Core temperature

obtained about the preload, contractility, and afterload of the heart. Modern pulmonary artery catheters also measure the mixed venous oxygen saturation, enabling the clinician to make a judgment about the balance between the oxygen supply and demand. With this information, therapy can be tailored to the individual patient's requirements.

Once correctly positioned, the balloon tip is inflated temporarily occluding the pulmonary artery. Transducing the catheter port just distal to the balloon provides the pulmonary capillary occlusion pressure. The pressure in the left atrium becomes the main determinant of pressure distal to the inflated balloon because a static column of blood links the two points across the pulmonary capillary bed. This occlusion pressure therefore can provide an estimate of left ventricular preload. The accurate recognition of the waveform indicating the occlusion pressure is vital; however, the ability of clinicians to recognize this waveform is poor.[13-15] The catheter must be in the correct position and the point at the end of expiration must be identified to exclude interference from extravascular intrathoracic pressures.

For the pulmonary capillary occlusion pressure to give an accurate estimation of left ventricular preload, a number of criteria must be met:

- No impedance to flow across the pulmonary capillary beds
- No disease of the mitral valve
- A linear relationship between pressure and volume (compliance) in the left ventricle

Many of these criteria are not valid in the critically ill and thus much like with the CVP the pulmonary capillary occlusion pressure represents only a poor marker of systemic preload.

The appropriate use of the pulmonary artery catheter relies on the user achieving an adequate level of cardiac output for any given situation. The cardiac output can be increased by increasing the preload of the heart titrated from the pulmonary artery occlusion pressure (Table 91-5) and then by manipulation of either the right ventricular or left ventricular afterload. The adequacy of the cardiac output can be assessed in relationship to the body's overall energy balance by a coordinated assessment of cardiac output and mixed venous oxygen saturation.

TABLE 91–4. PARAMETERS CALCULATED USING THE PULMONARY ARTERY CATHETER

- Systemic vascular resistance
- Stroke volume
- Oxygen delivery
- Oxygen consumption
- Pulmonary vascular resistance
- Left ventricular stroke work index
- Right ventricular stroke work index

TABLE 91–5. NORMAL VALUES OF CARDIAC PRESSURES OBTAINED FROM A PULMONARY ARTERY CATHETER IN A SPONTANEOUSLY BREATHING PATIENT

	Mean (mm Hg)	Range (mm Hg)
Right atrium	4	3-6
Right ventricle		
Systolic	25	20-30
Diastolic	4	2-8
Pulmonary artery		
Systolic	25	20-30
Diastolic	10	5-15
Mean	15	10-20
Pulmonary artery occlusion pressure	10	5-14

The mixed venous oxygen saturation is the venous saturation of oxygen in the pulmonary artery. It enables a quantification to be made of the overall oxygen extraction of the blood. The normal value for this is in the region of 70% to 75%. Any decrease in this variable is due to either a decrease in oxygen delivery or an increase in oxygen utilization. A thorough understanding of the factors that derive these variables therefore enables a complete understanding of the circulatory dysfunction for any given patient.

In recent years use of the pulmonary artery catheter has been surrounded by controversy (Table 91-6) after the publication of a large observational study linking it with a poor outcome.[16] It is still unclear whether the catheter itself is responsible for the decreased survival rate seen in this study or whether the patients who were treated with the use of this tool were in fact sicker[17] or the measurements obtained by the clinicians were not accurate enough to appropriately guide therapy. The one fact that is now incontrovertible is that the appropriate use of the variables measured from the pulmonary artery catheter is the single most important fact. Unfortunately, there is often little consensus as to how to use these variables and, therefore, the controversy still exists.

PULSE CONTOUR ANALYSIS

Analysis of the arterial pulse wave contour obtained from an intra-arterial line can provide a great deal of information over and above just the value for arterial pressure. This has led to the development of technologies for the continuous monitoring of cardiac output obtained by analyzing the pulse wave contour obtained from intra-arterial catheters placed in either the radial or femoral arteries.

TABLE 91–6. COMPLICATIONS ASSOCIATED WITH THE PULMONARY ARTERY CATHETER

Complications Associated with Catheter Insertion	
Minor arrhythmias	48%
Sustained arrhythmias	Uncommon
Arterial puncture	1%
Pneumothorax	1%
Complications When Catheter Is in Place	
Infection of insertion site	0-22%
Catheter-related sepsis	2%
Mural thrombus	28-61%
Pulmonary infarction	0.1-7%
Rupture of pulmonary artery	<0.1%
Death	<0.1%

Arterial pulse contour analysis is a technique of measuring and monitoring stroke volume on a beat-to-beat basis from the arterial pulse pressure waveform. This has several advantages over existing technologies, because the majority of critically ill patients already have arterial pressure lines transduced, allowing the technique to rapidly monitor changes in stroke volume and cardiac output on an almost continuous basis.

The fluctuations of blood pressure around a mean value are caused by the volume of blood (the stroke volume) forced into the arterial conduit by each systole.[18] The magnitude of this change in pressure—known as the pulse pressure—is a function of the magnitude of the stroke volume.

A number of factors exist that have made the transition of this concept into clinical reality technically challenging:

- The compliance of the aorta is not a linear relationship between pressure and volume. This nonlinearity prevents any simple approach for estimating volumes from the pressure change. There needs to be correction for this nonlinearity for any individual patient.[19]
- Wave reflection. The pulse pressure measured from an arterial trace is actually the combination of an incident pressure wave ejected from the heart and a reflected pressure wave from the periphery. To calculate the stroke volume, these two waves have to be recognized and separated. This is further complicated by the fact that the reflected waves change in size depending on the proximity of the sampling site to the heart and also the patient's age.
- Damping. As the change in pressure around a mean value describes the stroke volume, accurate pressure measurements are imperative. Unfortunately, pressure transducer systems used in routine clinical practice often suffer from being either underdamped or overdamped, leading to imperfect waveforms and measurements.
- Aortic flow during systole. Although the filling of the aorta is on an intermittent pulsatile basis, the outflow tends to be more continuous.

Despite these limitations a number of companies have developed systems to measure stroke volume from pulse contour techniques. Each of these companies has had to develop methods of calibrating the pulse contour changes for these factors on individual patients. This has been achieved with either transpulmonary thermodilution (PiCCO)[20] or lithium dilution (LiDCO)[21] methods. Whichever method is utilized, there is good clinical precision and accuracy demonstrated in a number of studies when compared with pulmonary artery catheterization.[22-24]

ESOPHAGEAL DOPPLER

The 19th century physicist Christian Doppler described the effect that bears his name, demonstrating that the frequency of signal transmitted toward or reflected from a moving object is altered proportionally to the velocity of the object. This observation has been widely used for measuring the speed of moving objects ranging from stars to cars to red blood cells.

Transcutaneous Doppler ultrasound is in general clinical use for measuring blood velocity in both peripheral and central veins and arteries. In the past 10 years or so the

technology has been further developed to measure blood velocity in the descending aorta from which cardiac output can be calculated. The two most commonly used commercially systems both use a flexible probe, which is inserted down into the esophagus to a length of approximately 40 cm from the mouth.

One system (Deltex CardioQ[25]) has a piezoelectric crystal mounted at 45 degrees on the tip of the disposable probe, which produces ultrasound at a continuous frequency of 4 MHz. The probe tip is adjusted to lie in the esophagus at a point alongside the descending aorta. The ultrasonic beam is transmitted into the lumen of the aorta insonating the moving red cells. Some of the ultrasound is reflected back to the crystal at a frequency proportional to the velocity of the moving red cells.

This shifted frequency is converted to a velocity using the Doppler equation:

$$V = f \times C/(2 \times Fo \times \cos Q)$$

where V = velocity of blood in cm/sec, f = Doppler shifted frequency, Fo = transmitted frequency, C = acoustic velocity in blood, and Q = angle of Doppler beam to blood vessel.

The velocity of the red blood cells thus obtained is converted to flow using a propriety algorithm, which assumes the cross-sectional diameter of the descending aorta based on a number of factors including age, gender, height, and weight. Because this measurement is made on the descending aorta it does not take into account flow to head and arms, which is assumed to be a constant 30% of the total cardiac output. Beat-by-beat values for cardiac output and stroke volume are calculated, and these values have been shown to correlate well with cardiac output measured by thermodilution.[25]

In contrast, the other commercially available product (Arrow Hemosonics[26]) uses a nondisposable probe over which is placed a disposable sheath; the whole device is then inserted into the esophagus. The pulsed Doppler transducer measures descending aortic red blood cell velocity. This is converted to flow by the continuous measurement of descending aortic diameter, which is obtained from an M mode echo signal provided by a separate transducer incorporated in the probe. Good correlation with independent measurements of cardiac output have also been obtained with this device. This technique allows cardiac output and stroke volume to be measured rapidly and relatively noninvasively and requires less training than required for use of the pulmonary artery catheter.

NICO HEMODYNAMIC MONITORING

The Novametrix noninvasive cardiac output monitor (NICO) measures cardiac output–based changes in respiratory CO_2 concentration caused by a brief period of rebreathing.[27] The measurement of cardiac output is accomplished by interpreting data collected by proprietary sensors that measure flow, airway pressure, and CO_2 concentration and then combining these signals to calculate CO_2 elimination. Using these variables, a technique known as Fick partial rebreathing is applied to calculate cardiac output. NICO can only be used effectively with mechanically ventilated patients in the operating room, ICU, or emergency department.

Potentially this device provides a completely noninvasive measurement of cardiac output. Its accuracy and reliability in critically ill patients is not yet proved, however, because clinical validation studies are not yet complete.[28]

ELECTRICAL IMPEDANCE CARDIOGRAPHY TECHNOLOGY

Electrical impedance cardiography technology measures the basal chest electrical impedance or resistance to flow in ohms.[29] The change of impedance across the chest wall is related to the change of flow of blood throughout the chest cavity. The impedance dz/dt (dz = change in impedance, dt = change in time) is produced by change in blood flow and volumes in the ascending aorta.

In devices using baseline impedance, large amounts of thoracic fluid such as in severe pulmonary edema may interfere with the impedance signal and dampen the waveform. The latest methods are baseline impedance independent. They provide continuous trend of heart rate and stroke volume and give derived cardiac output and index using stroke waveform morphology. Recent models of electrical impedance cardiography use advanced waveform morphology analysis to measure a filling index, the trend of which may be useful in monitoring response to therapy. Unfortunately, in view of its major limitations, its reliability in critically ill patients is very limited.

CONCLUSION

There are a number of different technologies for measuring cardiac performance. The simplest and most reliable of these are measurements of pressure. Measurements of flow and other variables of cardiac performance are more complex and less reliable. Individual clinicians must choose the appropriate parameters to measure and be aware of the various limitations of the measuring techniques. It is becoming clear that with the ability to measure the performance of individual parts of the cardiovascular system we are able to target therapy much more specifically, and there are a number of studies suggesting that selectively targeted therapy improves outcome.

ANNOTATED REFERENCES

Boyd O, Grounds RM, Bennett ED: A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 1993;270:2699-2707.

Important trial that demonstrated that perioperative increase of oxygen delivery with dopexamine hydrochloride significantly reduces mortality and morbidity in high-risk surgical patients.

Connors AF Jr, Speroff T, Dawson NV, et al: The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. JAMA 1996;276:889-897.

This prospective cohort study examined the association between the use of right heart catheterization (RHC) during the first 24 hours of care in the ICU and subsequent survival, length of stay, and intensity and cost of care in >5000 critically ill adult patients. The findings suggest that RHC was associated with increased mortality and increased utilization of resources.

Rhodes A, Cusack RJ, Newman PJ, et al: A randomised, controlled trial of the pulmonary artery catheter in critically ill patients. Intensive Care Med 2002;28:256-264.

This study compared the survival and clinical outcomes of critically ill adult patients treated with the use of a pulmonary artery catheter (PAC) to those treated without the use of a PAC. Their results suggest that the PAC is not associated with an increased mortality.

Chapter 92

ACUTE CORONARY SYNDROMES: PATHOPHYSIOLOGY AND DIAGNOSIS

William J. Brady • Chris A. Ghaemmaghami • Anna Baer • Andrew D. Perron

KEY POINTS

1. The electrocardiogram (ECG) is diagnostic for acute myocardial infarction (AMI) in only 50% of patients ultimately diagnosed with acute infarction. The remainder of these AMI patients demonstrate normal, nonspecifically abnormal, and confounding patterns.
2. Serum markers of myocardial injury are of value in ruling out myocardial infarction only when used in serial fashion. In most cases, isolated determinations are of little clinical value.
3. Echocardiography is a valuable tool in the AMI patient, enabling not only the determination of the diagnosis but also an assessment of current function and possible complication.
4. Atypical presentations of AMI are seen in up to 30% of infarct patients. The rate of atypical presentation is highest among the very elderly in whom mental status change, syncope, and other nonspecific symptom-sign complexes are seen.
5. The simultaneous presence of ST segment elevation and pathologic Q wave in the chest pain patient suspected of having AMI does not preclude the consideration for acute reperfusion therapies. Q waves can appear as early as 2 hours after the onset of AMI.

Angina pectoris was recognized in the 18th century; myocardial infarction (MI), however, was described approximately 200 years later. Simultaneous to the identification of MI was the initial introduction and subsequent application of the electrocardiogram (ECG)—the first objective method of assessing the coronary origin of the presentation. Over the next 50 years, angina pectoris and MI were further characterized and diagnosed; unfortunately, however, the management of ischemic heart disease did not progress as significantly. From this point in medical history until the 1960s, management consisted primarily of pain relief coupled with strict bed rest for prolonged periods and management of resultant congestive heart failure (CHF); acute complications such as cardiogenic shock and sudden cardiac death were invariably fatal events. Subsequently, the introduction and widespread use of cardiopulmonary resuscitation, external defibrillation, and antidysrhythmic agents gave the clinician a powerful tool in the management of sudden cardiac death and other malignant dysrhythmias. Overall management, however, was still aimed at the complications of ischemic heart disease rather than the syndrome itself.

With the recognition of the thrombotic nature of the acute coronary syndrome within the last several decades, the stage was set for the next most significant advance in the management of the more acute forms of ischemic heart disease, namely acute myocardial infarction (AMI). Early coronary angiography coupled with intra-arterial administration of streptokinase ushered in the era of acute reperfusion therapies, certainly the most significant advancement in the recent past. Clinicians were now able not only to treat the acute complications of the illness but also to interrupt, if not halt, the primary process, thereby markedly reducing morbidity and mortality.

EPIDEMIOLOGY

In the last decade, approximately 3.5 million people were admitted to the hospital with heart disease. Approximately 20% of these patients had AMI. Myocardial infarction occurs most often in patients over age 40 years. Based on 1989 statistics, an estimated 6.2 million Americans have significant coronary artery disease. Many of these people are at increased risk for sudden death or AMI. Approximately two thirds of sudden deaths from coronary artery disease take place outside the hospital and usually occur within 2 hours after onset of symptoms.

Ischemic heart disease, particularly the acute forms of the illness, is the leading cause of death for adults in the United States today; approximately 50% of these deaths result from sudden cardiac death. Fifteen percent of the fatalities occur prior to age 65 years, with the majority in women. Interestingly, a marked drop in the rate of mortality from ischemic heart disease has been reported over the past 5 decades in the United States, likely resulting from an overall reduction in the incidence of AMI as well as a pronounced decline in the case-fatality rate of established MI.[1,2]

PATHOPHYSIOLOGY

Ischemic heart disease describes the entire spectrum of illness, ranging from acute to chronic entities, related to coronary artery disease, including angina pectoris, AMI, cardiomyopathy, and malignant dysrhythmia. Acute coronary syndromes, an important subset of ischemic heart disease, are defined as unstable angina and AMI. AMI is defined as myocardial

necrosis. Consideration for the diagnosis of AMI requires two of the following three World Health Organization criteria: history of chest pain or equivalent, ECG change, or positive result on serum testing.[3] In the past, AMI was separated into Q wave (transmural) and non-Q wave (nontransmural) events. Recent opinion, however, has suggested that these descriptors fail to adequately describe the event, and the use of the terms ST segment elevation MI and non-ST segment elevation MI is urged.

In the ST segment elevation MI scenario, the patient's symptom presentation and diagnostic ECG provide the criteria for immediate diagnosis; a serum marker will ultimately become positive in the subsequent hours after onset. The non-ST segment elevation MI diagnosis is founded not only on the patient's clinical history and abnormal ECG but also on a positive serum marker. The actual pattern of serum marker abnormality has now become an important component of the definition of AMI. A sudden, marked increase in the serum troponin value that is not sustained over time (i.e., a clear peak in the serum concentration is found) is the first component of this pattern; this increase is then associated with a gradual decrease in the level over the next 7 to 10 days.[4] Importantly, no specific serum troponin value—either relative or absolute—is included in this description. Such elevations in the serum marker would, of course, require an association with a clinical event consistent with acute coronary syndrome, including evolutionary ECG changes. Furthermore, a minor elevation that is sustained over time, again not defined numerically, is not included in the definition as AMI; this scenario likely addresses the noncoronary elevation certain patients may exhibit. Non-ST segment elevation MI and ST segment elevation MI more appropriately describe the process with regard to the clinical presentation, underlying pathophysiology, urgent management considerations, and outcome.

The two primary intracoronary pathophysiologic events underlying the development of acute coronary syndrome include thrombus formation and vasospasm. The acute formation of thrombus within the coronary artery is considered a fundamental component in all forms of acute coronary syndrome. In the setting of either a structurally normal artery or preexisting coronary artery disease, initial endothelial damage produces platelet aggregation and resultant thrombus formation; in most cases, disruption of an atherosclerotic plaque provides the endothelial injury. Occlusion of the coronary artery then results, ranging from minimal, transient, asymptomatic obstruction to complete occlusion with prominent symptomatology—namely AMI. Coronary artery obstruction can lead to myocardial ischemia, hypoxia, acidosis, and ultimately MI.

In most instances of acute coronary syndrome, coronary vasospasm is also noted. The spasm results from both local and systemic events. Local vasoactive substances are released; autonomic nervous system stimulation increases with the proliferation of alpha-receptors; and endogenous sympathomimetic hormones such as epinephrine and serotonin are discharged into circulation—all culminating in coronary artery vasospasm and worsened myocardial perfusion. Coronary artery spasm with subsequent thrombus formation and without significant underlying coronary artery disease is involved in approximately 10% of cases of AMI.

Further myocardial injury at the cellular level occurs during the reperfusion phase, either by spontaneous or by therapeutically induced fibrinolysis. In particular, the introduction of calcium, oxygen, and cellular elements into ischemic myocardium can lead to irreversible myocardial damage that causes reperfusion injury, prolonged ventricular dysfunction (known as myocardial stunning), or reperfusion dysrhythmias. Neutrophils probably play an important role in reperfusion injury, occluding capillary lumens, decreasing blood flow, accelerating the inflammatory response, and resulting in the production of chemoattractants, proteolytic enzymes, and reactive oxygen species.

Additional issues to consider in the pathophysiology of AMI focus on initial, primary illness or concurrent medical events. Such considerations obviously have significant potential for impact on additional diagnostic and therapeutic issues; these presentations are reasonably likely in the undifferentiated, ill critical care patient. The patient with shock of varying cause may experience AMI due to the physiologic insult placed on the heart. For instance, the patient with distributive shock resulting from urosepsis or the patient with hypovolemic shock due to gastrointestinal hemorrhage may experience either non-ST segment elevation or ST segment elevation AMI. Furthermore, metabolic poisons such as cyanide, carbon monoxide, and hydrogen sulfide can disrupt myocardial cellular function, resulting in acute coronary syndrome.

CLINICAL FEATURES

THE HISTORY

The history—and the clinician's interpretation of the available history—is vital. In the critical care unit, however, the patient may be unable to offer a thorough history because of either active illness or instrumentation such as endotracheal intubation. If available, an appropriate history will enable the clinician to focus the evaluation, provide adequate therapies, secure a safe disposition, and minimize the need for additional investigations.

Angina pectoris, the chest pain associated with acute coronary syndrome, by definition includes a sense of choking, strangulation, or constriction. Common descriptions of the discomfort include not only pain but also pressure, squeezing, fullness, or heaviness. In some patients, the symptoms are perceived as gastrointestinal. The location for angina is substernal and left chest with radiation to the shoulders, arms, neck, or jaw. Patients with AMI, however, may also present with pain in the right chest. The duration of chest pain is valuable in determining its cause. Angina pectoris generally is short-lived, lasting less than 15 minutes. Patients with AMI usually experience more than 30 minutes of chest pain. Intermittent, sharp, localized chest discomfort lasting less than several seconds usually is not due to ACS. The symptoms of angina pectoris improve dramatically within 2 to 5 minutes after rest or nitroglycerin. If the pain persists for more than 10 minutes, the diagnosis of acute coronary syndrome or a noncardiac origin should be considered. Caution is also advised in the chest pain patient who appears to respond to antacid; over-reliance on this response as a major decision point in "ruling out" acute coronary syndrome is not encouraged. Many AMI patients experience associated symptoms such as dyspnea, diaphoresis, nausea, vomiting, dizziness, and anxiety; these various symptoms may be the primary complaint in patients presenting with AMI.

Risk factors that increase the likelihood for atherosclerosis and AMI—male gender, family history, cigarette smoking, hypertension, hypercholesterolemia, and diabetes mellitus—should be sought. Personal habits such as cigarette smoking and use of illicit drugs, particularly sympathomimetic substances such as cocaine, should be reviewed. Artificial or early menopause and the use of contraceptive pills may increase the likelihood of ischemic heart disease in women. If a patient has a history of coronary artery disease, a risk factor analysis is unwarranted because the risk of coronary artery disease is 100%.

There has been disagreement over whether these coronary risk factors should be considered in the clinician's medical decision-making. An early report[5] suggested that such factors, which were initially derived because of their ability to predict the development of coronary atherosclerosis and its complications over decades in association with other clinical variables such as ECG interpretation, have minimal predictive value acutely as to whether a patient is currently experiencing an AMI. More contemporary investigation in possible ACS patients suggests that the coronary risk factors, in fact, do have significant predictive value.[6]

Because angina is a visceral sensation that is often diffuse, some patients may have an anginal equivalent syndrome. Such anginal equivalent presentations describe patients who are experiencing acute coronary syndrome yet do not complain of typical chest pain; rather, these patients note atypical pain, dyspnea, weakness, diaphoresis, or emesis—these complaints, in fact, are the manifestation of the acute coronary syndrome event. Patients with altered cardiac pain perception (e.g., the elderly or patients with long-standing diabetes mellitus) are potentially at risk to present with anginal equivalent syndromes. A recent large survey of 434,877 confirmed AMI patients reported that a significant minority of these individuals—approximately 30%—lacked chest pain on presentation, noting only the anginal equivalent complaints.[7] The most frequently encountered anginal equivalent chief complaint is dyspnea, which is found in 10% to 30% of patients with AMI, often due to pulmonary edema.[7-9] Isolated emesis and diaphoresis are quite rare.[8,9]

The geriatric patient may also present atypically with acute weakness (3-8%) and syncope (3-5%).[10] Unexplained sinus tachycardia, bronchospasm resulting from cardiogenic asthma, and new-onset lower extremity edema have all been reported as anginal equivalent presentations for AMI in this age group. Among the very elderly, anginal equivalent syndromes typically involve neurologic presentations with acute mental status abnormalities and stroke. From the perspective of acute delirium, less than 1% of such patients in an emergency department population with altered mentation will be found to have AMI. AMI associated with acute stroke is noted in approximately 5% to 9% of patients.[10]

PHYSICAL EXAMINATION

The physical examination, although crucial to many life-threatening disease processes, is often not helpful in diagnosing AMI; AMI may be suggested, however, in the patient with obvious cardiac dysfunction, manifested by acute pulmonary edema or cardiogenic shock, or both. A change in mental status, poor peripheral perfusion, pronounced tachycardia, hypotension, diaphoresis, rales, jugular venous distension, and S3 and S4 heart sounds often provide evidence of significant myocardial dysfunction in patients with AMI. Patients with evidence of myocardial dysfunction, including S3 heart sound, S4 heart sound, or rales, on initial presentation are at much greater risk for adverse cardiovascular events, including nonfatal AMI, death, stroke, life-threatening dysrhythmia, and the requirement for cardiac surgery.

Caution should be exercised when attributing a chest wall source for pain based on palpation or movement. To safely relate the chest discomfort to a chest wall origin, the pain must be described as sharp or stabbing (i.e., pleuritic in nature) and be completely reproducible by palpation.[11] Up to 15% of patients with AMI may have some form of tenderness on chest wall palpation.[12]

DIAGNOSTIC STRATEGIES

ELECTROCARDIOGRAM

The ECG is used to establish the diagnosis of AMI or other noncoronary ailment, select appropriate therapy, determine the response to treatments, determine the correct in-patient disposition location, and predict risk of both cardiovascular complication and death. The ECG is an extremely powerful diagnostic study, which, if used in appropriate fashion, can guide the clinician in the evaluation of the chest pain patient suspected of AMI. An understanding of its shortcomings, however, in this application will only improve its use. From the perspective of the ECG diagnosis of AMI, the ECG has numerous shortcomings, including the "normal" and "nondiagnostic" interpretations, evolving AMI patterns, the non-ST segment elevation MI ECG presentation, confounding and mimicking patterns, and the isolated acute posterior wall AMI.

The ECG may manifest a range of ECG abnormalities (Fig. 92-1) in the patient with potential AMI, including the prominent T wave, T wave inversion, ST segment depression, ST segment elevation, and QA waves, among other findings. The earliest ECG finding resulting from ST segment elevation MI is the hyperacute T wave, which may appear minutes after the interruption of blood flow; the R wave also increases in amplitude at this stage. The hyperacute T wave, a short-lived structure that evolves rapidly on to ST segment elevation over a 5- to 30-minute period, is often asymmetric with a broad base; these T waves are also associated not infrequently with reciprocal ST segment depression in other ECG leads. Such a finding on the ECG is transient in the AMI patient; either apparent or progressive ST segment elevation is usually encountered at this stage. As the infarction progresses, the hyperacute T wave evolves into the giant R wave, particularly in the anterior wall AMI. The giant R wave is a transition structure from the hyperacute T wave to typical ST segment elevation; it essentially is a large monophasic R wave with pronounced ST segment elevation. Prominent T waves may be seen in patients with AMI as well as hyperkalemia, acute myopericarditis, benign early repolarization, left ventricular hypertrophy, and bundle branch block.

Within moments, the ST segment assumes a more easily recognized morphology. In approximately 85% of ST segment elevation MI patients, the initial upsloping portion of the ST segment is either convex or flat; if the ST segment is flat, it may be either horizontally or obliquely so. An analysis of the ST segment waveform can be particularly helpful in distinguishing

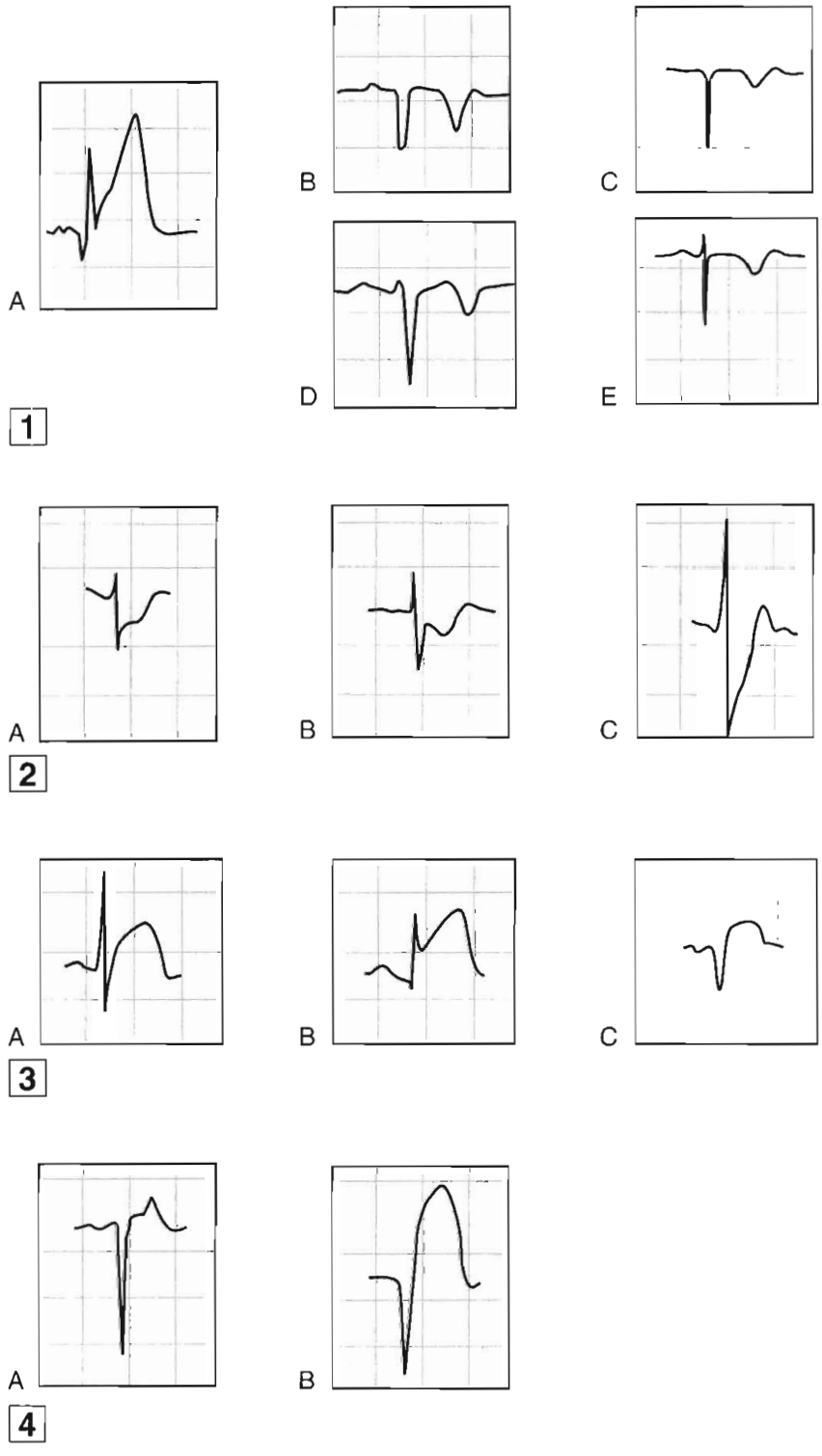


FIGURE 92–1. Electrocardiographic findings of acute myocardial infarction (AMI): **(1)** T wave abnormalities of AMI. **A.** Prominent, "hyperacute," T wave. **B-E.** T wave inversions of non-ST segment elevation MI. **(2)** ST segment depression. **A.** Flat. **B.** Downsloping. **C.** Upsloping. **(3)** ST segment elevation. **A.** Convex ST segment elevation. **B.** Obliquely straight ST segment elevation. **C.** Convex ST segment elevation. **(4)** Pathologic Q waves. **A.** Pathologic Q wave of completed myocardial infarction. **B.** Simultaneous ST segment elevation with pathologic Q wave 2 hours into the course of ST segment elevation MI.

among the various causes of ST segment elevation and identifying the AMI case. This technique uses the morphology of the initial portion of the ST segment/T wave—defined as beginning at the J point and ending at the apex of the T wave. Patients with noninfarctional ST segment elevation (i.e., early repolarization or left ventricular hypertrophy-related change) tend to have a concave morphology of the waveform. Conversely, patients with ST segment elevation due to AMI have either obliquely flat or convex waveforms. The use of this ST segment elevation waveform analysis in emergency room chest pain patients increases the specificity for the AMI diagnosis.[14] This morphologic observation should be used only as a guideline. As with most guidelines, it is not infallible.

Significant ST segment elevation occurring in at least two anatomically oriented leads is the primary ECG indication for fibrinolysis or urgent PCI. In that ST segment elevation represents a significant finding, a brief review of the various causes of ST segment elevation in the chest pain patient is warranted. Unfortunately, ST segment elevation in the chest pain patient less often results from AMI; in fact, only 20% to 30% of chest pain patients will have ST segment elevation MI—the remainder of these patients will have noninfarctional causes of the ST segment elevation.[14,15] Patients with chest pain may present electrocardiographically with ST segment elevation due to AMI, confounding patterns, or masquerading syndromes. In most instances, ST segment elevation resulting from AMI is easily noted. Confounding patterns such as left bundle branch block, ventricular paced rhythms, and left ventricular hypertrophy may obscure the typical ECG findings of AMI as well as produce noninfarctional ST segment elevation, which may lead the uninformed clinician astray. Other ST segment elevation patterns, including benign early repolarization and acute pericarditis, occur in the individual with chest discomfort and may suggest the incorrect diagnosis of AMI, exposing the patient to unnecessary and potentially dangerous therapies.

ST segment depression is generally considered to represent subendocardial, noninfarctional ischemia, although it may be the presenting ECG finding in the non-ST segment elevation MI patient. The morphology of subendocardial ischemic ST segment depression is classically horizontal or downsloping; upsloping ST segment depression is also seen, yet is less often associated with acute ischemia. With subendocardial ischemia, the ST segment depression is often diffuse and can be located in both the anterior and the inferior leads. ST segment depression also occurs as the primary ECG finding in non-ST segment elevation MI as well as a secondary, though important, manifestation in ST segment elevation MI, namely reciprocal ST segment depression; also, ST segment depression in the right precordial leads may represent posterior wall AMI. Nonischemic causes of ST segment depression include digoxin effect and repolarization changes seen in left ventricular hypertrophy, bundle branch block, and ventricular paced rhythm presentations.

Reciprocal ST segment depression, also known as reciprocal change, is defined as ST segment depression in leads separate and distinct from leads reflecting ST segment elevation. Importantly, this form of ST segment depression is not associated with situations in which altered intraventricular conduction produces deviation—such as bundle branch block, left ventricular hypertrophy, and ventricular paced rhythms. Reciprocal change in the setting of a ST segment elevation MI identifies a patient with an increased chance of poor outcome and, therefore, an individual who may benefit from a more aggressive approach. Furthermore, its presence on the ECG supports the diagnosis of AMI with very high sensitivity and positive predictive values greater than 90%. The use of reciprocal change in both prehospital and emergency room chest pain patients increases the diagnostic accuracy in the ECG recognition of AMI.[16,17] Reciprocal change is seen in approximately 75% of cases of inferior wall AMI and much less often in cases of anterior wall MI (30%).

Inverted T waves produced by acute coronary syndrome are classically narrow and symmetric; they are morphologically characterized by an isoelectric ST segment that is usually bowed upward (i.e., concave) and followed by a sharp symmetric downstroke. The terms *coronary T wave* and *coved T wave* have been used to describe these T wave inversions. Prominent, deeply inverted, and widely splayed T waves are more characteristic of the noninfarctional, nonischemic conditions such as cerebrovascular accident. An important subgroup of patients with noninfarctional angina often have deep T wave inversions in the precordial leads (V1 through V4); the T wave may also be biphasic in this same distribution. The syndrome, termed the left anterior descending T wave or Wellen syndrome, is important to recognize because it is highly specific for stenosis of the left anterior descending coronary artery with anterior wall AMI as the natural history. T wave inversion can also be caused by non-ST segment elevation MI and evolving states of ST segment elevation MI.

In general, Q waves represent established myocardial necrosis and rarely are the primary finding in the AMI patient. Pathologic Q waves may be caused by a previously unrecognized prior infarction, or conversely, a prior MI may mask ischemic extension in the same anatomic location. Q waves usually develop within 8 to 12 hours after a transmural AMI, yet they can be noted as early as 1 to 2 hours after the onset of complete coronary occlusion. As such, the simultaneous presence of Q waves and ST segment elevation does not preclude consideration of fibrinolytic therapy.

The ECG changes discussed previously may all be encountered in the AMI patient. Two basic ECG presentations of AMI, the ST segment elevation MI and non-ST segment elevation MI, warrant further comment. The ST segment elevation MI presents with ST segment elevation in at least two anatomically contiguous leads—a reasonably straightforward principle. On the contrary, the non-ST segment elevation MI can manifest with a range of ECG abnormalities, representing a diagnostic challenge and a potential failing of the ECG. Patients with non-ST segment elevation MI may present with obvious abnormality, such as ST segment depression or T wave abnormalities; these findings can be transient. In these cases, symmetric convex downward ST segment depression or inverted or biphasic T waves are characteristically seen. Alternatively, the ECG may only reveal nonspecific findings or appear initially normal. Lastly, the non-ST segment elevation MI patient may demonstrate only a confounding pattern such as left bundle branch block. Regardless of the non-ST segment elevation presentation, the non-ST segment elevation MI patient is diagnosed with AMI only after the return of a positive serum marker.

Several ECG patterns confound the diagnosis of AMI, including left bundle branch block, ventricular paced rhythms, and left ventricular hypertrophy. In the patient with left bundle branch block, the anticipated or expected ST segment/T wave configurations are discordant, directed on the opposite side of the isoelectric baseline from the terminal

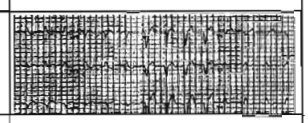
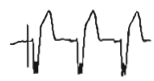
ECG Finding	Comment	Example
New LBBB	New onset and with appropriate clinical correlation	
Concordant ST Segment Elevation	ST segment elevation >1 mm // concordant with QRS complex	
Concordant ST Segment Depression in leads V1, V2, and / or V3	ST segment depression >1 mm in leads V1, V2, or V3	
Discordant ST Segment Elevation	ST segment elevation >5 mm discordant with QRS complex	

FIGURE 92–2. Electrocardiographic indications for reperfusion therapy in the left bundle branch block presentation.

portion of the QRS complex. This relationship is called QRS complex-T wave axes discordance (Fig. 92-2).[18,19] Loss of this discordance in patients with left bundle branch block may imply AMI. The clinician must realize, however, that the ECG is markedly compromised as a diagnostic tool in this setting. As with the left bundle branch block pattern, the right ventricular-paced rhythm and left ventricular hypertrophy patterns can both mimic and mask the manifestations of AMI. In ventricular paced rhythms, the principle of appropriate discordance should also be followed. An inspection of the ECG in patients with ventricular paced rhythms must be performed, looking for a loss of this QRS complex-T wave axes discordance. Loss of this normal discordance in patients with ventricular paced rhythms can suggest AMI.[20] Left ventricular hypertrophy is not uncommonly encountered on the ECG of chest pain patients. Its presence on the ECG, particularly the repolarization changes that alter the morphology of the ST segment and/or the T wave, can confound the early evaluation. These repolarization changes are seen in approximately 70% of cases and represent the new norm for the patient with electrocardiographic left ventricular hypertrophy.[21] Left ventricular hypertrophy is associated with poor R wave progression, producing a QS pattern in the right to mid-precordial leads. In most instances, the ST segment elevation is seen here along with prominent T waves. ST segment depression with inverted T wave is also seen in the lateral leads.

Several additional ECG tools can be employed by the clinician to further evaluate the chest pain patient suspected of AMI. These tools include additional ECG leads and ST segment surveillance. The additional-lead ECG improves the diagnostic power of the standard 12-lead ECG; with the addition of three leads, the 15-lead ECG is produced. In the 15-lead ECG, the posterior leads V8 and V9 image the posterior wall of the left ventricle (posterior AMI) and lead V4R evaluates the right ventricle (right ventricular infarction). The use of the additional leads can not only confirm the presence of AMI but also alter treatment decisions in acute coronary syndrome patients. In a study of all emergency room chest pain patients initially evaluated with a 12-lead ECG, Brady el al[22] reported that the 15-lead ECG provided a more accurate description of myocardial injury in those patients with AMI yet failed to alter rates of diagnoses or the use of reperfusion therapies or change disposition locations. Looking at a more select population of chest pain patients, Zalenski and colleagues[23] investigated the use of the 15-lead ECG in chest pain patients with a moderate to high pretest probability of AMI who were already identified as candidates for critical care admission. In this study, the authors reported an approximate 12% increase in sensitivity for the diagnosis of AMI. Potential clinical indications for obtaining the 15-lead ECG in chest pain patients include: (1) ST segment depression in leads V1 through V3; (2) ST segment elevation MI of the lateral or inferior wall; (3) isolated ST segment elevation in lead V1 or ST segment elevation in leads V1 and V2; and (4) the inferior or lateral AMI complicated by hypotension on presentation or after preload reducing medication administration. Figure 92-3 is an example of a 15-lead ECG with inferoposterior AMI with right ventricular infarction. Note the ST segment elevation in leads II, III, and aVf (inferior AMI), RV4 (right ventricular infarction), and leads V8 and V9 (posterior AMI); the ST segment depression with prominent R wave is also seen in leads V1 to V3.

Serial monitoring of the ST segment can also aid the clinician in the diagnosis of AMI as well as monitor the response to therapy. This can be accomplished using two different approaches: serial 12-lead ECG acquisition or ST segment trend monitoring. Either technique can demonstrate the evolution of ST segment/T wave changes in a number of different clinical scenarios, including the initially nondiagnostic ECG, the continuous chest pain patient with an initially

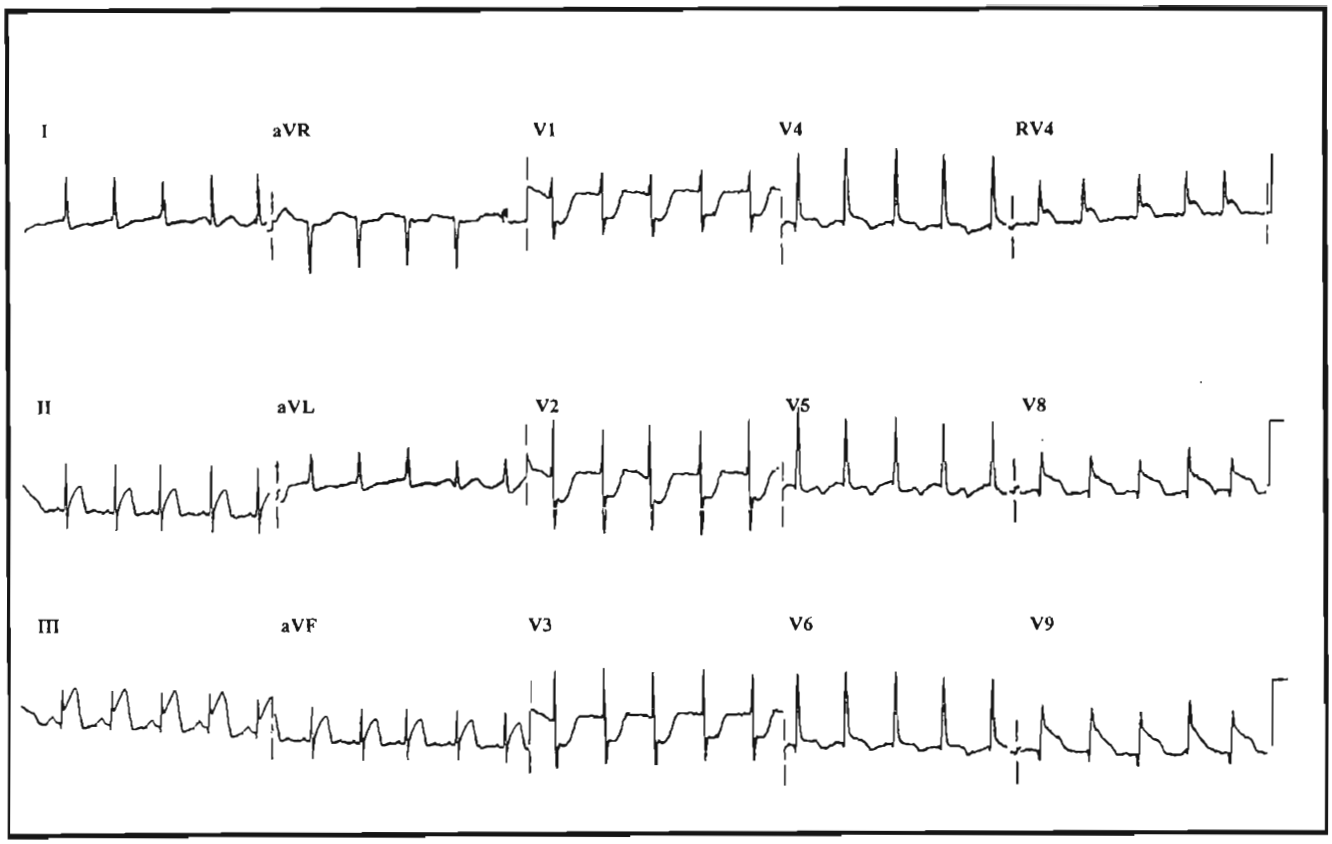


FIGURE 92–3. A 15-lead electrocardiogram showing inferoposterior acute myocardial infarction (AMI) with right ventricular (RV) infarction. Note the ST segment elevation in leads II, III, and aVf (inferior AMI), RV4 (RV infarction), and leads V8 and V9 (posterior AMI). The ST segment depression with prominent R wave is also seen in leads V1 to V3.

nondiagnostic ECG, and the individual with a confounding or masquerading ECG pattern. This increased level of monitoring may provide earlier evidence of coronary occlusion in patients with non-AMI acute coronary syndrome presentations. Potentially, serial ECGs can furnish an increased level of ECG monitoring in patients presenting with chest pain and a nondiagnostic ECG on presentation.[24-28] In the coronary care unit setting, serial ST segment surveillance initiated at admission offers additional clinical data with approximately 20% of patients revealing dynamic ECG change in the early stages of the hospital course.[29] ST segment monitoring has proved to be an effective method for noninvasive evaluation of reperfusion after delivery of fibrinolytic therapy in multiple investigations. In one series, Krucoff and colleagues[28] noted that angiographically proven reperfusion was detected with a sensitivity of 89% using serial ST segment trend monitoring, with a corresponding specificity of 82%.

SERUM MARKERS

The elevation of serum cardiac markers over several days of hospitalization has traditionally been the standard method for diagnosing AMI. Whereas creatinine phosphokinase-MB fraction once was the typical marker used by most clinical laboratories to indicate myocardial necrosis, now the troponins are the most commonly used serologic tests. Previously, detection of AMI by enzyme elevations over 48 to 72 hours was sufficient to establish the diagnosis of AMI. Because of the evolution of acute interventional modalities, however, significant time-sensitive pressure now exists to identify patients with AMI earlier after onset of the ailment. Particularly in patients with a nondiagnostic ECG, early serum markers of myocardial necrosis have the potential to alter the diagnostic course and treatment plans. Further, there are now clear data that indicate that elevations in serum markers, even in those not meeting traditional criteria for AMI, independently identify those patients at risk for poor outcome.[30-32]

Creatinine phosphokinase is an enzyme found in large quantities in cardiac and skeletal muscle. After AMI, increases in serum creatinine phosphokinase are detectable within 3 to 8 hours, with a peak at 12 to 24 hours after injury; assuming a single, one-time event, the levels will normalize within 3 to 4 days. The major problem that reduces the clinical utility of total creatinine phosphokinase as a diagnostic marker involves the widespread distribution of the enzyme in the body—not only in cardiac muscle but also in skeletal muscle, brain, kidney, lung, and gastrointestinal tract. The current major utility of the total creatinine phosphokinase determination in acute cardiac care is screening, to evaluate the need to perform the far more specific creatinine phosphokinase-MB assay.

Myocardial cells are by far the most abundant potential sources of creatinine phosphokinase-MB, and, as such, the

appearance of creatinine phosphokinase-MB in the serum is highly suggestive of AMI. Unfortunately, skeletal muscle does contain small amounts of creatinine phosphokinase-MB, particularly the musculature about the pelvis. As a consequence, abnormal creatinine phosphokinase-MB elevations can be seen in patients after trauma, those with muscular dystrophies, myositis, or rhabdomyolysis, and in those who have undertaken vigorous exercise.

The kinetics of creatinine phosphokinase-MB parallel those of total creatinine phosphokinase. In the setting of AMI, the enzyme is released and is detectable in the serum as early as 3 hours after onset of the necrosis. Creatinine phosphokinase-MB characteristically peaks at 12 to 24 hours and normalizes within 2 to 4 days after injury. Elevated creatinine phosphokinase-MB values identify a patient at considerable risk for poor outcome. As with total creatinine phosphokinase measurement, however, the peak creatinine phosphokinase-MB value does not correlate well with infarct size; in fact, studies demonstrate that an elevated creatinine phosphokinase-MB level is associated with a poor prognosis, regardless of the magnitude of the elevation.

The sensitivity of a single creatinine phosphokinase-MB determination in diagnosing AMI is entirely dependent on the elapsed time from chest pain onset. Values obtained within 3 hours of onset are very poor diagnostic tools, with a sensitivity of only 25% to 50%. As the time from symptom onset further increases, however, so does the sensitivity for AMI detection, ultimately approaching 100% at 8 to 12 hours.[33,34] False-positive elevations can result from noncoronary disease states such as pericarditis, myocarditis, skeletal muscle disease, rhabdomyolysis, trauma, and exercise.

Two myocardial-specific proteins—myocardial troponin T and troponin I—have become extremely important in the evaluation of patients suspected of having AMI. The cardiac troponins I and T are genetically distinct from those forms found in skeletal muscle, making them highly cardiac-specific markers. The biokinetics of troponin release are related to the location of the protein within the cell. Normally, small quantities of troponins are free in the cytosol, whereas the majority is entwined in the muscle fiber. Following injury, a biphasic rise in serum troponins is seen. This two-component pattern corresponds to the early release of the free cytoplasmic proteins followed by a prolonged rise with disruption of the actual muscle fiber, resulting in a sustained release of the troponins for approximately 7 days. Serum troponin concentrations begin to rise measurably in the serum at about the same time as creatinine phosphokinase-MB elevations become detectable—as early as 3 hours after onset—and therefore offer no particular benefit over the creatinine phosphokinase-MB regarding early detection of the event; the troponins, however, remain elevated for prolonged periods of time, ranging from 7 to 10 days. The cardiac-specific troponins are highly sensitive for the early detection of myocardial injury in patients with AMI. A positive test result is associated with significant risk while negative study (i.e., serial troponins) findings predict low risk.[35]

The sensitivity of the troponins approaches 50% within 3 to 4 hours of the event. The test finding is positive for AMI in about 75% at 6 hours after onset of symptoms; at 12 hours, the test is almost 100% sensitive for AMI.[33] Moreover, the presence of a positive troponin, even in the face of a nondiagnostic ECG and negative creatinine phosphokinase-MB assay, independently confers a prognosis on the patient that is similar to those suffering ST segment elevation MIs.[36,37] Thus, elevated troponin values appear to be excellent indicators of risk of subsequent death, AMI, and acute cardiovascular complications in all acute coronary syndrome patients, even those who do not meet traditional criteria for AMI. A negative test result, however, does not necessarily imply a favorable prognosis. One caveat for the troponins is that a number of systemic diseases can cause elevations in the serum levels of troponins without acute coronary syndrome (Table 92-1).

Myoglobin is attractive as an indicator for myocardial injury, because levels are elevated in the serum within 1 to 2 hours after symptom onset and peak 4 to 5 hours after AMI.[38] The sensitivity of myoglobin for AMI approaches 100% at 3 hours. Myocardial myoglobin is not currently distinguishable immunologically from skeletal muscle myoglobin, however, reducing its specificity to approximately 80% compared with 94% for immunochemical creatinine phosphokinase-MB determination 3 hours after emergency room presentation.[38] As with the troponins, myoglobin level is elevated in patients with renal failure because of reduced clearance, making this marker less useful in a patient population who tends to be at an elevated risk for acute coronary syndrome. Additionally, it also will be elevated in any clinical situation involving the skeletal muscle, such as trauma, exercise, and significant systemic illness.

Medical decision-making regarding serum marker use in the suspected AMI patient is complex. Serum markers are most often used in concert with each other and tested in a serial fashion. Relying solely on the result of a single negative assay can result in a missed diagnosis in up to 74% of patients.[39] Single testing strategies, however, may be of value when the clinician is evaluating a nonspecific presentation with illness course lasting greater than 72 to 96 hours. Trending results over time significantly reduces the chance of a missed diagnosis, particularly in acute presentations of short course. A number of studies support the assertion that the troponins approach 100% sensitivity and specificity for cardiac ischemia at 12 hours following an event.[33] These studies all caution, however, that such elevations will occur only with cell injury; hence, they are not appropriate markers for non-AMI acute coronary syndrome presentations. In the setting of an appropriate clinical history or diagnostic ECG changes, a strategy of serial cardiac marker testing is relatively

TABLE 92–1. DIFFERENTIAL DIAGNOSIS OF SERUM TROPONIN ELEVATIONS

Multiple trauma with shock
Cardiac trauma (contusion, cardioversion, myocardial biopsy, electrical injury)
Acute congestive heart failure
Hypertension
Renal failure
Hypothyroidism
Inflammatory states (myocarditis, Kawasaki disease, sarcoidosis)
Pulmonary embolism
Sepsis
Snake envenomation
Burns
Infiltrative diseases (amyloidosis, sarcoidosis, scleroderma)
Acute neurologic events (cerebrovascular accident, subarachnoid hemorrhage)

Data from Panteghini et al,[40] Wu et al,[41] and Armstrong et al.[42]

straightforward. Depending on the particular investigation employed, the clinician looks for the characteristic rise and fall of serial markers over a time-course for the diagnosis of AMI.[4] Most literature supports such serial testing in the acute setting for a period of 8 to 12 hours to adequately rule out myocardial infarction.[40,41]

The more challenging diagnostic situation is found in the critically ill patient with minimal rise in the serum marker and absence of a distinct cardiac event. It is clear, for instance, that troponin levels can be elevated in patients with renal failure or skeletal muscle diseases in the absence of ischemic coronary artery disease. In the renal failure patient, clinical suspicion of acute coronary syndrome must guide evaluation and management decisions; furthermore, the trending of values over time, seeking the characteristic rise and fall of serial markers as well as comparisons to "baseline" values will also improve the clinician's ability to use these diagnostic tests in appropriate fashion, thereby optimizing care. Patients with significant physiologic injury (e.g., sepsis, acute respiratory failure, multiple trauma, and shock) have also been found to have elevated troponin values. In these populations, the elevated levels correlate with left ventricular function and the presence of organ dysfunction, yet the data addressing hospital survival and length of stay are conflicting.

CHEST RADIOGRAPHY

In the setting of AMI, the chest radiograph does not assist in arriving at the diagnosis; other ancillary studies such as the ECG, serum markers, and echocardiography are the primary investigations. Rather, its use provides important information concerning the appropriate application of therapies (i.e., an evaluation of mediastinal width in the consideration of fibrinolytic agent use and the determination of pulmonary congestion in the consideration of acute parenteral beta-adrenergic blocking therapy). Further, the presence of CHF on the chest radiograph places the patient in a higher risk group of AMI patients who may benefit from an aggressive therapeutic approach.

The chest radiograph is obtained in the vast majority of patients who present with AMI. Evidence of pulmonary congestion is noted radiographically in approximately one third of such patients. Radiographic findings often parallel the clinical examination findings. AMI patients who develop CHF based on physical examination have an increased mortality risk, as reported by the Killip classification; the chest radiograph provides prognostic data. The chronicity of the CHF syndrome may also be suggested by the heart size. Patients who present with AMI complicated by pulmonary edema and who have a normal heart size most often have no past history of CHF. In fact, AMI is the most frequent cause of pulmonary edema with a normal cardiac size. In other instances, patients with AMI who manifest an enlarged cardiac silhouette on the chest radiograph frequently have a preexisting history of CHF, anterior wall infarct, and multiple-vessel coronary artery disease (Fig. 92-4).[42]

ECHOCARDIOGRAPHY

Echocardiography is a very useful diagnostic tool in the cardiac evaluation of the critically ill patient; an adequate echocardiogram is an excellent means of assessment of cardiac function at the bedside, including cardiac function

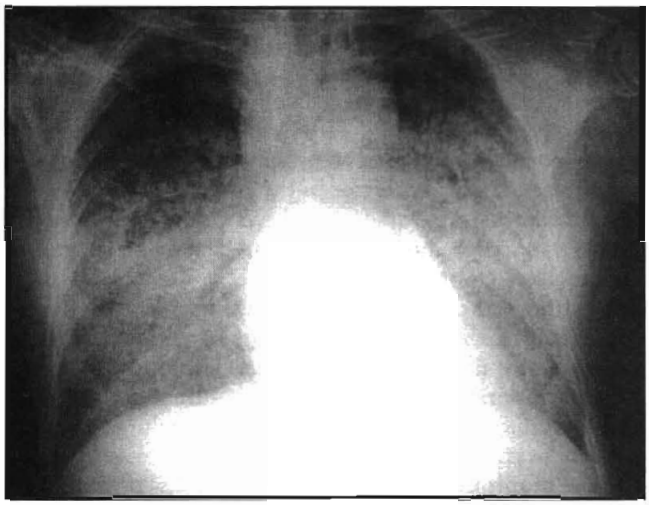


FIGURE 92–4. Chest radiograph showing cardiomegaly and pulmonary edema in an acute myocardial infarction patient with cardiogenic shock and multivessel coronary artery disease.

(ejection fraction) of the left ventricle, general cardiac anatomy, valvular anatomy and function, and the pericardial space. Perhaps most importantly in this application in the AMI patient, transthoracic echocardiography is used to evaluate left ventricular wall motion. The echocardiogram is able to detect regional wall motion abnormalities—an important data point in the clinical evaluation of the potential acute coronary syndrome patient. Chest pain patients with nondiagnostic, mimicking, or confounding ECGs represent a diagnostic problem; two-dimensional echocardiography may provide an answer to this clinical dilemma. The presence of a focal wall motion abnormality in a patient with an appropriate history suggestive of acute coronary ischemia provides strong clinical evidence of acute coronary syndrome, including AMI. In fact, the presence of a regional wall motion abnormality in these patients provides a sensitivity of 88% to 94% for the diagnosis of AMI in the coronary care unit.[43] The recent introduction of contrast echocardiography, the "bubble" echocardiogram, in this setting will only improve its diagnostic utility. In addition, a transthoracic echocardiogram not only allows for the diagnosis of the various mechanical and functional complications of AMI but also affords the opportunity to diagnose other pathology, including issues that may have contributed to the AMI (proximal aortic dissection with involvement of the coronary arteries) or alternative explanations of the chest discomfort.

Body habitus, patient cooperation, and ventilatory status can affect the quality of a transthoracic echocardiogram. Additional limitations include the experience of the operator as well as the expertise of the reader interpreting the study findings. Furthermore, the inability of the two-dimensional echocardiogram to distinguish between myocardial ischemia and myocardial infarction must be recognized by the clinician. Echocardiography is typically less expensive than radionuclide ventriculography and offers more anatomic detail while avoiding the use of radionuclides. Echocardiography can also be performed rapidly in the acute care setting. Transesophageal echocardiography can be performed in patients in whom more definitive information is required, particularly involving the cardiac valves and proximal aorta. The technique is similar, with the notable exception of probe placement, which is into

the patient's esophagus. Compared with transthoracic echocardiography, transesophageal echocardiography offers a more precise image of valvular structure and function. Cardiac functional assessment is otherwise similar to transthoracic echocardiography. In unstable patients suspected of having aortic dissection, a transesophageal echocardiogram can be used at the bedside or in the surgical suite.

Candidates for transesophageal echocardiography must be NPO (nothing by mouth) for the procedure, be completely cooperative, and demonstrate the ability to swallow. Furthermore, these patients must have an adequate platelet count and lack esophageal pathologic conditions, including varices and other causes of upper gastrointestinal bleeding. Patients must receive adequate sedation and analgesia to lessen the discomfort associated with the procedure. As such, patients with potential respiratory compromise must be closely monitored during the procedure; "prophylactic" endotracheal intubation may be necessary in certain instances. Since transesophageal echocardiography is an invasive procedure, it is important to be certain that the information sought cannot be obtained from a transthoracic echocardiogram. Complications of transesophageal echocardiograms include injury to the teeth or mouth, bleeding, respiratory compromise, aspiration, and esophageal perforation.

INVASIVE HEMODYNAMIC MONITORING

Invasive hemodynamic monitoring in the AMI patient includes intra-arterial line placement and right heart catheterization. The need for an arterial line for continuous systemic blood pressure monitoring in the AMI patient is unusual. In most instances, noninvasive blood pressure monitoring coupled with serial, focused examinations of the patient suffice. Potential indications for intra-arterial line placement for continuous systemic blood pressure monitoring include the use of continuous infusion cardioactive medications (inotropic, vasopressor, vasodilator, and antihypertensive agents), cardiogenic shock, recurrent or persistent hypotension unresponsive to appropriate therapy, and severe pulmonary edema.

Right heart catheterization, the placement of a pulmonary artery catheter, allows for precise determination of the patient's hemodynamic status. Such information allows for determination of the cardiac output, vascular resistance, and pulmonary capillary wedge pressure. Although the array of clinical data provided by right heart catheterization is impressive, the vast majority of AMI patients do not require such extensive and invasive hemodynamic monitoring; in fact, many intensivists have questioned the utility of right heart catheterization.[44] More useful monitoring techniques include continuous ECG monitoring (for dysrhythmia), ST segment trend monitoring (for evolution of acute coronary syndrome), and noninvasive blood pressure determinations. Additionally, serial, focused physical examinations provide important clinical data: repeat assessments of the patient's general appearance, mental status, jugular venous pressure, lung fields, and peripheral perfusion provide, in most instances, appropriate and adequate information regarding the patient's hemodynamic status.

In general, a pulmonary artery catheter should be considered in patients with persistent or recurrent systemic hypotension unresponsive to adequate therapy; such patients with concurrent acute CHF can be more closely scrutinized with adjustment of the various therapies. Such monitoring also allows for precise and immediate titration of cardioactive and vasoactive medications to the hemodynamic status. The diagnosis of the various functional and mechanical complications of AMI is best made using the examination and selected, noninvasive investigations (ECG, chest radiograph, and echocardiogram). Potential indications for placement of a pulmonary artery catheter in the AMI patient include cardiogenic shock, recurrent or persistent hypotension unresponsive to appropriate therapy, severe pulmonary edema, the combination of persistent hypotension with pulmonary congestion, concurrent use of intra-aortic balloon counterpulsation, and various complications of AMI (left ventricular rupture, pericardial tamponade, papillary muscle dysfunction, and profound right ventricular infarction).

CARDIAC CATHETERIZATION

Cardiac catheterization, also known as coronary angiography, is used to evaluate the anatomy of the coronary arteries; left ventricular function can also be assessed. Access is usually obtained through the right femoral artery; the left femoral artery and both brachial and radial arteries, however, can be used as well. Once the coronary anatomy has been evaluated, coronary lesions (Fig. 92-5) that are appropriate for intervention can be treated with balloon angioplasty or coronary stent placement, or both. Fractional flow reserve is a technique that can be used to evaluate the significance of a lesion by measuring the pressures proximally and distally to the lesion.

In the critically ill patient, many clinical issues and scenarios exist that can be evaluated and addressed via coronary angiography, including diagnostic and therapeutic considerations. The diagnosis of AMI can be established via coronary angiography, although such information is usually obtained via other, noninvasive means such as the ECG, serum markers, and echocardiogram. In situations in which the diagnosis is in question, however, coronary angiography provides information regarding the status of the coronary arteries and left ventricular function in the AMI setting. Furthermore, the patient who has suffered AMI and experiences recurrent ischemia or continued infarction despite

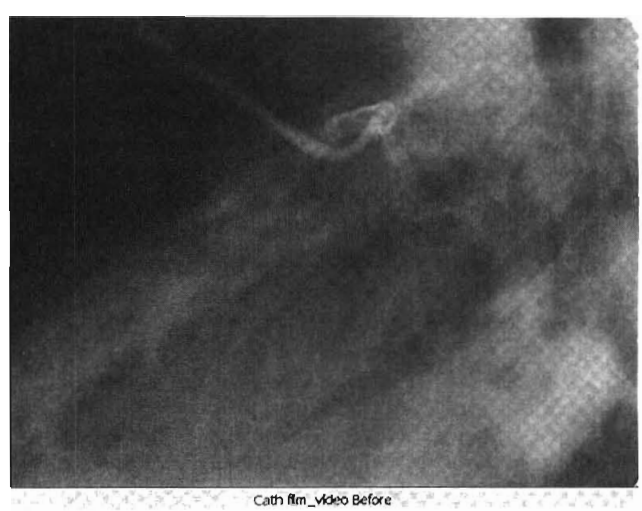


FIGURE 92–5. Coronary angiography with obstructive coronary lesion and thrombus (arrow).

adequate revascularization therapy can be studied in the catheterization laboratory. Current information suggests that rescue angioplasty may be advantageous in patients whose infarct-related arteries fail to reperfuse after fibrinolytic therapy.[45] Some centers routinely catheterize patients after fibrinolytic therapy to determine whether successful reperfusion has occurred and to perform angioplasty if necessary and anatomically feasible. Other centers catheterize patients after fibrinolytic therapy only if there is clinical evidence that the infarct-related artery has failed to open, such as continued chest pain or persistent ST segment elevation. Routine performance of coronary angiography after fibrinolysis for risk stratification prior to discharge represents an additional, though controversial, indication for cardiac catheterization.

The structure and function of both native and prosthetic valves can be assessed at the time of coronary angiography. Additional information obtained in the catheterization laboratory includes right heart catheterization and myocardial biopsy findings. The diagnosis of aortic dissection or aortic aneurysm can also be made in the catheterization laboratory via aortography. If aortic dissection or aneurysm is suspected, however, it should be investigated via computed tomography-angiography or conventional aortography prior to cardiac catheterization.

When preparing a patient for the cardiac catheterization laboratory, several important issues must be considered and addressed, *assuming the clinical situation permits,* including contrast dye allergy, renal function, intravascular volume status, and platelet count and coagulation ability. The physician should obtain a detailed allergy history from the patient. Patients who are allergic to contrast dye or shellfish need to be premedicated with prednisone and diphenhydramine. Also, contrast dye is nephrotoxic; patients who have a history of renal insufficiency may be candidates for *N*-acetylcysteine therapy prior to the study. These patients should also be adequately hydrated prior to receiving dye. Patients should have adequate platelet counts and normal to minimally abnormal coagulation times. Careful consideration must be made prior to sending a patient with thrombocytopenia or coagulopathy for a catheterization procedure. Complications of cardiac catheterization include hemorrhage (both local at the puncture site and regional to the retroperitoneum), pseudoaneurysm, arteriovenous fistula, AMI, stroke, cholesterol embolism, cardiac dysrhythmia, cardiac valve damage, and death.

ANNOTATED REFERENCES

Brady WJ, Perron AD, Martin ML, et al: Electrocardiographic ST segment elevation in emergency department chest pain center patients: Etiology responsible for the ST segment abnormality. Am J Emerg Med 2001;19:25-28.

This study reports the cause of electrocardiographic ST segment elevation in adult chest pain patients presenting to the emergency department. Of note, AMI was an infrequent cause of the ST segment abnormality; the left bundle branch block and left ventricular hypertrophic patterns were the most frequent causes of ST segment elevation. Therapeutic considerations, such as fibrinolysis, must be made with this electrocardiographic differential diagnosis in mind.

The Joint European Society of Cardiology/American College of Cardiology Committee: Myocardial Infarction Redefined—A Consensus Document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. J Am Coll Cardiol 2000;36:959-969.

This consensus document redefines acute myocardial infarction with reference to patient complaint, electrocardiographic abnormality, and serum marker. Of importance is the description of the serum marker abnormality that continues to stress serial testing with the phrase "typical rise and fall" of the value relative to the clinical presentation. This issue is important with respect to the troponins, providing the clinician with information to distinguish noncoronary causes of elevated troponin values from ACS-related presentations.

Ornato JP, Peberdy MA, Jesse RL, et al: Value of coronary artery disease risk factors in judging whether chest pain accompanied by a normal or nondiagnostic ECG in the emergency department is due to acute cardiac ischemia. J Am Coll Cardiol 1996;27:31A.

This study explores the issue of classic CAD risk factors and their importance (i.e., impact) in the early medical decision-making of the possible ACS patient.

Zalenski RJ, Cook D, Rydman R: Assessing the diagnostic value of ECG containing leads V4R, V8, and V9: the 15-lead ECG. Ann Emerg Med 1993;22:786-793.

This study stresses the use of additional ECG leads in the chest pain patient. The right ventricular and posterior areas of the heart are poorly imaged with the ECG. These areas may harbor infarction not detected via standard ECG imaging. This study highlights the importance of the additional ECG leads and their impact on clinical care.

Hamm CW, Goldmann BU, Heeschen C, et al: Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. N Engl J Med 1997;337:1648-1653.

This study stresses the importance of the serum troponin and its risk prognostication in the chest pain patient suspected of ACS—an elevated value is associated with high risk while a normal value is associated with very low risk.

Chapter 93

ACUTE CORONARY SYNDROMES: MANAGEMENT AND COMPLICATIONS

Steven M. Hollenberg

KEY POINTS

1. Myocardial infarction is diagnosed by a compatible clinical history, evolution of characteristic electrocardiographic changes, and an increase and decrease in cardiac enzyme levels.
2. All patients with suspected myocardial ischemia should be given aspirin upon presentation to the emergency department.
3. Patients with myocardial ischemia are divided by presentation with or without ST elevation, in accordance with treatment strategies. Patients with ST elevation benefit from immediate reperfusion with thrombolytic agents or direct angioplasty.
4. The promptness of reperfusion is more important than the mode by which it is accomplished. Reperfusion should be considered up to 12 hours after the onset of symptoms.
5. Risk stratification is the key to initial management of patients with non-ST elevation acute coronary syndromes.
6. In patients with high-risk non-ST elevation acute coronary syndromes, use of low-molecular-weight heparin, glycoprotein IIb/IIIa inhibition, and an early invasive approach should be considered.
7. Aspirin, beta-blockers, angiotensin converting enzyme inhibitors, and statins have been shown to decrease the rate of mortality after myocardial infarction.
8. Echocardiography is extremely useful for the diagnosis of complications after myocardial infarction. Invasive hemodynamic monitoring may be necessary in some cases as well.
9. Cardiogenic shock usually results from a myocardial infarction and is a medical emergency. The key to achieving a good outcome is an organized approach with rapid diagnosis and prompt initiation of therapy to maintain blood pressure and cardiac output.
10. Expeditious coronary revascularization is crucial in patients with cardiogenic shock. When available, emergency cardiac catheterization and revascularization with angioplasty or coronary surgery appears to improve survival and represents standard therapy at this time.
11. In hospitals without direct angioplasty capability, stabilization of patients with cardiogenic shock with intra-aortic balloon pump and thrombolysis followed by transfer to a tertiary care facility may be the best option.

DEFINITION AND CLINICAL MANIFESTATIONS

Acute coronary syndromes account for nearly 2 million hospitalizations annually in the United States, and, if patients who die before reaching the hospital are included, the mortality rate may be as high as 25%. Acute coronary syndromes are a family of disorders that share similar pathogenic mechanisms and represent different points along a common continuum. They include ST elevation myocardial infarction (MI), non-ST segment elevation MI, and unstable angina pectoris. The common link between the various types of acute coronary syndrome is the rupture of a vulnerable, but previously quiescent, coronary atherosclerotic plaque. Exposure of plaque contents to the circulating blood pool triggers the release of vasoactive amines and activation of platelets and the coagulation cascade. The extent of resultant platelet aggregation, thrombosis, vasoconstriction, and microembolization dictates the clinical manifestations of the syndrome.

The acute coronary syndromes have traditionally been classified into Q-wave MI, non-Q wave MI, and unstable angina. More recently, classification has shifted and has become based on the initial electrocardiogram (ECG): patients are divided into three groups: those with ST elevation (ST elevation MI), without ST elevation but with enzyme evidence of myocardial damage (non-ST elevation MI), and those with unstable angina. Classification according to presenting ECG coincides with current treatment strategies, since patients presenting with ST elevation benefit from immediate reperfusion and should be treated with thrombolytic therapy or urgent revascularization, whereas fibrinolytic agents are not effective in other patients with acute coronary syndrome.

ST ELEVATION MYOCARDIAL INFARCTION

Symptoms suggestive of MI may be similar to those of ordinary angina but are usually greater in intensity and duration.

Nausea, vomiting, and diaphoresis may be prominent features, and stupor and malaise attributable to low cardiac output can occur. Compromised left ventricular function may result in pulmonary edema with development of pulmonary bibasilar crackles and jugular venous distention; a fourth heart sound can be present with small infarcts or even mild ischemia, but a third heart sound is usually indicative of more extensive damage.

Patients presenting with suspected myocardial ischemia should undergo a rapid evaluation and should be treated with oxygen, sublingual nitroglycerin (unless systolic pressure is less than 90 mm Hg), and aspirin, 160 to 325 mg orally.[1] Narcotics should be used to relieve pain and also reduce anxiety, the salutary effects of which have been known for decades and should not be underestimated. A 12-lead ECG should be obtained and interpreted expeditiously.

ST-segment elevation of at least 1 mV in two or more contiguous leads provides strong evidence of thrombotic coronary occlusion, and the patient should be considered for immediate reperfusion therapy. The diagnosis of ST elevation MI can be limited in the presence of preexisting left bundle-branch block or permanent pacemaker. Nonetheless, new left bundle-branch block with a compatible clinical presentation should be considered acute MI and treated accordingly. Indeed, recent data suggest that patients with ST elevation MI and new left bundle-branch block may stand to gain greater benefit from reperfusion strategies than those with ST elevation and preserved ventricular conduction.[2]

THROMBOLYTIC THERAPY

Early reperfusion of an occluded coronary artery is indicated for all eligible candidates. Overwhelming evidence from multiple clinical trials demonstrates the ability of thrombolytic agents administered early in the course of an acute MI to reduce infarct size, preserve left ventricular function, and reduce short-term and long-term mortality.[3-5] Patients treated early derive the most benefit.[5] Indications and contraindications for thrombolytic therapy are listed in Table 93-1. Because of the small, but nonetheless significant, risk of a bleeding complication, most notably intracranial hemorrhage, selection of patients with acute MI for administration of a thrombolytic agent should be undertaken with prudence and caution. That is of special importance in intensive care unit (ICU) patients, who may have a predisposition to bleeding complications because of multiple factors. Contraindications can be regarded as absolute or relative. In the surgical patient, thrombolysis may pose a prohibitive risk and emergency coronary angiography (with percutaneous coronary intervention as clinically indicated) may be preferable.

In contrast to the treatment of ST elevation MI, thrombolytics have shown no benefit and an increased risk of adverse events when used for the treatment of unstable angina/non-ST elevation MI.[6] Based on these findings, there is currently no role for thrombolytic agents in these latter syndromes.

Thrombolytic Agents

Streptokinase is a single-chain protein produced by α-hemolytic streptococci. Streptokinase is given as a 1.5 million unit intravenous infusion over 1 hour, which produces a systemic lytic state for about 24 hours. Hypotension with infusion usually responds to fluids and a decreased infusion rate, but allergic reactions are possible. Hemorrhagic complications are the most feared side-effect, with a rate of intracranial hemorrhage of approximately 0.5%. Streptokinase produces coronary arterial patency approximately 50% to 60% of the time and has been shown to decrease mortality by 18% compared to placebo.[3]

Tissue plasminogen activator (t-PA) is a recombinant protein that is more fibrin-selective than streptokinase and produces a higher early coronary patency rate (70-80%). The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial was a large (41,021 patient) clinical trial comparing streptokinase to t-PA in patients with ST elevation MI, and it demonstrated a significant survival benefit for t-PA (1.1% absolute, 15% relative reduction).[7] The GUSTO angiographic substudy showed that the difference in patency rates explains the difference in clinical efficacy between these two agents.[8] t-PA is usually given in an accelerated regimen consisting of a 15 mg bolus, 0.75 mg/kg (up to 50 mg) intravenously over the initial 30 minutes, and 0.5 mg/kg (up to 35 mg) over the next 60 minutes. Allergic reactions do not occur because t-PA is not antigenic, but the rate of intracranial hemorrhage may be slightly higher than with streptokinase, around 0.7%.

Reteplase is a deletion mutant of t-PA with an extended half-life and is given as two 10 U boluses 30 minutes apart. Reteplase was originally evaluated in angiographic trials that demonstrated improved coronary flow at 90 minutes compared to t-PA, but subsequent trials showed similar 30-day mortality rates.[9] Why enhanced patency with reteplase did not translate into lower mortality is uncertain.

TABLE 93–1. INDICATIONS FOR AND CONTRAINDICATIONS TO THROMBOLYTIC THERAPY IN ACUTE MYOCARDIAL INFARCTION

Indications
Symptoms consistent with acute myocardial infarction
Electrocardiogram showing 1 mm (0.1 mV) ST elevation in at least two contiguous leads, or new left bundle branch block
Presentation within 12 hours of symptom onset
Absence of contraindications
Contraindications
Absolute
Active internal bleeding
Intracranial neoplasm, aneurysm, or atrioventricular malformation
Stroke or neurosurgery within prior 6 weeks
Trauma or major surgery within prior 2 weeks that could be a potential source of serious rebleeding
Aortic dissection
Relative
Prolonged (>10 minutes) or clearly traumatic cardiopulmonary resuscitation*
Noncompressible vascular punctures
Severe uncontrolled hypertension (>200/110 mm Hg)*
Trauma or major surgery within prior 6 weeks (but more than 2 weeks ago)
Preexisting coagulopathy or current use of anticoagulants with INR >2-3
Active peptic ulcer
Infective endocarditis
Pregnancy
Chronic severe hypertension

*Could be an absolute contraindication in low-risk patients with myocardial infarction.

Tenecteplase is a genetically engineered t-PA mutant with amino acid substitutions that result in prolonged half-life, resistance to plasminogen-activator inhibitor-1, and increased fibrin specificity. Tenecteplase is given as a single bolus, with the dose adjusted for weight. A single bolus of tenecteplase has been shown to produce coronary flow rates identical to those seen with accelerated t-PA, with equivalent 30-day mortality and bleeding rates.[10] Based on these results, single-bolus tenecteplase is an acceptable alternative to t-PA that can be given as a single bolus.

Because these newer agents in general have equivalent efficacy and side effect profiles, at no current additional cost compared to t-PA, and because they are simpler to administer, they have gained popularity. The ideal thrombolytic agent has not yet been developed. Newer recombinant agents with greater fibrin specificity, slower clearance from the circulation, and more resistance to plasma protease inhibitors are being studied.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION IN ACUTE MYOCARDIAL INFARCTION

The major advantages of primary percutaneous coronary intervention over thrombolytic therapy include a higher rate of normal (TIMI grade 3-4) flow, lower risk of intracranial hemorrhage, and the ability to stratify risk based on the severity and distribution of coronary artery disease. Patients ineligible for thrombolytic therapy should obviously be considered for primary percutaneous coronary intervention. In addition, data from several randomized trials have suggested that percutaneous coronary intervention is preferable to thrombolytic therapy for several subsets of patients with acute MI who are at higher risk. The PAMI trial showed improved results with percutaneous coronary intervention in patients older than 75 years of age, those with anterior infarctions, and those with hemodynamic instability.[11] The largest of these trials is the GUSTO-IIb Angioplasty Substudy, which randomized 1138 patients. At 30 days, there was a clinical benefit in the combined primary endpoints of death, nonfatal reinfarction, and nonfatal disabling stroke in the patients treated with percutaneous transluminal coronary angioplasty compared to t-PA, but no difference in the "hard" endpoints of death and MI at 30 days.[12]

It should be noted that these trials were performed in institutions in which a team skilled in primary angioplasty for acute MI was immediately available, with standby surgical backup, allowing for prompt reperfusion of the infarct-related artery. More important than the method of revascularization is the time to revascularization, and that revascularization should be achieved in the most efficient and expeditious manner possible.[13] Procedural volume is important as well.[14]

Recent meta-analyses comparing direct percutaneous transluminal coronary angioplasty with thrombolytic therapy have suggested lower rates of mortality and reinfarction among those receiving direct percutaneous transluminal coronary angioplasty.[15,16] Thus, direct angioplasty, if performed in a timely manner (ideally within 60 minutes) by highly experienced personnel, may be the preferred method of revascularization, since it offers more complete revascularization with improved restoration of normal coronary blood flow and detailed information about coronary anatomy. There are certain subpopulations in which primary percutaneous coronary intervention is clearly preferred, and other populations in which the data are suggestive of benefit. These subsets are listed in Table 93-2.

TABLE 93–2. SITUATIONS IN WHICH PRIMARY ANGIOPLASTY IS PREFERRED IN ACUTE MYOCARDIAL INFARCTION

Clear Preference
Contraindications to thrombolytic therapy
Cardiogenic shock
Patients in whom uncertain diagnosis prompted cardiac catheterization, which revealed coronary occlusion
Possible Preference
Elderly patients (>75 years old)
Hemodynamic instability
Patients with prior coronary artery bypass grafting
Large anterior infarction
Patients with a prior myocardial infarction

Coronary Stenting and Glycoprotein IIb/IIIa Antagonists

Primary angioplasty for acute MI results in a significant reduction in mortality but is limited by the possibility of abrupt vessel closure, recurrent in-hospital ischemia, reocclusion of the infarct-related artery, and restenosis. The use of coronary stents has been shown to reduce restenosis and adverse cardiac outcomes in both routine and high-risk percutaneous coronary intervention.[17] The PAMI Stent Trial was designed to test the hypothesis that routine implantation of an intracoronary stent in the setting of MI would reduce angiographic restenosis and improve clinical outcomes compared to primary balloon angioplasty alone. This large, randomized, multicenter trial involving 900 patients did not show a difference in mortality at 6 months but did show improvement in ischemia-driven target vessel revascularization and less angina in the stented patients compared to percutaneous transluminal coronary angioplasty alone.[18]

Glycoprotein IIb/IIIa receptor antagonists inhibit the final common pathway of platelet aggregation, blocking crosslinking of activated platelets, and their use in percutaneous intervention has become routine.[19] The benefits of glycoprotein IIb/IIIa inhibition and coronary stenting appear to be additive.[20,21] Thus, combining glycoprotein IIb/IIIa antagonism and stenting in acute MI makes theoretical sense and has now been tested in two large clinical trials. The ADMIRAL trial evaluated abciximab as an adjunct to primary percutaneous transluminal coronary angioplasty and stenting in 300 acute MI patients. Abciximab used in conjunction with stenting improved coronary patency before stenting and resulted in a nearly 50% relative risk reduction in the incidence of death, recurrent MI, and urgent revascularization at 30 days, although this was associated with an increased incidence of minor bleeding.[22] The CADILLAC trial randomized 2082 patients to either angioplasty alone, angioplasty plus abciximab stenting alone, or stenting plus abciximab. The composite endpoint of death, reinfarction, disabling stroke, and repeat revascularization was reduced with addition of abciximab to angioplasty, and outcomes were better with stenting (but abciximab added to stenting alone did not improve outcomes, although the event rate was low).[23] Based on the results of these trials, stenting has become routine for patients with percutaneous coronary intervention in the

setting of acute MI, usually with the addition of glycoprotein IIb/IIIa inhibition.

In patients who fail thrombolytic therapy, salvage percutaneous transluminal coronary angioplasty is indicated, although the initial success rate is lower than that of primary angioplasty, reocclusion is more common, and the mortality rate is higher. The RESCUE trial focused on a subset of acute MI patients with anterior infarction and showed a reduction in the combined endpoint of death or congestive heart failure at 30 days in the group receiving salvage percutaneous transluminal coronary angioplasty.[24]

There is no convincing evidence to support empirical delayed percutaneous transluminal coronary angioplasty in patients without evidence of recurrent or provocable ischemia after thrombolytic therapy. The TIMI IIB trial and other studies suggest that a strategy of "watchful waiting" allows for identification of patients who will benefit from revascularization.[25]

ADJUNCTIVE THERAPIES IN ST ELEVATION MYOCARDIAL INFARCTION

Aspirin

Aspirin is the best known and the most widely used of all the antiplatelet agents because of low cost and relatively low toxicity. Aspirin inhibits the production of thromboxane A2 by irreversibly acetylating the serine residue of the enzyme prostaglandin H2 synthetase. Aspirin has been shown to reduce mortality among patient with acute infarction to the same degree as thrombolytic therapy, and its effects are additive to those of thrombolytics.[26] In addition, aspirin reduces the risk of reinfarction.[27,28] Unless contraindicated, all patients with a suspected acute coronary syndrome (ST elevation myocardial infarction, non-ST elevation MI, unstable angina) should be given aspirin as soon as possible.

Heparin

Administration of full-dose heparin after thrombolytic therapy with t-PA is essential to diminish reocclusion after successful reperfusion.[3,26] Dosing should be adjusted to weight, with a bolus of 60 U/kg up to a maximum of 4000 U and an initial infusion rate of 12 U/kg/hr up to a maximum of 1000 U/hr, with adjustment to keep the partial thromboplastin time between 50 and 70 seconds.[1] Heparin should be continued for 24 to 48 hours.

Nitrates

Nitrates have a number of beneficial effects in acute myocardial infarction. They reduce myocardial oxygen demand by decreasing preload and afterload and may also improve myocardial oxygen supply by increasing subendocardial perfusion and collateral blood flow to the ischemic region.[29] Occasional patients with ST elevation due to occlusive coronary artery spasm may have dramatic resolution of ischemia with nitrates. In addition to their hemodynamic effects, nitrates also reduce platelet aggregation. Despite these benefits, the GISSI-3 and ISIS-4 trials failed to show a significant reduction in mortality from routine acute and chronic nitrate therapy.[30,31] Nonetheless, nitrates are still first-line agents for the symptomatic relief of angina pectoris and when myocardial infarction is complicated by congestive heart failure.

Beta-Blockers

Beta-blockers are beneficial both in the early management of myocardial infarction and as long-term therapy. In the prethrombolytic era, early intravenous atenolol was shown to significantly reduce reinfarction, cardiac arrest, cardiac rupture, and death.[32] In conjunction with thrombolytic therapy with t-PA, immediate beta-blockade with metoprolol resulted in a significant reduction in recurrent ischemia and reinfarction, although the mortality rate was not decreased.[25]

Administration of intravenous beta-blockade should be considered for all patients presenting with acute myocardial infarction, especially those with continued ischemic discomfort and sympathetic hyperactivity manifested by hypertension or tachycardia. Therapy should be avoided in patients with moderate or severe heart failure, hypotension, severe bradycardia or heart block, and severe bronchospastic disease. Metoprolol can be given as a 5 mg intravenous bolus, repeated every 5 minutes for a total of three doses. Because of its brief half-life, esmolol may be advantageous in situations in which precise control of the heart rate is necessary or rapid drug withdrawal may be needed if adverse effects occur.

Oral beta-blockade has been clearly demonstrated to decrease mortality after acute myocardial infarction[33,34] and should be initiated in all patients who can tolerate it, even if they have not been treated with intravenous beta-blockers. Diabetes mellitus is not a contraindication.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) generates angiotensin II from angiotensin I and also catalyzes the breakdown of bradykinin. Thus, ACE inhibitors can decrease circulating angiotensin II levels and increase levels of bradykinin, which in turn stimulates production of nitric oxide by endothelial nitric oxide synthase. In the vasculature, ACE inhibition promotes vasodilation and tends to inhibit smooth muscle proliferation, platelet aggregation, and thrombosis.

Angiotensin-converting enzyme inhibitors have been shown unequivocally to improve hemodynamics, functional capacity and symptoms, and survival in patients with chronic congestive heart failure.[35,36] Moreover, ACE inhibitors prevent the development of congestive heart failure in patients with asymptomatic left ventricular dysfunction.[37] This information was the spur for trials evaluating the benefit of prophylactic administration of ACE inhibitors in the post-myocardial infarction period. The SAVE trial showed that patients with left ventricular dysfunction (ejection fraction <40%) after myocardial infarction had a 21% improvement in survival after treatment with the ACE inhibitor captopril.[38] A smaller but still significant reduction in mortality was seen when all patients were treated with captopril in the ISIS-4 study.[31] The HOPE trial randomized 9297 patients with documented vascular disease or those at high-risk for atherosclerosis (diabetes plus at least one other risk factor) in the absence of heart failure to treatment with the tissue-selective ACE inhibitor ramipril (target dose 10 mg/day) or placebo.[39] An impressive 22% reduction in the combined endpoint of cardiovascular death, myocardial infarction, and stroke was observed, as well as improved survival that was additive to the benefits of aspirin and beta-blockers.[39] The mechanisms responsible for the benefits of ACE inhibitors probably include limitation in the progressive left ventricular dysfunction and enlargement (remodeling) that often occur after infarction, but a reduction in ischemic events was seen as well.

Immediate intravenous ACE inhibition with enalapril has not been shown to be beneficial,[40] but oral ACE inhibition should be started early in the hospital course. Patients should be started on low doses of oral agents (captopril 6.25 mg three

times daily) and rapidly increased to the range demonstrated beneficial in clinical trials (captopril 50 mg three times daily, enalapril 10 to 20 mg twice daily, lisinopril 10 to 20 mg once daily, or ramipril 10 mg once daily).

Lipid-Lowering Agents

There is extensive epidemiologic, laboratory, and clinical evidence linking cholesterol and coronary artery disease. Total cholesterol level has been linked to the development of coronary artery disease events with a continuous and graded relation.[41] Most of this risk is due to low-density lipoprotein cholesterol. A number of large primary and secondary prevention trials have shown that low-density lipoprotein cholesterol lowering is associated with a reduced risk of coronary disease events. Earlier lipid-lowering trials used bile-acid sequestrants (cholestyramine), fibric acid derivatives (gemfibrozil and clofibrate), or niacin in addition to diet. The reduction in total cholesterol in these early trials was 6% to 15% and was accompanied by a consistent trend toward a reduction in fatal and nonfatal coronary events.[42]

More impressive results have been achieved using HMG-CoA reductase inhibitors (statins). Statins have been demonstrated to decrease the rate of adverse ischemic events in patients with documented coronary artery disease in the 4S trial[43] as well as in the CARE study[44] and the LIPID trial.[45]

The goal of treatment is a low-density lipoprotein cholesterol level less than 100 mg/dL.[46] Maximum benefit may require management of other lipid abnormalities (elevated triglycerides, low high-density lipoprotein [HDL] cholesterol level) and treatment of other atherogenic risk factors.

Calcium Channel Blockers

Randomized clinical trials have not demonstrated that routine use of calcium channel blockers improves survival after myocardial infarction.[47] In fact, meta-analyses suggest that high doses of the short-acting dihydropyridine nifedipine increase mortality in patients after myocardial infarction.[48] Adverse effects of calcium-channel blockers include bradycardia, atrioventricular block, and exacerbation of heart failure. The relative vasodilating, negative inotropic effects, and conduction system effects of the various agents must be considered when they are employed in this setting. Diltiazem is the only calcium channel blocker that has been proven to have tangible benefits, reducing reinfarction and recurrent ischemia in patients with non-Q-wave infarctions who do not have evidence of congestive heart failure.[49]

Calcium channel blockers may be useful for patients whose postinfarction course is complicated by recurrent angina, because these agents not only reduce myocardial oxygen demand but inhibit coronary vasoconstriction. For hemodynamically stable patients, diltiazem can be given, starting at 60 to 90 mg orally every 6 to 8 hours. In patients with severe left ventricular dysfunction, long-acting dihydropyridines without prominent negative inotropic effects such as amlodipine, nicardipine, or the long-acting preparation of nifedipine may be preferable; increased mortality with these agents has not been demonstrated.

NON-ST ELEVATION MYOCARDIAL INFARCTION

The key to initial management of patients with acute coronary syndromes who present without ST elevation is risk stratification. The overall risk of a patient is related to both the severity of preexisting heart disease and the degree of plaque instability. Risk stratification is an ongoing process that begins with hospital admission and continues through discharge.

Braunwald has proposed a classification for unstable angina based on severity of symptoms and clinical circumstances for risk stratification.[50] The risk of progression to acute myocardial infarction or death in acute coronary syndromes increases with age. ST segment depression on the ECG identifies patients at higher risk for clinical events.[50] Conversely, a normal ECG confers an excellent short-term prognosis. Biochemical markers of cardiac injury are also predictive of outcome. Elevated levels of troponin T are associated with an increased risk of cardiac events and a higher 30-day mortality rate and, in fact, were more strongly correlated with 30-day survival than ECG category or creatine kinase-MB level in an analysis of data from the GUSTO-II trial.[51] Conversely, low levels are associated with low event rates, although the absence of troponin elevation does not guarantee a good prognosis and is not a substitute for good clinical judgment.

ANTIPLATELET THERAPY

As previously noted, aspirin is a mainstay of therapy for acute coronary syndromes. Both the VA Cooperative Study Group[27] and the Canadian Multicenter Trial[52] showed that aspirin reduces the risk of death or myocardial infarction by approximately 50% in patients with unstable angina or non-Q-wave MI. Aspirin also reduces events after resolution of an acute coronary syndrome and should be continued indefinitely.

Clopidogrel or ticlopidine, thienopyridines that inhibit ADP-induced platelet activation and are more potent than aspirin, can be used in place of aspirin if necessary. Thienopyridines are used in combination with aspirin when intracoronary stents are placed. Clopidogrel is generally better tolerated than ticlopidine, since the risk of neutropenia is much lower.

In the CURE trial, 12,562 patients were randomized to receive clopidogrel or placebo in addition to standard therapy with aspirin, within 24 hours of unstable angina symptoms.[53] Clopidogrel significantly reduced the risk of myocardial infarction, stroke, or cardiovascular death from 11.4% to 9.3% ($P < .001$).[53] It should be noted that this benefit came with a 1% absolute increase in major, non-life-threatening bleeds ($P = .001$) as well as a 2.8% absolute increase in major or life-threatening bleeds associated with coronary artery bypass graft surgery (CABG) within 5 days ($P = .07$).[53] These data have raised concerns about giving clopidogrel prior to information about the coronary anatomy.

Clopidogrel has also been tested for secondary prevention of events. The CAPRIE trial, a multicenter trial of 19,185 patients with known vascular disease (prior stroke, myocardial infarction, or peripheral vascular disease), randomized patients to either 75 mg/day of clopidogrel or 325 mg aspirin.[54] After an average follow-up of 1.6 years, patients treated with clopidogrel had significantly fewer cardiovascular events than patients treated with aspirin (5.8% vs 5.3%, a relative risk reduction of 8.7%).[54]

ANTICOAGULANT THERAPY

Heparin is an important component of primary therapy for patients with unstable coronary syndromes without ST elevation. When added to aspirin, heparin has been shown

to reduce refractory angina and the development of myocardial infarction,[28] and a meta-analysis of the available data indicates that addition of heparin reduces the composite endpoint of death or myocardial infarction.[55]

Unfractionated heparin, however, can be difficult to administer, because the anticoagulant effect is unpredictable in individual patients; this is due to binding of heparin to heparin-binding proteins and heparin inhibition by several factors released by activated platelets, most notably platelet factor 4. Therefore, the activated partial thromboplastin time must be monitored closely. The potential for heparin-associated thrombocytopenia is also a safety concern.

Low-molecular-weight heparins, which are obtained by depolymerization of standard heparin and selection of fractions with lower molecular weight, have several advantages. Because they bind less avidly to heparin binding proteins, there is less variability in the anticoagulant response and a more predictable dose-response curve, obviating the need to monitor APTT. The incidence of thrombocytopenia is lower but not absent, and patients with heparin-induced thrombocytopenia with anti-heparin antibodies cannot be switched to low-molecular-weight heparins. Low-molecular-weight heparin is less susceptible to inactivation by platelet factor 4. Finally, low-molecular-weight heparins have longer half-lives and can be given by subcutaneous injection. These properties make treatment with low-molecular-weight heparins at home after hospital discharge feasible. Since evidence suggests that patients with unstable coronary syndromes may remain in a hypercoagulable state for weeks or months, the longer duration of anticoagulation possible with low-molecular-weight heparins may be desirable.

Several trials have documented beneficial effects of low-molecular-weight heparin therapy in unstable coronary syndromes. The ESSENCE trial showed that the low-molecular-weight heparin enoxaparin reduced the combined endpoint of death, myocardial infarction, or recurrent ischemia at both 14 and 30 days when compared with heparin.[56] Similar results were found in the TIMI 11B trial comparing enoxaparin to heparin.[57] A meta-analysis of these two very similar trials demonstrated a 23% 7-day and an 18% 42-day reduction in the harder endpoint of death or myocardial infarction.[58] Dalteparin, another low-molecular-weight heparin, is also available, but the evidence for its efficacy is not nearly as compelling as that for enoxaparin.[59]

Although the low-molecular-weight heparins are substantially easier to administer than standard heparin, and long-term administration can be contemplated, they are also more expensive. Specific considerations with the use of low-molecular-weight heparins include decreased clearance in renal insufficiency and the lack of a commercially available test to measure the anticoagulant effect. Low-molecular-weight heparins should be given strong consideration in high-risk patients, but whether substitution of low-molecular-weight heparin for heparin in all patients is cost effective is uncertain.

GLYCOPROTEIN IIB/IIIA ANTAGONISTS

Given the central role of platelet activation and aggregation in the pathophysiology of unstable coronary syndromes, attention has focused on platelet glycoprotein IIb/IIIa antagonists, which inhibit the final common pathway of platelet aggregation. Three agents are currently available. Abciximab is a chimeric murine-human monoclonal antibody Fab fragment that binds with relatively high affinity to platelet receptors, giving it a short plasma half-life (10 to 30 minutes) but a long duration of biologic action by virtue of the strength of the bond formed with the surface of the activated platelet. Tirofiban is a small-molecule, synthetic nonpeptide agent with a half-life of approximately 2.5 hours and a lower receptor affinity than abciximab. Eptifibatide is a small-molecule, cyclic heptapeptide with a 2-hour half-life.

The benefits of glycoprotein IIb/IIIa inhibitors as adjunctive treatment in patients undergoing percutaneous intervention have been substantial and consistently observed. Abciximab has been most extensively studied,[21,60,61] but a benefit for eptifibatide has also been demonstrated.[62] In acute coronary syndromes, the evidence supporting the efficacy of GP IIb/IIIa inhibitors is somewhat less impressive. Five major trials have been completed (the "4 P's" and GUSTO-IV). In the PRISM trial, tirofiban reduced the rate of death, myocardial infarction, or refractory ischemia when compared to heparin from 5.6% to 3.8% ($P < .01$) at 48 hours, but there was no difference at 30 days (7.1% vs 5.8%, $P = .11$).[63] In the subsequent PRISM-PLUS trial, tirofiban added to heparin reduced the rate of death, myocardial infarction, or refractory ischemia at 30 days from 11.9% to 8.7% ($P = .03$).[64] In the PURSUIT trial, eptifibatide reduced the rate of death or MI from 15.7% to 14.2% ($P = .04$) at 30 days.[65] The PARAGON trial with lamifiban did not show a significant benefit with glycoprotein IIb/IIIa inhibition.[66] In the GUSTO-IV acute coronary syndromes trial, however, abciximab did not produce an improvement; in fact, the rate of death or myocardial infarction was slightly higher with abciximab in the treatment group.[67] This trial included patients for whom percutaneous intervention was not planned; when patients with refractory angina and planned angioplasty were randomized to receive abciximab or placebo from 24 hours prior to the procedure through 1 hour following percutaneous transluminal coronary angioplasty in the CAPTURE trial, the primary endpoint, death, myocardial infarction, or urgent revascularization at 30 days, was reduced by glycoprotein IIb/IIIa inhibition, and the rate of myocardial infarction before percutaneous transluminal coronary angioplasty was reduced as well.[68] When patients were grouped into those with and without increased troponin, the benefit was confined to the positive troponin group.[68]

Recent meta-analyses have found a relative risk reduction of 40% for glycoprotein IIb/IIIa therapy adjunctive to percutaneous coronary intervention, and a reduction of 11% for glycoprotein IIb/IIIa inhibitors in non-ST elevation MI acute coronary syndromes.[19] Additional analysis suggests that glycoprotein IIb/IIIa inhibition is most effective in high-risk patients, those with either ECG changes or elevated troponin.[19] The benefits appear to be restricted to patients undergoing percutaneous intervention, which may not be entirely surprising.

INTERVENTIONAL MANAGEMENT

Cardiac catheterization can be undertaken in patients presenting with symptoms suggestive of unstable coronary syndromes for one of several reasons: to assist with risk stratification, as a prelude to revascularization, and to exclude significant epicardial coronary stenosis as a cause of symptoms when the diagnosis is uncertain.

An early invasive approach has now been compared to a conservative approach in several prospective studies.

Two earlier trials had negative findings. The TIMI IIIb study randomized 1473 patients to early angiography or conservative management with angiography and revascularization only for recurrent chest pain or provocable ischemia.[6] No significant difference was found in the combined endpoint of death, myocardial infarction, or positive treadmill test result at 6 weeks. There was, however, a high (64%) crossover rate from the conservative to the invasive arm, and hospital stays were lower with the early invasive approach.[8] The VANQWISH trial of 920 patients with non-Q wave myocardial infarction actually showed an increase in the primary endpoint of death or myocardial infarction with an invasive strategy, although overall mortality was not significantly different.[69] Difficulties with this trial included the fact that only 44% of patients randomized to the invasive arm underwent revascularization, compared with 33% in the conservative arm, and very high surgical mortality rate (11.6%).[69] It is important to realize that these trials were performed before widespread use of coronary stenting and platelet glycoprotein IIb/IIIa inhibitors, both of which have now been shown to improve outcomes after angioplasty.

More recently, a substudy of the FRISC II study, which used the low-molecular-weight heparin dalteparin, randomized 2457 patients to an early invasive or a noninvasive strategy and found a significantly lower mortality rate in the invasive group at 30 days, which was maintained at 1 year.[70] The TACTICS TIMI-18 trial used aspirin, heparin, and tirofiban in 2220 patients and found a significant reduction in the combined endpoint of death, myocardial infarction, or readmission for acute coronary syndrome with invasive management.[71] It is important to recognize that both of these trials selected high-risk patients (identified on the basis of either ECG changes or enzyme elevations) for inclusion. Addition of adjunctive antiplatelet therapy beyond the use of aspirin alone in conjunction with reperfusion may also have contributed to the improved outcomes with invasive strategies in these more recent trials.

Risk stratification is the key to managing patients with non-ST elevation MI acute coronary syndromes. One possible algorithm for managing patients with non-ST elevation MI is shown in Figure 93-1. An initial strategy of medical management with attempts at stabilization is warranted in patients with lower risk, but patients at higher risk should be considered for cardiac catheterization. Pharmacologic and mechanical strategies are intertwined in the sense that selection of patients for early revascularization will influence the choice of antiplatelet and anticoagulant medication. When good clinical judgment is employed, early coronary angiography in selected patients with acute coronary syndromes can lead to better management and lower morbidity and mortality.

COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION

POSTINFARCTION ISCHEMIA

Causes of ischemia after infarction include reduced myocardial oxygen supply due to coronary reocclusion or spasm, mechanical problems which increase myocardial oxygen demand, and extracardiac factors such as hypertension, anemia, hypotension, or hypermetabolic states. Nonischemic causes of chest pain, such as postinfarction pericarditis and acute pulmonary embolism, should also be considered.

Immediate management includes aspirin, beta-blockade, intravenous nitroglycerin, heparin, consideration of calcium-channel blockers, and diagnostic coronary angiography. Post-infarction angina is an indication for revascularization. Percutaneous transluminal coronary angioplasty can be performed if the culprit lesion is suitable. CABG should be considered for patients with left main disease, those with three-vessel disease, and those unsuitable for percutaneous transluminal coronary angioplasty. If the angina cannot be controlled medically or is accompanied by hemodynamic instability, an intra-aortic balloon pump should be inserted.

VENTRICULAR FREE WALL RUPTURE

Ventricular free wall rupture typically occurs during the first week after infarction. The classic patient is elderly, female, and hypertensive. Early use of thrombolytic therapy reduces

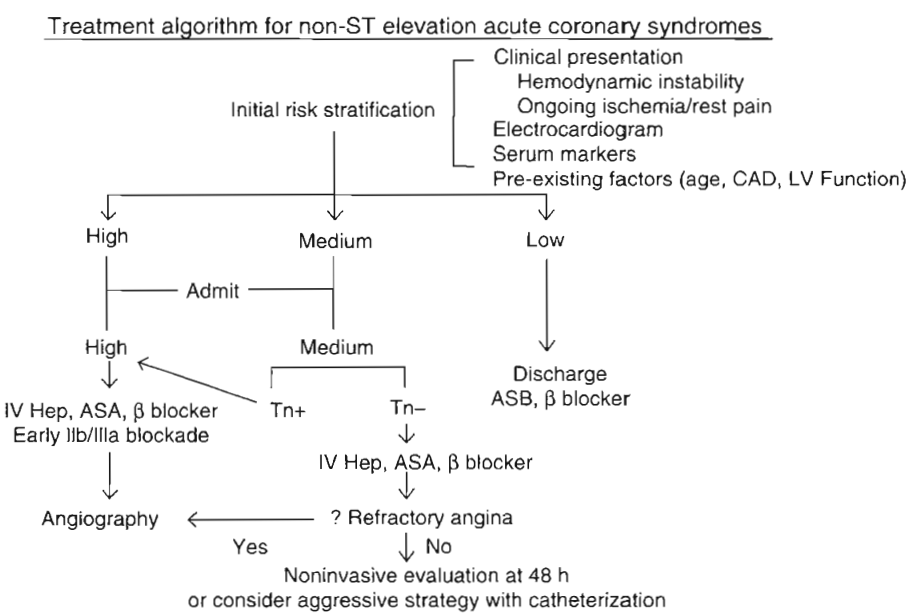


FIGURE 93–1. Possible treatment algorithm for patients with non-ST elevation acute coronary syndromes. ASA, aspirin; Hep, heparin; IV, intravenous; Tn, troponin.

the incidence of cardiac rupture, but late use may actually increase the risk. Free wall rupture presents as a catastrophic event with shock and electromechanical dissociation. Salvage is possible with prompt recognition, pericardiocentesis to relieve acute tamponade, and thoracotomy with repair.[72] Emergency echocardiography or pulmonary artery catheterization can help make the diagnosis.

VENTRICULAR SEPTAL RUPTURE

Septal rupture manifests as severe heart failure or cardiogenic shock, with a pansystolic murmur and parasternal thrill. The hallmark finding is a left-to-right intracardiac shunt ("step-up" in oxygen saturation from right atrium to right ventricle), but the diagnosis is most easily made with echocardiography.

Rapid institution of intra-aortic balloon pumping and supportive pharmacologic measures is necessary. Operative repair is the only viable option for long-term survival. The timing of surgery has been controversial, but most authorities now suggest that repair should be undertaken early, within 48 hours of the rupture.[73]

ACUTE MITRAL REGURGITATION

Ischemic mitral regurgitation is usually associated with inferior myocardial infarction and ischemia or infarction of the posterior papillary muscle, although anterior papillary muscle rupture can also occur. Papillary muscle rupture typically occurs 2 to 7 days after acute myocardial infarction and presents dramatically with pulmonary edema, hypotension, and cardiogenic shock. When a papillary muscle ruptures, the murmur of acute mitral regurgitation may be limited to early systole because of rapid equalization of pressures in the left atrium and left ventricle. More importantly, the murmur may be soft or inaudible, especially when cardiac output is low.[74]

Echocardiography is extremely useful in the differential diagnosis, which includes free wall rupture, ventricular septal rupture, and infarct extension with pump failure. Hemodynamic monitoring with pulmonary artery catheterization may also be helpful. Management includes afterload reduction with nitroprusside and intra-aortic balloon pumping as temporizing measures. Inotropic or vasopressor therapy may also be needed to support cardiac output and blood pressure. Definitive therapy, however, is surgical valve repair or replacement, which should be undertaken as soon as possible, since clinical deterioration can be sudden.[74,75]

RIGHT VENTRICULAR INFARCTION

Right ventricular infarction occurs in up to 30% of patients with inferior infarction and is clinically significant in 10%.[76] The combination of a clear chest x-ray with jugular venous distention in a patient with an inferior wall myocardial infarction should lead to the suspicion of a coexisting right ventricular infarct. The diagnosis is substantiated by demonstration of ST segment elevation in the right precordial leads (V_{3R} to V_{5R}) or by characteristic hemodynamic findings on right heart catheterization (elevated right atrial and right ventricular end-diastolic pressures with normal to low pulmonary artery occlusion pressure and low cardiac output). Echocardiography can demonstrate depressed right ventricular contractility.[77] Patients with cardiogenic shock on the basis of right ventricular infarction have a better prognosis than those with left-sided pump failure.[76] This may be due in part to the fact that right ventricular function tends to return to normal over time with supportive therapy,[78] although such therapy may need to be prolonged.

In patients with right ventricular infarction, right ventricular preload should be maintained with fluid administration. In some cases, however, fluid resuscitation may increase pulmonary capillary occlusion pressure but may not increase cardiac output, and overdilation of the right ventricle can compromise left ventricular filling and cardiac output.[78] Inotropic therapy with dobutamine may be more effective in increasing cardiac output in some patients, and monitoring with serial echocardiograms may also be useful to detect right ventricular overdistention.[78] Maintenance of atrioventricular synchrony is also important in these patients to optimize right ventricular filling.[77] For patients with continued hemodynamic instability, intra-aortic balloon pumping may be useful, particularly because elevated right ventricular pressures and volumes increase wall stress and oxygen consumption and decrease right coronary perfusion pressure, exacerbating right ventricular ischemia.

Reperfusion of the occluded coronary artery is also crucial. A study using direct angioplasty demonstrated that restoration of normal flow resulted in dramatic recovery of right ventricular function and a mortality rate of only 2%, whereas unsuccessful reperfusion was associated with persistent hemodynamic compromise and a mortality rate of 58%.[79]

CARDIOGENIC SHOCK

Epidemiology and Pathophysiology

Cardiogenic shock, resulting either from left ventricular pump failure or from mechanical complications, represents the leading cause of in-hospital death after myocardial infarction.[80] Despite advances in the management of heart failure and acute myocardial infarction, until very recently, clinical outcomes in patients with cardiogenic shock have been poor, with reported mortality rates ranging from 50% to 80%.[81] Patients may have cardiogenic shock at initial presentation, but shock often evolves over several hours.[82,83]

Cardiac dysfunction in patients with cardiogenic shock is usually initiated by myocardial infarction or ischemia. The myocardial dysfunction resulting from ischemia worsens that ischemia, creating a downward spiral (Fig. 93-2). Compensatory mechanisms that retain fluid in an attempt to maintain cardiac output may add to the vicious cycle and further increase diastolic filling pressures. The interruption of this cycle of myocardial dysfunction and ischemia forms the basis for the therapeutic regimens for cardiogenic shock.

Initial Management

Maintenance of adequate oxygenation and ventilation are critical. Many patients require intubation and mechanical ventilation, if only to reduce the work of breathing and facilitate sedation and stabilization before cardiac catheterization. Electrolyte abnormalities should be corrected, and morphine (or fentanyl if systolic pressure is compromised) used to relieve pain and anxiety, thus reducing excessive sympathetic activity and decreasing oxygen demand, preload, and afterload. Arrhythmias and heart block can have major effects on cardiac output and should be corrected promptly with antiarrhythmic drugs, cardioversion, or pacing.

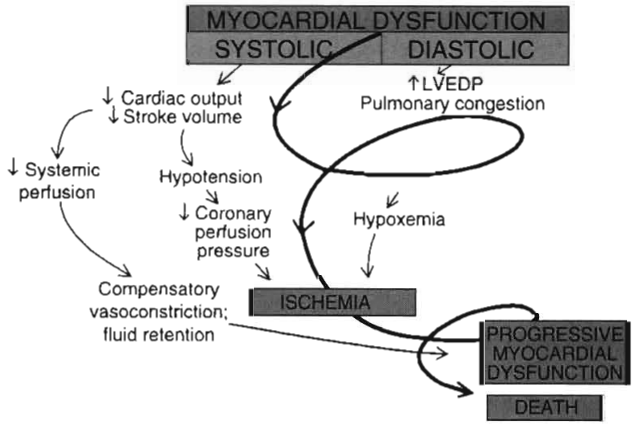


FIGURE 93–2. The "downward spiral" in cardiogenic shock. Stroke volume and cardiac output fall with left ventricular dysfunction, producing hypotension and tachycardia that reduce coronary blood flow. Increasing ventricular diastolic pressure reduces coronary blood flow, and increased wall stress elevates myocardial oxygen requirements. All of these factors combine to worsen ischemia. The falling cardiac output also compromises systemic perfusion. Compensatory mechanisms include sympathetic stimulation and fluid retention to increase preload. These mechanisms can actually worsen cardiogenic shock by increasing myocardial oxygen demand and afterload. Thus, a vicious circle can be established. LVEDP, left ventricular end-diastolic pressure. (Adapted with permission from Hollenberg SM, Kavinsky CJ, Parrillo JE: Cardiogenic shock. Ann Intern Med 1999; 131:47-59.)

The initial approach to the hypotensive patient should include fluid resuscitation unless frank pulmonary edema is present. Patients are commonly diaphoretic, and relative hypovolemia may be present in as many as 20% of patients with cardiogenic shock. Fluid infusion is best initiated with predetermined boluses titrated to clinical endpoints of heart rate, urine output, and blood pressure. Ischemia produces diastolic as well as systolic dysfunction, and thus elevated filling pressures may be necessary to maintain stroke volume in patients with cardiogenic shock. Patients who do not respond rapidly to initial fluid boluses or those with poor physiologic reserve should be considered for invasive hemodynamic monitoring. Optimal filling pressures vary from patient to patient; hemodynamic monitoring can be used to construct a Starling curve at the bedside, identifying the filling pressure at which cardiac output is maximized. Maintenance of adequate preload is particularly important in patients with right ventricular infarction.

When arterial pressure remains inadequate, therapy with vasopressor agents may be required to maintain coronary perfusion pressure. Maintenance of adequate blood pressure is essential to break the vicious circle of progressive hypotension with further myocardial ischemia. Dopamine increases both blood pressure and cardiac output and is usually the initial choice in patients with systolic pressures less than 80 mm Hg. When hypotension remains refractory, norepinephrine may be necessary to maintain organ perfusion pressure. Phenylephrine, a selective $alpha_1$-adrenergic agonist, may be useful when tachyarrhythmias limit therapy with other vasopressors. Vasopressor infusions need to be titrated carefully in patients with cardiogenic shock to maximize coronary perfusion pressure with the least possible increase in myocardial oxygen demand. Hemodynamic monitoring, with serial measurements of cardiac output, filling pressures, and other parameters, such as mixed venous oxygen saturation, allows for titration of the dosage of vasoactive agents to the minimum dose required to achieve the chosen therapeutic goals.[84]

Following initial stabilization and restoration of adequate blood pressure, tissue perfusion should be assessed. If tissue perfusion remains inadequate, inotropic support or intra-aortic balloon pumping should be initiated. If tissue perfusion is adequate but significant pulmonary congestion remains, diuretics can be employed. Vasodilators can be considered as well, depending on the blood pressure.

In patients with inadequate tissue perfusion and adequate intravascular volume, cardiovascular support with inotropic agents should be initiated. Dobutamine, a selective $beta_1$-adrenergic receptor agonist, can improve myocardial contractility and increase cardiac output and is the initial agent of choice in patients with systolic pressures greater than 80 mm Hg. Dobutamine may exacerbate hypotension in some patients and can precipitate tachyarrhythmias. Use of dopamine may be preferable if systolic pressure is less than 80 mm Hg, although tachycardia and increased peripheral resistance may worsen myocardial ischemia. In some situations, a combination of dopamine and dobutamine can be more effective than either agent used alone. Phosphodiesterase inhibitors such as milrinone are less arrhythmogenic than catecholamines but have the potential to cause hypotension and should be used with caution in patients with tenuous clinical status.

Intra-aortic balloon counterpulsation reduces systolic afterload and augments diastolic perfusion pressure, increasing cardiac output and improving coronary blood flow.[85] These beneficial effects, in contrast to those of inotropic or vasopressor agents, occur without an increase in oxygen demand. Intra-aortic balloon counterpulsation does not, however, produce a significant improvement in blood flow distal to a critical coronary stenosis and has not been shown to improve mortality when used alone without reperfusion therapy or revascularization. In patients with cardiogenic shock and compromised tissue perfusion, intra-aortic balloon counterpulsation can be an essential support mechanism to stabilize patients and allow time for definitive therapeutic measures to be undertaken.[85,86] In appropriate settings, more intensive support with mechanical assist devices can also be implemented.

Reperfusion Therapy

Although thrombolytic therapy reduces the likelihood of subsequent development of shock after initial presentation,[83] its role in the management of patients who have already developed shock is less certain. The available randomized trials[3,7,26,87] have not demonstrated that fibrinolytic therapy reduces mortality in patients with established cardiogenic shock. On the other hand, in the SHOCK Registry,[88] patients treated with fibrinolytic therapy had a lower in-hospital mortality rate than those who were not (54% vs. 64%, $P = .005$), even after adjustment for age and revascularization status (OR 0.70, $P = .027$).

Fibrinolytic therapy is clearly less effective in patients with cardiogenic shock than in those without. The explanation for this lack of efficacy appears to be the low reperfusion rate achieved in this subset of patients. The reasons for decreased thrombolytic efficacy in patients with cardiogenic shock probably include hemodynamic, mechanical, and metabolic factors that prevent achievement and maintenance of infarct-related artery patency.[89] Attempts to increase reperfusion rates by increasing blood pressure with aggressive inotropic

and pressor therapy and intra-aortic balloon counterpulsation make theoretical sense, and two small studies support the notion that vasopressor therapy to increase aortic pressure improves thrombolytic efficacy.[89,90] The use of intra-aortic balloon pumping to augment aortic diastolic pressure may increase the effectiveness of thrombolytics as well.

To date, emergency percutaneous revascularization is the only intervention that has been shown to consistently reduce mortality rates in patients with cardiogenic shock. An extensive body of observational and registry studies has shown consistent benefits from revascularization. Notable among these is the GUSTO-I trial, in which patients treated with an "aggressive" strategy (coronary angiography performed within 24 hours of shock onset with revascularization by percutaneous transluminal coronary angioplasty or bypass surgery) had significantly lower mortality (38% compared with 62%).[91] The National Registry of Myocardial Infarction-2 (NRMI-2) collected 26,280 shock patients with cardiogenic shock in the setting of myocardial infarction between 1994 and 1997, similarly supporting the association between revascularization and survival.[92] Improved short-term mortality was noted in patients who then underwent revascularization during the reference hospitalization, either via percutaneous transluminal coronary angioplasty (12.8% mortality vs 43.9%) or CABG (6.5% vs 23.9%).[93] These data complement the GUSTO-I substudy data and are important not only because of the sheer number of patients from whom these values are derived but also because NRMI-2 was a national cross-sectional study, which more closely represents general clinical practice than carefully selected trial populations. These studies cannot be regarded as definitive due to their retrospective design, but two randomized controlled trials have now evaluated revascularization for patients with myocardial infarction.

The SHOCK study was a randomized, multicenter international trial that assigned patients with cardiogenic shock to receive optimal medical management—including intra-aortic balloon counterpulsation and thrombolytic therapy—or cardiac catheterization with revascularization using percutaneous transluminal coronary angioplasty or CABG.[93,94] The trial enrolled 302 patients and was powered to detect a 20% absolute decrease in 30-day all-cause mortality rates. Mortality at 30 days was 46.7% in patients treated with early intervention and 56% in patients treated with initial medical stabilization, but this difference did not quite reach statistical significance ($P = .11$).[93] At 6 months, the absolute risk reduction with early invasive therapy in the SHOCK trial was 13% (50.3% compared with 63.1%, $P = .027$),[93] and this risk reduction was maintained at 12 months (mortality 53.3% vs 66.4%, $P < .03$).[94] Subgroup analysis showed a substantial improvement in mortality rates in patients younger than 75 years of age at both 30 days (41.4% versus 56.8%, $P = .01$) and 6 months (44.9% versus 65.0%, $P = 0.003$).[93]

The SMASH trial was independently conceived and had a very similar design, although a more rigid definition of cardiogenic shock resulted in enrollment of sicker patients and a higher mortality rate.[95] The trial was terminated early because of difficulties in patient recruitment, and enrolled only 55 patients. In the SMASH trial, a similar trend in 30-day absolute mortality reduction similar to that in the SHOCK trial of 9% was observed (69% mortality in the invasive group vs. 78% in the medically managed group; RR = 0.88; 95% CI = 0.6-1.2; P = NS).[95] This benefit was also maintained at 1 year.

When the results of both the SHOCK and SMASH trials are put into perspective with results from other randomized, controlled trials of patients with acute myocardial infarction, an important point emerges: despite the moderate *relative* risk reduction (for the SHOCK trial 0.72, CI 0.54-0.95; for the SMASH trial, 0.88, CI 0.60-1.20) the *absolute* benefit is important, with 9 lives saved for 100 patients treated at 30 days in both trials, and 13.2 lives saved for 100 patients treated at 1 year in the SHOCK trial. This latter figure corresponds to a number needed to treat (NNT) of 7.6, one of the lowest figures ever observed in a randomized, controlled trial of cardiovascular disease.

On the basis of these randomized trials, the presence of cardiogenic shock in the setting of acute myocardial infarction is a class I indication for emergency revascularization, either by percutaneous intervention or CABG.[1]

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This study involved 9297 high-risk patients (55 years or older, with vascular disease or diabetes plus one other cardiovascular risk factor) randomized to ramipril or placebo for a mean of 5 years. Ramipril significantly reduced the rates of death, myocardial infarction, and stroke.

Chapter 94

INVASIVE CARDIAC PROCEDURES: PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY, MITRAL AND AORTIC VALVULOPLASTY

Christian Spaulding • Olivier Varenne

KEY POINTS

1. **Percutaneous transluminal coronary angioplasty** (PTCA) is safe and effective. Stents are usually implanted during the procedure. A combination of clopidogrel and low-dose aspirin must be prescribed before and after the procedure. Platelet glycoprotein IIb/IIIa receptor inhibitors are effective primarily in patients with high-risk lesions or acute coronary syndromes.
2. **Restenosis** occurs in 30% to 50% of cases after balloon angioplasty, 3 to 6 months after the procedure. The incidence of restenosis is 25% to 50% less if stents are implanted. Drug-eluting stents further reduce this rate.
3. In patients with **unstable coronary artery disease and signs of ischemia** on electrocardiography or raised levels of biochemical markers of myocardial damage, an invasive approach with early (<24 hours) angiography is the preferred strategy. Preprocedure treatment includes aspirin, clopidogrel, heparin, and platelet glycoprotein IIb/IIIa receptor inhibitors.
4. **Primary PTCA is the most effective therapy for acute myocardial infarction,** especially in high-risk situations (cardiogenic shock, right ventricular infarction).
5. **Percutaneous mitral valvuloplasty is an accepted alternative to surgery in selected patients.** The mid- and long-term results of percutaneous aortic valvuloplasty are disappointing; it is therefore reserved for patients with severe comorbidities that preclude aortic valve replacement or as a "bridge" to definitive surgical correction.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Chronic ischemic heart disease is usually due to obstruction of the coronary arteries by atherosclerosis. It is the leading cause of mortality and morbidity in economically developed countries. Percutaneous transluminal coronary angioplasty (PTCA) has emerged as a major therapeutic option in patients with coronary artery atherosclerosis. The first PTCA in a patient was performed by Andreas Grüntzig in Zurich in September 1977.[1] PTCA was initially limited to the treatment of discrete stenoses in proximal segments of a coronary artery. Improvements in equipment and technique have increased the success rate and have led to its use in patients with complex stenoses or in high-risk clinical situations, such as acute coronary syndromes[2,3] or cardiac arrest.[4] PTCA is currently the most widely used coronary revascularization technique.

THE PROCEDURE

Vascular access is usually obtained through the femoral artery, where a sheath is introduced with the use of local anesthesia. A 5 to 8 Fr. guiding catheter is advanced through the sheath to the ostium of the coronary artery to be dilated. Once the guiding catheter is positioned in the coronary ostium, angiography of the diseased artery is performed to visualize the stenosis and the arterial segments proximal and distal to it (Fig. 94-1*A*). A flexible guidewire is advanced through the guiding catheter, navigated across the stenosis by rotating and advancing its angulated tip, and positioned in the distal arterial segment. The deflated balloon angioplasty catheter is advanced over the wire and positioned at the stenosis. The positions of the guidewire and balloon catheter are confirmed periodically by injecting contrast medium into the coronary artery through the guiding catheter. Once it is positioned, the balloon is usually inflated for 1 to 2 minutes at 3 to 12 atmospheres of pressure with a mixture of saline and contrast medium so that the inflation can be visualized (see Fig. 94-1*B* and *C*). Many patients have angina, electrocardiographic evidence of ischemia, or both during balloon inflation, because the coronary artery is temporarily occluded. Most often, a stent is implanted after balloon angioplasty (Fig. 94-2). Balloon-expandable stents are most commonly used. Before implantation, the stent is crimped on a balloon. The stent-balloon device is then positioned on the predilated site (see Fig. 94-1*D*), and the stent is implanted in the coronary artery wall by a short balloon inflation (see Fig. 94-1*E*). The balloon catheter is deflated

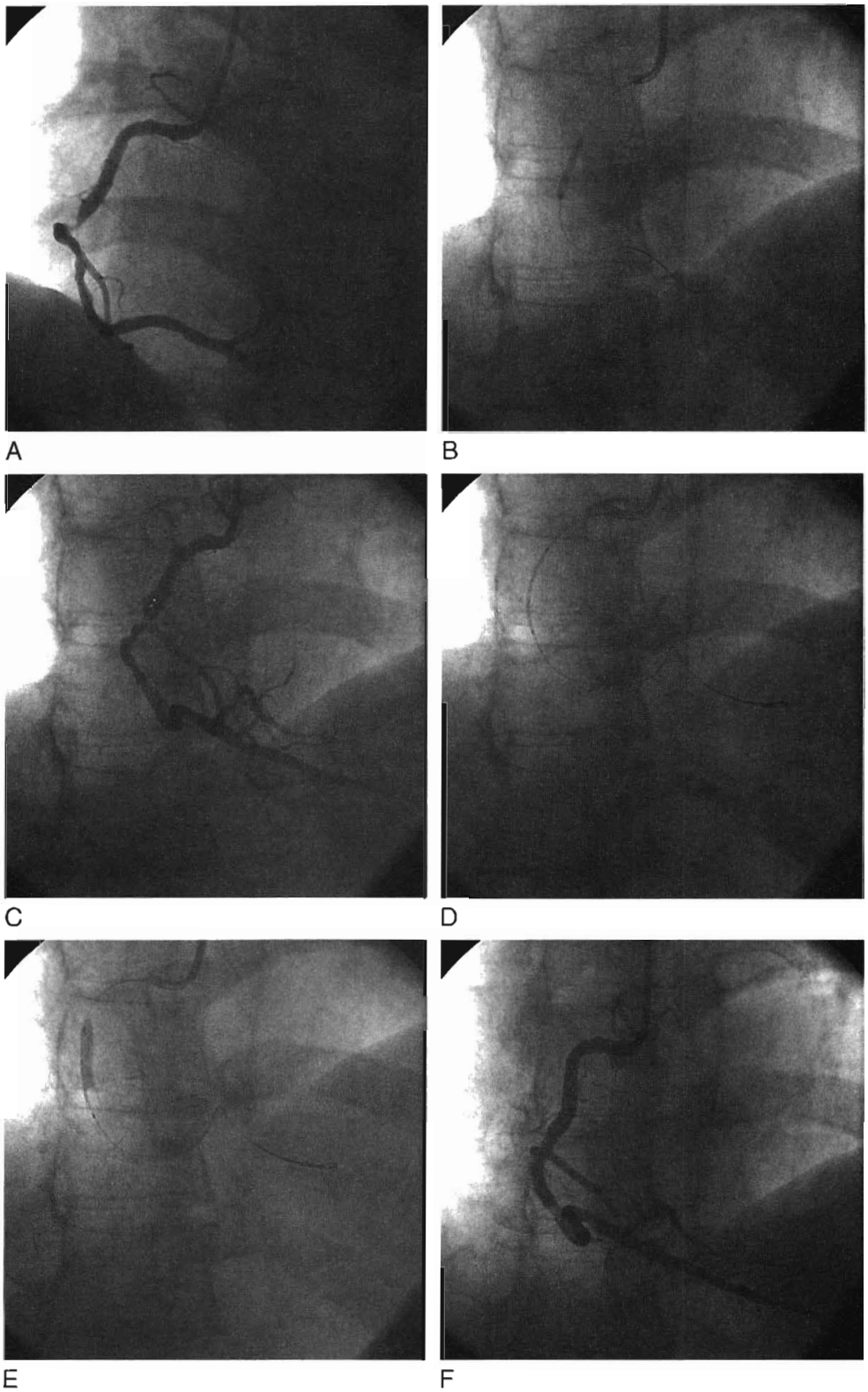


FIGURE 94–1. Coronary angioplasty procedure. *A*, Critical stenosis in the midsegment of a right coronary artery. *B*, Inflation of a 3.5-mm-diameter angioplasty balloon. *C*, Angiographic control after balloon inflation. *D*, Placement of a 3.5-mm-diameter, 18-mm-long metal stent. *E*, Inflation of the balloon. *F*, Final result.

and pulled out. The result is evaluated by injecting contrast medium (see Fig. 94-1*F*). If the result is satisfactory, the guidewire is removed. If the angiographic result is unsatisfactory, the guidewire remains in place. The balloon catheter can be replaced by a larger one, or another stent can be implanted. At the end of the procedure, a final angiogram is obtained to confirm that the result is satisfactory.

Recent improvements in stent profiles allow direct stent implantation without prior balloon dilatation. Direct stenting shortens the duration of the procedure and reduces

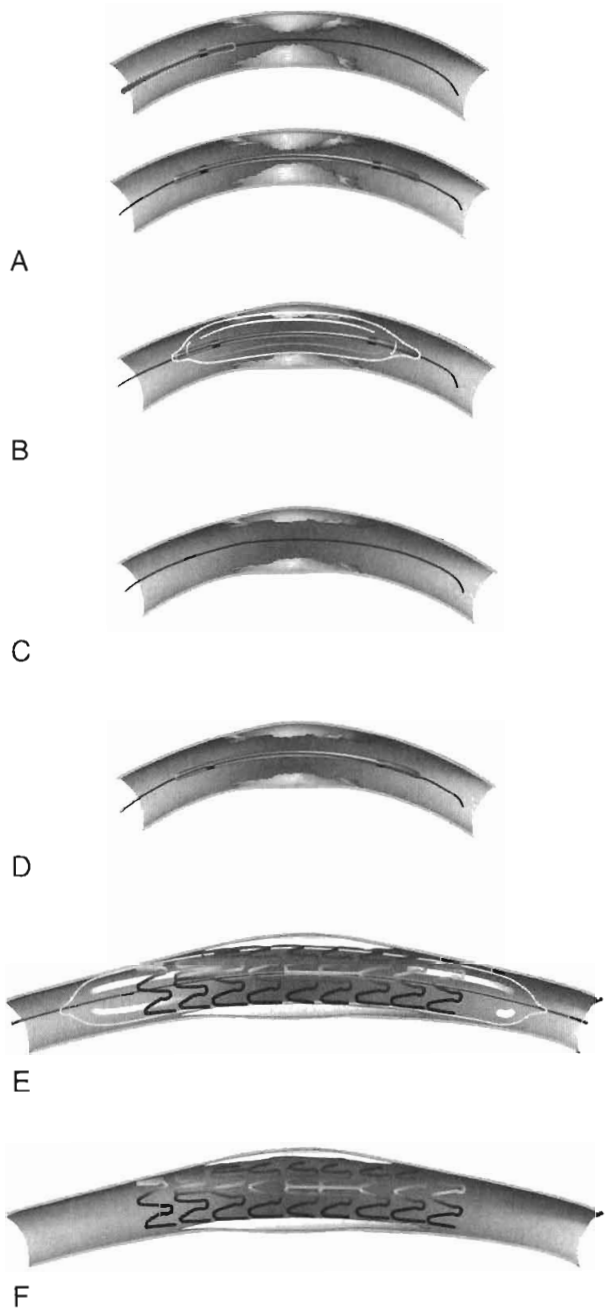


FIGURE 94–2. Implantation of a coronary stent. *A*, Placement of the balloon catheter. *B*, Predilatation with the balloon catheter. *C*, The balloon is withdrawn. *D*, Placement of the coronary stent, which has been crimped on a balloon catheter. *E*, Inflation of the balloon, and expansion of the stent. *F*, Withdrawal of the balloon catheter and the final result.

costs and can be applied in approximately 50% to 60% of cases.[5]

PRE- AND POSTPROCEDURE MANAGEMENT AND MEDICATIONS

The combination of low-dose aspirin (75 to 325 mg) and clopidogrel has been shown to reduce the incidence of acute stent occlusion after PTCA and is considered essential therapy before coronary interventions.[6,7] In the CREDO trial, patients were randomly assigned to receive a 300-mg clopidogrel loading dose (n = 1053) or placebo (n = 1063) 3 to 24 hours before PTCA. Thereafter, all patients received clopidogrel, 75 mg/day, through day 28. From day 29 through 12 months, patients in the loading-dose group received clopidogrel, 75 mg/day, and those in the control group received placebo. Aspirin was administered in all patients. Long-term (1 year) clopidogrel therapy significantly reduced the risk of adverse events. A loading dose of clopidogrel administered at least 3 hours before the procedure did not reduce adverse events at 28 days, but subgroup analysis suggests that an interval of at least 15 hours between the loading dose and PTCA improves outcome.[8,9] Unfractionated heparin (typically 5000 to 10,000 units) is administered intravenously during PTCA to decrease the incidence of coronary artery thrombosis,[10] but it is usually not continued after the procedure. Intracoronary nitrates are given at the beginning of and during the procedure to prevent vasospasm.

Although the mainstay of antiplatelet and anticoagulation therapy for PTCA is the combination of clopidogrel and aspirin before and after the procedure and heparin during it, the use of platelet glycoprotein IIb/IIIa inhibitors has emerged as a powerful adjunctive therapy. The platelet glycoprotein IIb/IIIa receptor binds fibrinogen to crosslink platelets and can be blocked irreversibly by inhibitors such as abciximab, eptifibatide, and tirofiban. Several multicenter, randomized studies have compared heparin and aspirin to an additional treatment with platelet glycoprotein IIb/IIIa receptor inhibitors in patients undergoing PTCA and showed a significant reduction in major clinical events.[11-18] The greatest treatment benefit of platelet glycoprotein IIb/IIIa inhibitors appears to be in procedures on high-risk lesions or in patients with severe clinical patterns, such as acute coronary syndromes with ST segment changes or elevation of biologic markers of myocardial necrosis.[19] In this setting, platelet glycoprotein IIb/IIIa inhibitors should be administered before the procedure and continued at least 12 to 18 hours afterward.

The femoral arterial sheath is usually removed immediately after PTCA. Hemostasis is obtained by either manual compression or the use of closure devices. The patient remains in bed for 6 to 12 hours. Patients with stable angina and an uncomplicated procedure are usually discharged the day after removal of the sheath. Medications prescribed at the time of discharge depend on the underlying condition. Most often, the post-PTCA regimen includes low-dose aspirin (75 to 325 mg/day), clopidogrel (75 mg/day), a beta blocker or a calcium antagonist, and a statin.

Although the femoral artery remains the most widely used approach for diagnostic and therapeutic procedures, the radial artery is used increasingly to reduce the local complication rate and increase the patient's comfort. The sheath is pulled out immediately after the procedure, and hemostasis is obtained by applying a pressure dressing for several hours.[20] Immediate ambulation is feasible, and hospital discharge on the same day is possible in selected cases.[21]

EFFICACY OF THE PROCEDURE

PTCA of a nonoccluded coronary artery is successful in more than 95% of patients.[22] In the remaining patients, PTCA is unsuccessful because the stenosis cannot be crossed with either the guidewire or the balloon catheter, or because the stenosis is not adequately dilated despite the use of an appropriately sized balloon and stents. In 3% to 5% of cases,

the vessel abruptly occludes (abrupt closure) during or immediately after the procedure. Reopening of the artery is attempted with repeat balloon inflations and multiple stent implantation. Stenting for abrupt closure (bailout stenting) has virtually eliminated the need for urgent coronary bypass surgery after failed PTCA. The most challenging lesions (long, angulated, calcified, or associated with intraluminal thrombus) carry a lower success rate.[23,24] PTCA also has a lower initial success rate (50% to 70%) in patients with chronically occluded arteries, because it may be difficult to manipulate the guidewire through a chronically occluded region.[25,26] In patients with recurrent angina after bypass surgery, the success rate of PTCA performed for properly selected stenoses of saphenous and arterial bypass grafts is close to that of native arteries, but the incidence of late events (myocardial infarction, repeat PTCA or other surgery) is higher.[27,28]

MECHANISMS OF CORONARY ARTERY DILATATION

The mechanisms by which PTCA increases the size of the arterial lumen have been studied in animals and cadavers.[29-32] Balloon-induced barotrauma causes endothelial denudation, cracking and disruption of the atherosclerotic plaque, and stretching or tearing of the media and adventitia (Fig. 94-3). These brutal and profound changes account for the post-PTCA angiographic features of intraluminal haziness, intimal flap, or dissection (Fig. 94-4). Intracoronary ultrasound imaging, which provides a cross-sectional view of the artery within the lumen, detects dissection of the arterial wall—sometimes extensive—in 50% to 80% of patients who have undergone successful PTCA.[33,34] These morphologic alterations open up new pathways for blood flow, leading to an increased luminal size. Balloon inflation may be deleterious, however, causing plaque hemorrhage, extensive dissection resulting in luminal compromise, platelet deposition, and thrombus formation.

In the weeks after successful PTCA, favorable remodeling of the disrupted plaque and endothelialization at the sites of intimal injury result in an increased luminal size. Angiographic studies indicate that intimal disruption usually resolves within 1 month after successful PTCA.[35]

RESTENOSIS

In patients who have undergone successful PTCA, recurrence of the stenosis, or restenosis, is the main limitation to long-term, event-free survival. Several definitions of restenosis have been suggested, but it is most commonly defined as more than a 50% narrowing of the diameter of the lumen at the site of a previously successful PTCA. Restenosis occurs in about 30% to 50% of patients in whom a coronary artery stenosis has been dilated by balloon alone.[36-38] Restenosis typically occurs 1 to 6 months after PTCA.[36]

The process of restenosis is multifactorial. Injury of the vessel initiates release of thrombogenic, vasoactive, and mitogenic factors.[39] Endothelial and deep-vessel injury leads to platelet aggregation, thrombus formation, inflammation, and activation of macrophages. These events induce the production and release of growth factors and cytokines, which in turn may promote their own synthesis and release from target cells.[40] A self-perpetuating process is initiated that results in the migration of smooth muscle cells from their usual location in the arterial media to the intima, where they change to a synthetic phenotype, produce extracellular matrix, and proliferate, thereby resulting in a stenosis within the vessel lumen. Intimal thickening accounts for about 30% of the loss in lumen diameter 6 months after coronary interventions. In addition, arterial remodeling occurs in the weeks after PTCA and can be evaluated using serial intravascular ultrasound imaging to measure the reduction in the cross-sectional area of the vessel.[41,42]

More than 70 trials enrolling more than 15,000 patients have evaluated various drugs to limit restenosis after PTCA.[43] Only one trial, using probucol, has shown beneficial results.[44] However, probucol must be administered 1 month before the procedure. In contrast, coronary stenting significantly reduces the incidence of restenosis because it produces large lumens and staves off pathologic remodeling.[45,46] Several multicenter, randomized trials showed that the incidence of restenosis is 25% to 50% lower after coronary stenting than after balloon angioplasty. Recently, drug-eluting stents have been developed to further reduce the restenosis rate. Stents are covered with a polymer that allows progressive delivery of antiproliferative drugs, such as sirolimus or paclitaxel, that inhibit smooth muscle cell proliferation. The restenosis rate is dramatically reduced with drug-eluting stents, with no increase in the acute complication rate. In the RAVEL trial, no restenosis was noted in patients receiving a drug-eluting stent, versus 26.6% in the bare metal stent group.[47] The SIRIUS trial included patients with more complex lesions, but a similar benefit was noted: restenosis occurred in 8.9% of patients receiving a drug-eluting stent, versus 36.3% of patients with bare metal stents.[48] Several large, ongoing randomized trials are testing

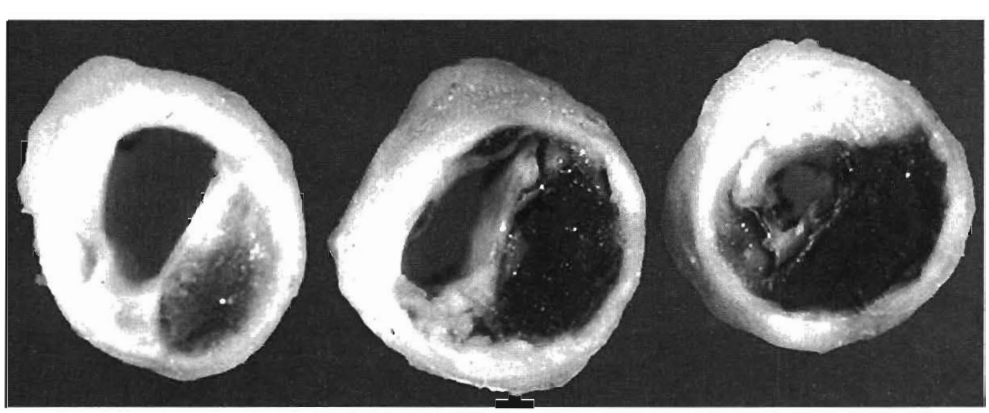


FIGURE 94–3. Pathologic specimen after coronary angioplasty. Balloon inflation has created plaque rupture with hemorrhage.

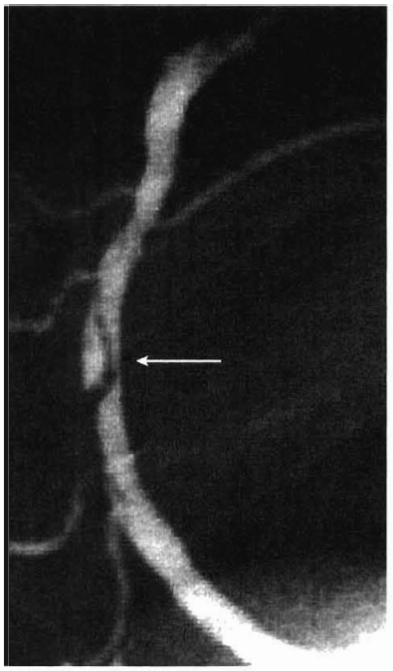


FIGURE 94–4. Arterial dissection (*arrow*) after balloon inflation in the midsegment of a right coronary artery.

the use of drug-eluting stents in various clinical situations, such as small vessels, acute myocardial infarction, and multivessel angioplasty. The widespread use of drug-eluting stents is currently limited by their availability and cost. Nevertheless, a sharp increase in the use of these devices is expected.[49]

OTHER CORONARY INTERVENTIONS

DIRECTIONAL ATHERECTOMY, LASER ANGIOPLASTY, AND ROTATIONAL ATHERECTOMY

Directional atherectomy extracts atherosclerotic tissue from the coronary artery with a cutting blade spinning at 5000 revolutions per minute in the tip of the atherectomy device.[50] During laser angioplasty, light emitted from optical fibers at the catheter tip vaporizes atheromatous tissue.[51] Rotational atherectomy uses a diamond-studded burr spinning at about 180,000 revolutions per minute to excavate calcified or fibrotic plaque.[52] In several randomized trials, these devices have not reduced the rates of late clinical events after coronary angioplasty,[53-55] and they are seldom used in current clinical practice.

CATHETER-BASED RADIOTHERAPY

Intracoronary gamma irradiation with iridium 192 has been proposed to prevent angiographic and clinical recurrence in patients undergoing treatment for in-stent restenosis.[56,57] Iridium 192 halves the need for repeat target lesion and vessel revascularization at 6 months and 5 years. However, this approach is time-consuming and technically difficult and is currently used only in selected cases of diffuse in-stent restenosis in highly specialized centers.

COMPARISON OF CLINICAL APPLICATIONS

Whether to recommend medical therapy, angioplasty, or surgical treatment remains a difficult decision in the care of individual patients with coronary artery disease. Nonetheless, the results of several clinical trials allow general guidelines to be developed.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY VERSUS MEDICAL THERAPY

PTCA has been compared with medical therapy for stable angina in several studies. In the Angioplasty Compared with Medicine study, patients with stable angina and single-vessel coronary disease were randomly assigned to treatment with PTCA or medical therapy.[58,59] In the Medicine, Angioplasty or Surgery study, patients with stable angina and a stenosis of the proximal left anterior descending artery were randomly assigned to medical therapy, PTCA, or bypass surgery of the left internal thoracic artery.[60] The Randomized Intervention Treatment of Angina (RITA-2) trial compared the long-term effects of PTCA and medical care in patients with coronary artery disease considered suitable for either treatment.[61] The Asymptomatic Cardiac Ischemia Pilot (ACIP) study randomized patients to three treatment strategies: angina-guided drug therapy, angina- plus ischemia-guided drug therapy, or revascularization by angioplasty or bypass surgery.[62] These studies suggest that PTCA provides more complete relief of angina than medical therapy does.

The TIMI IIIB study addressed the benefit of PTCA for patients with unstable angina or non–Q wave myocardial infarction.[63] This study enrolled 2220 patients with unstable angina and myocardial infarction without ST segment elevation who had electrocardiographic evidence of changes in the ST segment or T wave, elevated levels of cardiac markers, a history of coronary artery disease, or all three findings. Patients were randomly assigned to an early invasive strategy, which included routine catheterization within 4 to 48 hours and revascularization as appropriate, or to a more conservative (selectively invasive) strategy, in which catheterization was performed only if the patient had objective evidence of recurrent ischemia or an abnormal stress test. At 6 months, the rate of the primary endpoint (a composite of death, nonfatal myocardial infarction, and rehospitalization for acute coronary syndrome) was 15.9% with the early invasive strategy and 19.4% with the conservative strategy (odds ratio, 0.78; 95% confidence interval, 0.62 to 0.97; $P = 0.025$). In the FRISC II trial, 2457 patients were randomly assigned to invasive or noninvasive treatment and 3 months of dalteparin or placebo. After 1 year, in 100 patients, an invasive strategy saved 1.7 lives, prevented 2.0 nonfatal myocardial infarctions and 20 readmissions, and provided earlier and better symptom relief at the cost of 15 more patients with coronary artery bypass grafting and 21 more with percutaneous transluminal angioplasty.[64] An invasive approach with early (<24 hours) angiography is therefore the preferred strategy in patients with unstable coronary artery disease and signs of ischemia on electrocardiography or raised levels of biochemical markers of myocardial damage. Preprocedural treatment should include aspirin, clopidogrel, heparin, and platelet glycoprotein IIb/IIIa receptor inhibitors.

In patients with acute myocardial infarction, PTCA performed without prior thrombolytic therapy (primary PTCA) by an experienced team results in a lower risk of death or re-infarction than thrombolytic therapy does.[65-67] Stenting during primary angioplasty for acute myocardial infarction further reduces the occurrence of adverse events at 6 and 12 months.[68-70] Early administration of abciximab in patients with acute myocardial infarction improves coronary patency before stenting, the success rate of the stenting procedure, the rate of coronary patency at 6 months, left ventricular function, and clinical outcomes.[71] In patients with acute myocardial infarction complicated by cardiogenic shock, emergency revascularization improves survival at 6 months.[72] PTCA performed after failed thrombolytic therapy reduces adverse cardiac events and improves left ventricular function at 1 month.[73] In patients with right ventricular infarction, complete reperfusion of the right coronary artery by angioplasty results in dramatic recovery of right ventricular performance, as assessed by echocardiography, and an excellent clinical outcome.[74] In cardiac arrest, a strategy of immediate coronary angiography followed by angioplasty, if necessary, may increase survival.[4]

Thus, the results of clinical trials comparing PTCA with medical therapy suggest that the benefit of angioplasty depends on the severity and acuity of the clinical presentation. A gradient of risk extends across the spectrum of patients with coronary artery disease. At one end of the spectrum, patients with stable angina and one- or two-vessel disease treated medically are at low risk of nonfatal myocardial infarction. PTCA reduces angina more effectively, with a low risk of complications, but it does not lower the risk of death, myocardial infarction, or future revascularization procedures. In practice, initial revascularization by PTCA is proposed in this setting if the amount of myocardium at risk is high and if the lesions seem at low risk for procedure-related complications. At the other end of the spectrum, patients with acute coronary syndromes have a high risk of major complications and death that is significantly improved by PTCA and potent antithrombotic regimens.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY VERSUS BYPASS SURGERY

Several studies have compared PTCA with bypass surgery for patients with multivessel coronary artery disease. Despite the use of different protocols, the studies have yielded consistent results.[75-81] Major complications, such as death or myocardial infarction, occur with similar frequencies 1 to 5 years after angioplasty or bypass surgery. However, there is an increased need for repeat revascularization procedures in patients who are randomized to PTCA. In addition, in the BARI study, diabetic patients had higher rates of survival 5 years after treatment with bypass surgery.[75] New randomized trials comparing PTCA with bypass surgery are now being performed with the use of drug-eluting stents.

In practice, most patients with multivessel disease have diffuse lesions or chronic occlusions that are not amenable to PTCA. Bypass surgery therefore remains the preferred therapeutic option in this subset of patients, such as those with left main and triple-vessel coronary artery disease with critical obstruction of the proximal left anterior descending artery or left ventricular dysfunction. Nondiabetic patients with multivessel coronary disease who are good candidates for either PTCA or bypass surgery can be reassured that both revascularization approaches are followed by equivalent rates of major complications. However, the invasive nature of bypass surgery must be weighed against the likelihood of repeated procedures after PTCA. Whether the use of drug-eluting stents will reduce the rate of re-intervention after angioplasty in patients with multivessel disease and change these guidelines remains to be proved by ongoing trials

MITRAL VALVULOPLASTY

In patients with severe mitral stenosis, surgical mitral commissurotomy alleviates symptoms and improves mid- and long-term prognosis. Percutaneous mitral valvuloplasty was first applied in 1984 to young patients with rheumatic mitral stenosis using a transseptal approach.[82] The technique is widely accepted as an alternative to surgical repair or replacement in such cases, as well as in patients with more rigid calcific lesions. Selection of patients is based on the echocardiographic features of the mitral valve.[83]

The transseptal approach is the most commonly used technique. After puncture of the intra-arterial septum with a needle and a long sheath, a large (23- to 25-mm diameter) valvuloplasty balloon is advanced through the atrial opening and positioned across the mitral valve. Stepwise inflation of this balloon results in separation of the fused commissures, similar to the surgical technique of mitral commissurotomy.

Overall procedure mortality is 1% to 2%. Long-term follow-up studies demonstrate preservation of the improved mitral orifice.[84]

AORTIC VALVULOPLASTY

Calcific aortic stenosis in an adult is the most common indication for the more than 25,000 aortic valve replacements performed in the Unites States each year. With the evident success of balloon valvuloplasty for mitral stenosis, percutaneous aortic balloon valvuloplasty was proposed as an alternative to surgery. The balloon catheter is advanced retrogradely through the aortic stenosis using a femoral approach in most cases. Mid- and long-term results are disappointing; improvement in the orifice area is less than that obtained with a valve replacement, and echocardiographic follow-up shows recurrence of aortic stenosis in most cases.[85] Aortic valvuloplasty is therefore reserved for adult patients with severe calcific aortic stenosis who have severe comorbidities that preclude aortic valve replacement, or it is used in patients as a "bridge" to definitive surgical correction.[83,84] Preliminary results involving the percutaneous transcatheter implantation of a heart valve prosthesis for aortic stenosis are promising.[86]

CONCLUSION

The past 20 years have seen the explosive growth of interventional techniques. PTCA has become the most widely used method of coronary revascularization. Coronary stenting has revolutionized the practice of interventional cardiology by partially overcoming the limitations of coronary balloon angioplasty, such as abrupt vessel closure and restenosis. In patients with stable angina, PTCA reduces symptoms more effectively than medical therapy does, with

a low risk of complications. Patients with acute coronary syndromes have a high risk of major complications and death that can be significantly reduced by PTCA. Drug-eluting stents further reduce the restenosis rate and will almost certainly enhance or expand clinical indications, especially in patients with multivessel disease. As with all new techniques, careful validation of their utility will be necessary to ensure their optimal use in patient care.

ANNOTATED REFERENCES

Andersen HR, Nielsen TT, Rasmussen K, et al: A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. N Engl J Med 2003;349:733-742.

In this study, 1572 patients with acute myocardial infarction were randomized to treatment with angioplasty or accelerated treatment with intravenous alteplase; 1129 patients were enrolled at 24 referral hospitals, and 443 patients were enrolled at 5 invasive treatment centers. The primary endpoint (a composite of death, re-infarction, or disabling stroke) was reached in 8.5% of the patients in the angioplasty group, compared with 14.2% of those in the fibrinolysis group (P = 0.002). A reperfusion strategy involving the transfer of patients to an invasive treatment center for primary angioplasty is superior to on-site fibrinolysis, provided the transfer takes 2 hours or less.

Bowers TR, O'Neill WW, Grines C: Effect of reperfusion on biventricular function and survival after right ventricular infarction. N Engl J Med 1998;338:933-940.

Echocardiographic studies were performed before and after angioplasty in 53 patients with acute right ventricular infarction. Complete reperfusion of the right coronary artery by angioplasty resulted in the dramatic recovery of right ventricular performance and an excellent clinical outcome. In contrast, unsuccessful reperfusion was associated with impaired recovery of right ventricular function, persistent hemodynamic compromise, and a high mortality rate.

Hochman JS, Sleeper LA, Webb JG: Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK investigators: Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock? N Engl J Med 1999;341:625-634.

Patients with shock due to left ventricular failure complicating myocardial infarction were randomly assigned to emergency revascularization (152 patients) or initial medical stabilization (150 patients). Revascularization was accomplished by either coronary artery bypass grafting or angioplasty. Intra-aortic balloon counterpulsation was performed in 86% of the patients in both groups. Six-month mortality was lower in the revascularization group than in the medical therapy group (50.3% versus 63.1%; P = 0.027). Early revascularization should be strongly considered for patients with acute myocardial infarction complicated by cardiogenic shock.

Moses JW, Leon MB, Popma JJ, et al: Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315-1323.

Drug-eluting stents significantly reduce the occurrence of restenosis. It occurred in 8.9% of patients receiving drug-eluting stents, versus 36.3% of patients with bare metal stents.

Wallentin L, Lagerqvist B, Husted S, et al: Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: The FRISC II invasive randomised trial. Lancet 2000;356:9-16.

In this study, 2457 patients were randomly assigned to invasive or noninvasive treatment. After 1 year, in 100 patients, an invasive strategy saved 1.7 lives, prevented 2.0 nonfatal myocardial infarctions and 20 readmissions, and provided earlier and better symptom relief. An invasive approach with early (<24 hours) angiography is therefore the preferred strategy in patients with unstable coronary artery disease and signs of ischemia on electrocardiography or raised levels of biochemical markers of myocardial damage.

Chapter 95
SUPRAVENTRICULAR ARRHYTHMIAS

John Camm • Irina Savelieva

KEY POINTS

1. **Supraventricular tachycardia** (SVT) is characterized by narrow QRS complexes, but differentiating SVT from ventricular tachycardia may be necessary when bundle branch block, rate-dependent aberrancy, and antidromic atrioventricular (AV) reentry tachycardia are present.
2. **If the diagnosis of SVT cannot be proved**, the arrhythmia should be treated as ventricular tachycardia.
3. **Immediate direct-current (DC) cardioversion** is the treatment for any hemodynamically unstable tachycardia.
4. **In hemodynamically stable paroxysmal junctional tachycardias** (AV nodal reentry tachycardia and AV reentry tachycardia), vagotonic maneuvers should be tried first, because they may terminate tachycardia in about 50% patients without the need to resort to pharmacologic therapy.
5. Intravenous adenosine, verapamil, and esmolol are **first-line drug therapies for paroxysmal junctional tachycardias**, but adenosine and verapamil should not be used for wide complex tachycardias and atrial fibrillation with preexcitation.
6. **DC cardioversion or pharmacologic conversion** with intravenous ibutilide or flecainide is appropriate for the termination of atrial fibrillation associated with preexcitation syndrome.
7. **Intravenous verapamil, diltiazem, esmolol, metoprolol, and propranolol** can rapidly accomplish rate control in atrial fibrillation but may be less effective in atrial flutter.
8. **Beta blockers are preferable** in atrial fibrillation associated with thyrotoxicosis.
9. **Pharmacologic cardioversion of atrial fibrillation** in the absence of severe underlying heart disease can be attained using oral or intravenous flecainide or propafenone and intravenous ibutilide, but the last is more effective in atrial flutter.
10. **Propafenone and flecainide may result in atrial flutter** with slow atrial rates and 2:1 or 1:1 AV conduction, and verapamil, diltiazem, or beta blockers should be available to treat this complication; ibutilide can significantly prolong the QT interval and cause polymorphic ventricular tachycardia that, if sustained, may require DC cardioversion.
11. **Intravenous amiodarone should be considered as first-line drug therapy** in patients with severely impaired left ventricular function.
12. Digoxin is not useful for **rate control** in the emergency setting.
13. **Accelerated AV rhythm and atrial tachycardia with AV block** commonly occur as a result of digitalis toxicity; digitalis withdrawal is the usual therapy.
14. **Anticoagulation is indicated if atrial fibrillation or flutter persists for more than 48 hours or if the duration is unknown**; anticoagulation and rate control should be the initial therapy in these patients.
15. **An alternative approach is transesophageal echocardiography**, to exclude the presence of atrial thrombi or dense spontaneous echo contrast, and short-term anticoagulation with low-molecular-weight heparin, followed by DC or pharmacologic cardioversion.
16. Patients with **paroxysmal junctional tachycardias, atrial tachycardia, atrial flutter, and first-onset or recurrent atrial fibrillation** should be referred to a cardiologist for long-term management; effective nonpharmacologic therapies are available for these arrhythmias.

CLASSIFICATION AND EPIDEMIOLOGY

Supraventricular arrhythmias include rhythms arising from the sinus node and the adjacent atrial tissue (inappropriate sinus tachycardia, sinoatrial reentry tachycardia), both the right and the left atria (atrial tachycardia, flutter, and fibrillation), the atrioventricular (AV) node (AV nodal reentry tachycardia, accelerated ectopic junctional rhythm), and the AV node with involvement of an accessory pathway or multiple pathways (AV reentry tachycardia) (Fig. 95-1).

ATRIOVENTRICULAR NODAL REENTRY TACHYCARDIA AND ATRIOVENTRICULAR REENTRY TACHYCARDIA

AV nodal reentry tachycardia and AV reentry tachycardia are usually referred to as paroxysmal supraventricular

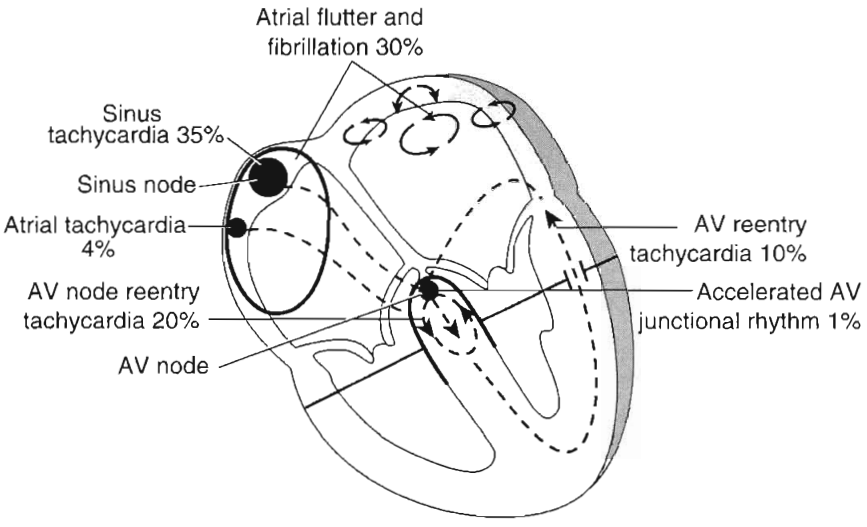


FIGURE 95–1. Supraventricular tachyarrhythmias encountered in the emergency setting. AV, atrioventricular.

tachycardias and are often seen in young patients with little or no structural heart disease, although a congenital heart abnormality giving rise to increased atrial pressure and dilatation (e.g., Ebstein's anomaly, atrial septal defect, Fallot's tetralogy) can coexist in a small percentage of patients with these arrhythmias.[1] The first presentation is common between age 12 and 30 years, and the prevalence is approximately 2.5 per 1000. Women are twice as likely as men to present with AV nodal reentry tachycardia.

ATRIAL FLUTTER AND FIBRILLATION

Atrial fibrillation is the most common supraventricular arrhythmia, affecting 1% to 2% of the general population, especially the elderly. It is usually associated with cardiovascular pathologies, among which hypertension and congestive heart failure prevail.[2] About one third of patients, however, present with no underlying heart disease and are considered to have "lone" atrial fibrillation. The epidemiology of isolated atrial flutter is largely unknown and is believed to be in the range of 0.037% to 0.88% per 1000 person-years, but nearly half these patients also have atrial fibrillation as a coexistent arrhythmia.

ATRIAL TACHYCARDIA

Atrial tachycardia affects 0.34% to 0.46% of patients with arrhythmias and is common in younger individuals following surgical correction of congenital heart disease and in the elderly, in whom it often occurs in association with atrial fibrillation.

OTHER SUPRAVENTRICULAR TACHYCARDIAS

Inappropriate sinus tachycardia and sinoatrial reentry tachycardia are less well defined clinical and electrocardiographic entities, and their prevalence and associated conditions are not well appreciated. Sinoatrial reentry tachycardia is found incidentally in 1.8% to 16.9% of patients undergoing electrophysiologic study for other supraventricular tachyarrhythmias.

CLINICAL PRESENTATION

The leading symptom of most supraventricular tachyarrhythmias, particularly AV nodal reentry tachycardia and AV reentry tachycardia, is rapid, regular palpitations, usually with an abrupt onset; they can occur spontaneously or be precipitated by simple movements. A common feature of tachycardias that involve circulation through the AV node is termination by Valsalva's maneuvers. In younger individuals with no structural heart disease, the rapid heart rate can be the main pathologic finding. Other symptoms may include anxiety, dizziness, dyspnea, neck pulsation, central chest pain, weakness, and occasionally polyuria due to the release of atrial natriuretic peptide in response to increased atrial pressures (more common in atrial tachycardia and AV nodal reentry tachycardia). Prominent jugular venous pulsations due to atrial contractions against closed AV valves may be observed during AV nodal reentry or AV reentry tachycardia.

True syncope is relatively uncommon unless uncontrolled tachycardia over 200 beats per minute is sustained for a long period, especially in patients who remain standing. Syncope has been reported in 10% to 15% of patients, usually just after onset of the arrhythmia or in association with a prolonged pause following its termination. However, in older patients with concomitant heart disease such as aortic stenosis, hypertrophic cardiomyopathy, and cerebrovascular disease, significant hypotension and syncope may result from profound hemodynamic collapse associated with only moderately fast ventricular rates.

It is essential to recognize that patients presenting with AV reentry tachycardia may also present with atrial fibrillation. If an accessory pathway has a short antegrade effective refractory period (<250 msec), it may conduct to the ventricles at an extremely high rate and cause ventricular fibrillation. The incidence of sudden death is 0.15% to 0.39% per patient-year, and it may be the first manifestation of the disease in younger individuals.

Irregular palpitations may be due to atrial premature beats, atrial flutter with varying AV conduction block, atrial fibrillation, or multifocal atrial tachycardia. Although highly symptomatic, these arrhythmias usually have a benign hemodynamic prognosis. However, in patients with depressed

ventricular function, uncontrolled atrial fibrillation can reduce cardiac output and precipitate hypotension and congestive heart failure. Atrial fibrillation in association with slow AV conduction or complete block (Frederick's syndrome) may result in hemodynamic collapse. Inappropriate sinus tachycardia and nonparoxysmal accelerated junctional rhythm are characterized by relatively slow heart rates and gradual onset and termination.

ELECTROCARDIOGRAPHY

Whenever possible, a 12-lead electrocardiogram (ECG) should be taken during tachycardia. If a patient with an arrhythmia is hemodynamically unstable, a monitor strip should be obtained from the defibrillator before electrical discharge.

NARROW-COMPLEX TACHYCARDIAS

The typical ECG feature is narrow QRS complexes less than 120 msec. In this case, the tachycardia is almost always supraventricular, and the differential diagnosis relates to its mechanism (Fig. 95-2).

WIDE-COMPLEX TACHYCARDIAS

The differential diagnostic features of wide-complex tachycardias favoring a supraventricular origin of the arrhythmia include, but are not limited to, preexistent bundle branch block; rate-dependent aberrancy; antidromic AV reentry tachycardia, when an accessory pathway conducts and excites the ventricles retrogradely; and prominent electrolyte abnormalities (e.g., hypokalemia) resulting in QRS widening (Fig. 95-3). If the diagnosis of supraventricular tachycardia cannot be proved, the patient should be treated as if ventricular tachycardia is present. Immediate direct-current (DC) cardioversion is the treatment for any hemodynamically unstable tachycardia.

ATRIOVENTRICULAR NODAL REENTRY TACHYCARDIA

MECHANISM

In AV nodal reentry tachycardia, there are two functionally and anatomically different pathways within the AV node: one is characterized by a short effective refractory period and slow conduction, and the other has a longer effective refractory period and faster conduction. In sinus rhythm, the atrial impulse that depolarizes the ventricles usually conducts through the fast pathway. If the atrial impulse (e.g., an atrial premature beat) occurs early, when the fast pathway is still refractory, the slow pathway takes over in propagating the atrial impulse to the ventricles; it then travels back through the fast pathway, which by then has recovered its excitability, thus initiating the most common "slow-fast," or typical, AV nodal reentry tachycardia.

ELECTROCARDIOGRAPHIC PRESENTATION

In sinus rhythm, the ECG is usually normal, unless other unrelated abnormalities are present. During AV nodal reentry tachycardia, the rhythm is regular, with narrow QRS complexes and a rate of 140 to 250 beats per minute. The atria are activated retrogradely, producing the inverted P waves in leads II, III, and avF. Because atrial and ventricular depolarization occurs simultaneously, the P waves are often obscured by the QRS complexes and cannot be detected on the surface ECG (Fig. 95-4*A*). However, in about one third of cases of slow-fast AV nodal reentry tachycardia, a terminal positive deflection in lead avR or V_1 (or both), imitating right bundle branch block, or pseudo–S waves in the inferiorly oriented leads may be present, reflecting retrograde activation of the atria. Tachycardia using these pathways in reverse ("fast-slow," or long RP, tachycardia) is less common (5% to 10% of cases).

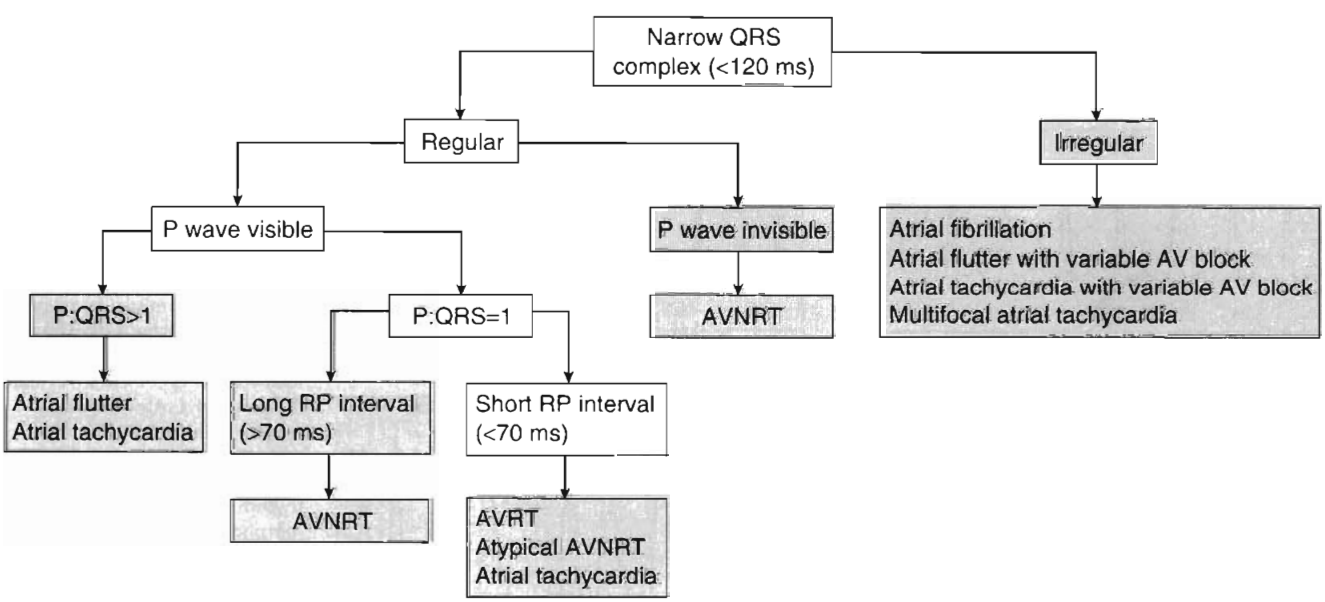


FIGURE 95–2. Differential diagnosis for narrow QRS complex (presumably supraventricular) tachycardias. Note that ventricular tachycardia may present with the narrow QRS complexes (e.g., fascicular tachycardia). AV, atrioventricular; AVNRT, atrioventricular nodal reentry tachycardia; AVRT, atrioventricular reentry tachycardia.

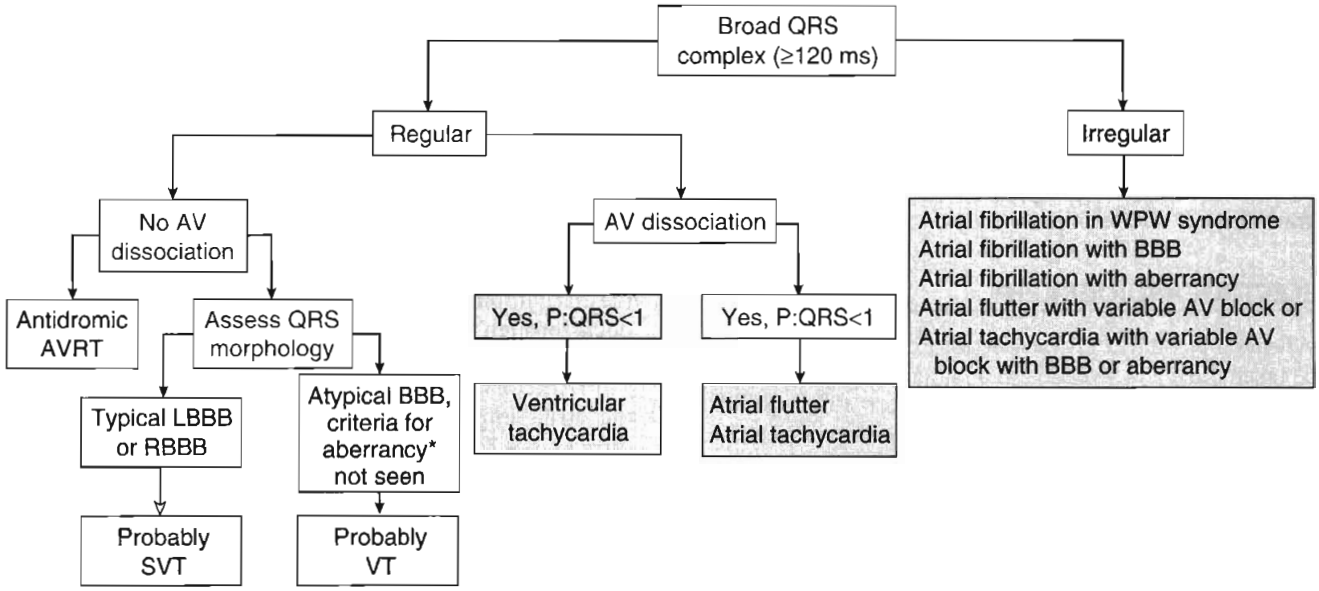


FIGURE 95–3. Differential diagnosis for wide QRS complex tachycardias. AV, atrioventricular; AVRT, atrioventricular reentry tachycardia; BBB, bundle branch block; LBBB, left bundle branch block; RBBB, right bundle branch block; SVT, supraventricular tachycardia; WPW, Wolff-Parkinson-White; VT, ventricular tachycardia.
*Criteria for aberrancy: rate dependency, triphasic QRS complexes, rSR in V_1, with R>, QRS width <140 msec, QRS deflections are discordant in precordial leads, absence of fusion and capture beats.

ATRIOVENTRICULAR REENTRY TACHYCARDIA

ACCESSORY PATHWAYS

AV reentry tachycardia occurs as a result of an anatomically distinct AV connection, termed an accessory pathway, produced by incomplete separation of the atria and ventricles during fetal development. The most common accessory pathways of the AV type (often called Kent's bundles) are located around the mitral or tricuspid annulus. In about 10% of cases, they are multiple.

Accessory pathways are capable of conduction in either or both directions. Accessory pathways that are capable of antegrade conduction are referred to as "manifest," demonstrating a delta wave during sinus rhythm when the atrial impulses conduct over the accessory pathway without encountering AV delay. The PR interval is short (<120 msec), and the QRS complex is wide; this occurs because the atrial impulse enters a nonspecialized ventricular myocardium, and depolarization progresses slowly at first, giving rise to the delta wave before it is overtaken by a depolarization wavefront propagating via the normal conduction tissue. An accessory pathway that is capable of only retrograde conduction is termed "concealed" and does not produce a short PR interval or a delta wave during sinus rhythm.

MECHANISM AND ELECTROCARDIOGRAPHIC PRESENTATION

The reentry circuit of orthodromic AV reentry tachycardia involves the AV node and an accessory pathway, with the impulses conducting from the atria to the ventricles over

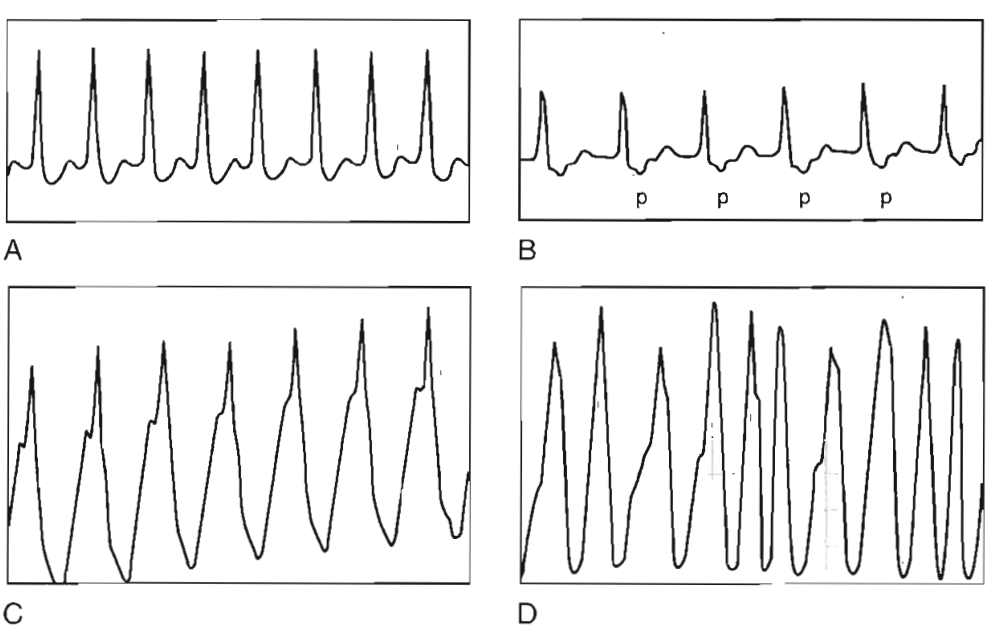


FIGURE 95–4. *A*, Atrioventricular nodal reentry tachycardia, slow-fast type. Note the narrow QRS complexes and the absence of P waves. *B*, Atrioventricular reentry orthodromic tachycardia. The retrograde inverted P waves follow the QRS complexes in leads II, III, and avF. *C*, Atrioventricular reentry antidromic tachycardia with wide QRS complexes. An electrocardiogram during sinus rhythm with a QRS complex morphology identical to that seen during tachycardia may be helpful in the diagnosis. *D*, Atrial fibrillation in preexcitation syndrome with a fast ventricular rate response.

TABLE 95–1. VAGAL MANEUVERS TO TERMINATE TACHYCARDIA

Carotid Sinus Massage

Ensure that there is no significant carotid artery disease (carotid bruits)
Monitor the electrocardiogram continuously
Place the patient in the supine position with the head slightly extended
Start with right carotid sinus massage
Apply firm rotatory or steady pressure to the carotid artery at the level of the third cervical vertebra for 5 sec
If no response, massage the left carotid sinus
Generally, right carotid sinus massage decreases sinus node discharge, and left carotid sinus massage slows atrioventricular conduction
Do not massage both carotids at the same time
A single application of carotid sinus pressure is effective in about 20% to 30% of patients with paroxysmal supraventricular tachycardias; multiple applications terminate tachycardia in about 50% of patients
Asystole is a potential but rare complication

Valsalva's Maneuver

Valsalva's maneuver involves an abrupt voluntary increase in intrathoracic and intra-abdominal pressures by straining
Monitor the electrocardiogram continuously
Place the patient in the supine position
The patient should not take a deep inspiration before straining
Ideally, the patient blows into a mouthpiece of a manometer against the pressure of 30-40 mm Hg for 15 sec
Alternatively, the patient strains for 15 sec while breath-holding
Transient acceleration of tachycardia usually occurs during the strain phase as a result of sympathetic excess
On release of strain, the rate of tachycardia slows because of the compensatory increase in vagal tone (baroreceptor reflex); it may terminate in about 50% of patients
Termination of tachycardia may be followed by pauses and ventricular ectopics

the AV node and traveling in the reverse direction through the accessory pathway (see Fig. 95-4*B*). In antidromic AV reentry tachycardia, the reentrant impulses conduct antegradely from the atria to the ventricles via an accessory pathway and retrogradely via the AV node or a second accessory pathway (see Fig. 95-4*C*). Antidromic AV reentry tachycardia is uncommon (<10% of cases). Atrial fibrillation is usually encountered in patients with antegradely conducting pathways (see Fig. 95-4*D*).

ACUTE MANAGEMENT

In an emergency, distinguishing between AV nodal reentry tachycardia and AV reentry tachycardia may be difficult, but it is usually not critical, because both tachycardias respond to the same treatment. If the patient is hemodynamically stable, vagal maneuvers, including carotid sinus massage, Valsalva's maneuver, and facial immersion in cold water, can terminate tachycardia in about 50% patients (Table 95-1).[3,4] Commercially available gel packs can be used as cold compresses instead of facial immersion, but the most important element is wet nostrils and breath-holding.

PHARMACOLOGIC TERMINATION

AV blocking agents, such as adenosine, verapamil, diltiazem, and beta blockers, are effective in terminating both AV nodal reentry and AV reentry tachycardia (Table 95-2).[1]

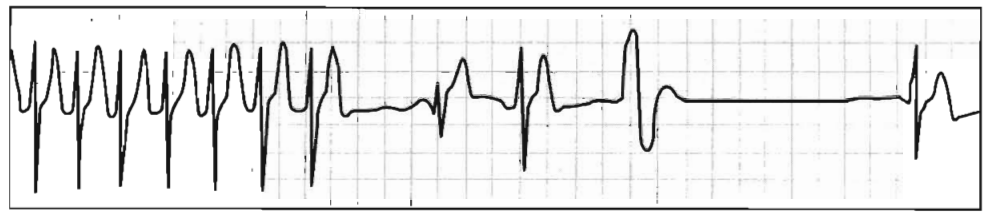
Adenosine

Intravenous (i.v.) adenosine is effective in diagnosing, rate slowing, and occasionally terminating the narrow-complex tachycardias.[5] Adenosine usually terminates AV nodal reentry tachycardia and AV reentry tachycardia but rarely interrupts the atrial flutter circuit and does not suppress automatic atrial tachycardia; it can, however, produce high-degree AV

TABLE 95–2. ACUTE PHARMACOLOGIC RATE CONTROL IN ATRIAL TACHYARRHYTHMIAS

Drug	Route of Administration	Dose	Onset	Potential Adverse Effects
Verapamil	Intravenous	5-10 mg (0.075-0.15 mg/kg) over 2 min; if no response, additional 5-10 mg after 15-30 min; 3-10 mg every 4-6 h for rate control	3-5 min	Hypotension, bradycardia, heart block, possible deterioration of ventricular function in the presence of organic heart disease
Diltiazem	Intravenous	0.25 mg/kg over 2 min; if no response, additional 0.35 mg/kg after 15-30 min; followed by 5-15 mg/h infusion for rate control	2-7 min	
Esmolol	Intravenous	0.5 mg/kg over 1 min, followed by 0.05-0.2 mg/kg/min for 4 min; if no response after 5 min, 0.5 mg/kg for 1 min, followed by 0.1 mg/kg for 4 min; infusion 0.05-0.2 mg/kg/min for rate control	2-3 min	Hypotension, bradycardia, heart block, possible deterioration of ventricular function in the presence of organic heart disease
Metoprolol	Intravenous	2.5-5 mg over 2 min followed by repeat doses if necessary (total 10-15 mg)	5 min	
Atenolol	Intravenous	2.5 mg over 2 min, followed by repeat doses if necessary (total 10 mg) or infusion 0.15 mg/kg for 20 min	5-10 min	
Propranolol	Intravenous	1 mg over 1 min (total 10-12 mg; 0.15 mg/kg)	5 min	
Digoxin	Intravenous	0.5-1 mg, followed by 0.25 mg every 2-4 h (maximum, 1.5 mg)	30-60 min	Bradycardia, atrioventricular block, atrial arrhythmias, ventricular tachycardia

Intravenous amiodarone can also be effective in rate control, especially in patients with poor left ventricular function, but there is insufficient evidence to support this recommendation. The rate-slowing effect of amiodarone is usually delayed by 1-2 hours.



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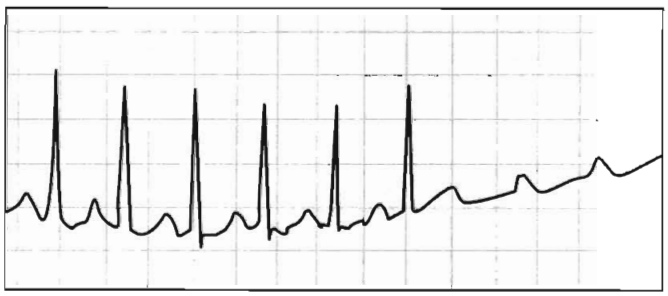

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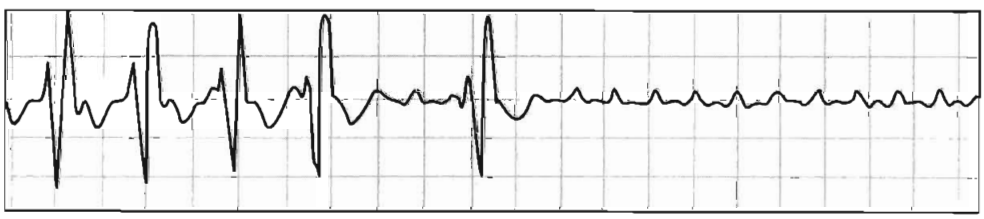

C

FIGURE 95–5. *A,* Adenosine usually terminates atrioventricular reentry tachycardias. *B* and *C,* It rarely interrupts the atrial flutter circuit or suppresses automatic focal atrial tachycardia but produces high-degree atrioventricular block during which the tachycardia persists.

block during which the tachycardia persists (Fig. 95-5). It has no effect on most ventricular tachycardias. Adenosine is advantageous compared with verapamil because of its rapid onset and the absence of a negative inotropic effect in patients with poor left ventricular function and those with significant hypotension.

Adenosine is administered as a very rapid 3- to 6-mg i.v. bolus; if this is ineffective, another 6- to 12-mg bolus can be given 2 to 5 minutes later. Adenosine is metabolized very quickly, with an effective half-life of 10 seconds. Adverse effects, including dyspnea, facial flushing, and chest tightness, are therefore short-lived, but in about 12% of patients, adenosine may shorten the atrial effective refractory period and provoke atrial flutter or fibrillation or accelerate conduction over the accessory pathway and produce a rapid ventricular response. In a proportion of patients, ventricular premature beats and nonsustained ventricular tachycardia may occur after the successful termination of supraventricular tachycardia.[6] Some individuals, particularly heart transplant recipients, are unusually sensitive to adenosine and require a lower dose (1 mg).

Verapamil and Diltiazem

Verapamil is administered intravenously as a 5- to 10-mg bolus over 2 minutes, and the effect on tachycardia is expected in 5 to 10 minutes. If necessary, a second bolus of 10 mg can be given 30 minutes after the initial dose. Vagal maneuvers can be effective at this stage. Verapamil should not be used for wide-complex tachycardias. Intravenous verapamil is contraindicated in patients with poor left ventricular function or heart failure, and it should not be administered after pretreatment with oral and especially i.v. beta blockers. It should not be used for atrial fibrillation associated with preexcitation syndrome, because it may result in acceleration of conduction over antegradely conducting accessory pathway, especially with a short effective refractory period, a rapid ventricular response, and ventricular fibrillation. DC cardioversion or pharmacologic conversion with i.v. ibutilide or flecainide is appropriate for termination of atrial fibrillation with preexcitation. Diltiazem is an alternative to verapamil, but lower effective rates have been reported with this drug.[7]

Beta Blockers

Among beta blockers, esmolol, administered as an i.v. infusion at a rate of 50 to 200 μg/kg per minute, is the agent of choice because of its rapid onset. More readily available i.v. metoprolol, atenolol, and propranolol can also be considered (see Table 95-2). Excessive bradycardia caused by AV node blocking agents can be countered with i.v. injection of atropine 0.6 to 2.4 mg in divided doses of 0.6 mg.

Other Antiarrhythmic Agents

Because adenosine, verapamil, diltiazem, and beta blockers are so highly effective in terminating AV nodal reentry tachycardia and AV reentry tachycardia, specific antiarrhythmic drugs such as propafenone, flecainide, sotalol, ibutilide, and amiodarone are seldom needed in the acute setting. Digoxin is not useful because it is often ineffective and may facilitate conduction over the accessory pathway, shorten the atrial effective refractory period, and promote atrial fibrillation.

ATRIAL PACING

In patients with implantable devices, antitachycardia pacing facilities can be used to terminate the arrhythmia. However, there is also a risk of inducing atrial fibrillation with a rapid

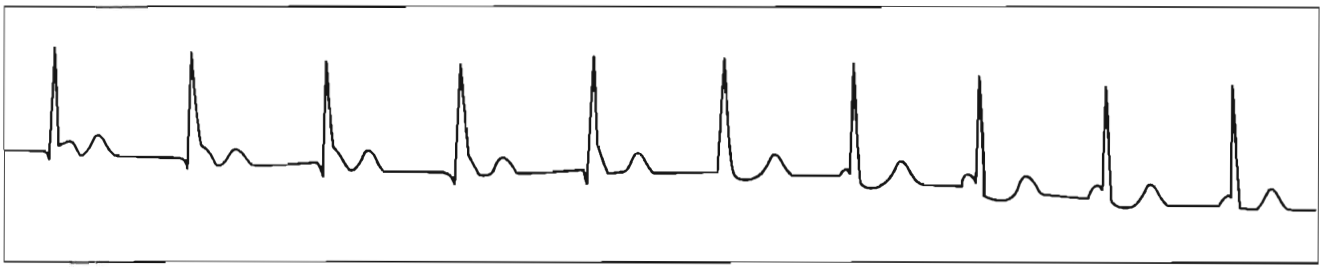

FIGURE 95–6. Accelerated junctional rhythm with independent sinus node activity.

ventricular response in a patient with an antegradely conducting accessory pathway.

LONG-TERM MANAGEMENT

Patients with AV nodal reentry tachycardia and AV reentry tachycardia should be referred to a cardiologist for electrophysiologic evaluation and long-term management. Both pharmacologic and nonpharmacologic alternatives, including ablation of an accessory pathway, are widely available.

ACCELERATED ATRIOVENTRICULAR RHYTHM

Accelerated AV rhythm is produced by abnormal automaticity in the AV node. It is a narrow QRS complex tachycardia (unless bundle branch block is present), with the ventricular rate ranging from 70 to 250 beats per minute. AV dissociation is also present, because the atria are activated normally by the sinus node impulse while the ventricles are depolarized from an accelerated junctional site (Fig. 95-6). This arrhythmia is commonly due to digitalis toxicity, and drug withdrawal is the usual therapy. If the rate of the AV node pacemaker is not fast, atropine can be given to increase the sinus node discharge until it resumes its dominance.

ATRIAL FIBRILLATION AND ATRIAL FLUTTER

Atrial fibrillation with a fast ventricular response is the most common supraventricular arrhythmia encountered in the emergency department in both younger adults with first-onset arrhythmia and older patients presenting with decompensation. Atrial flutter shares these clinical presentations and requires similar initial therapy. The acute management of both arrhythmias is therefore considered together.

ATRIAL FLUTTER

Mechanism

The classification of atrial flutter is based on the ECG presentation and electrophysiologic mechanisms. The most common type is typical isthmus-dependent atrial flutter. Incisional reentry atrial flutter occurs after surgical correction for congenital heart disease. There are also various forms of atypical flutters, such as atypical right atrial isthmus-dependent flutter (double-wave and lower loop reentry) and left atrial flutter, whose circuit contains the pulmonary vein or mitral valve annulus.[8]

Typical, or isthmus-dependent, atrial flutter involves a macro-reentrant right atrial circuit around the tricuspid annulus. The wavefront circulates down the lateral wall of the right atrium, through the eustachian ridge between the tricuspid annulus and the inferior vena cava, and up the interatrial septum, giving rise to the most frequent pattern, referred to as counterclockwise flutter. Reentry can also occur in the opposite direction (clockwise or reverse flutter).

Electrocardiographic Presentation

Atrial flutter is usually an organized atrial rhythm with an atrial rate typically between 250 and 350 beats per minute. In the more common counterclockwise flutter, F waves are negative in leads II, III, avF, and V_{5-6} and positive in leads V_{1-2} (Fig. 95-7*A*). Typical clockwise atrial flutter is characterized by positive F waves in leads II, III, and avF and negative waves in leads V_{1-2}.

Treatment with propafenone, flecainide, and amiodarone to prevent recurrent atrial fibrillation without adding an AV blocking agent (beta blocker or nondihydropyridine calcium antagonist) can organize the arrhythmia into typical atrial flutter with AV conduction of 1:1 or 2:1, producing a ventricular rate response of 150 beats per minute or higher (see Fig. 95-7*B*). The probability of 1:1 conduction is increased in the presence of an accessory pathway with a short effective refractory period.

Long-Term Management

The precise mechanism of atrial flutter is important for long-term management (e.g., catheter ablation) but has little influence on the initial approach. Patients with all types of atrial flutter should be referred for electrophysiologic evaluation with a view to ablation.

ATRIAL FIBRILLATION

Electrocardiographic Presentation

Atrial fibrillation is defined as rapid oscillations or fibrillatory f waves that vary in size, shape, and timing (see Fig. 95-7*C*). The ventricular response rate is variable and depends on the rate and regularity of atrial activity, the refractory properties of the AV node itself, and the balance between sympathetic and parasympathetic tone. The RR intervals are irregular unless the patient has complete AV block or a paced rhythm.

Classification

The clinical classification of atrial fibrillation includes first detected, paroxysmal, persistent, and permanent forms of the arrhythmia and is essential for deciding between rhythm restoration and rate control. First-onset atrial fibrillation, if the duration of the episode is less than 48 hours, is a clear

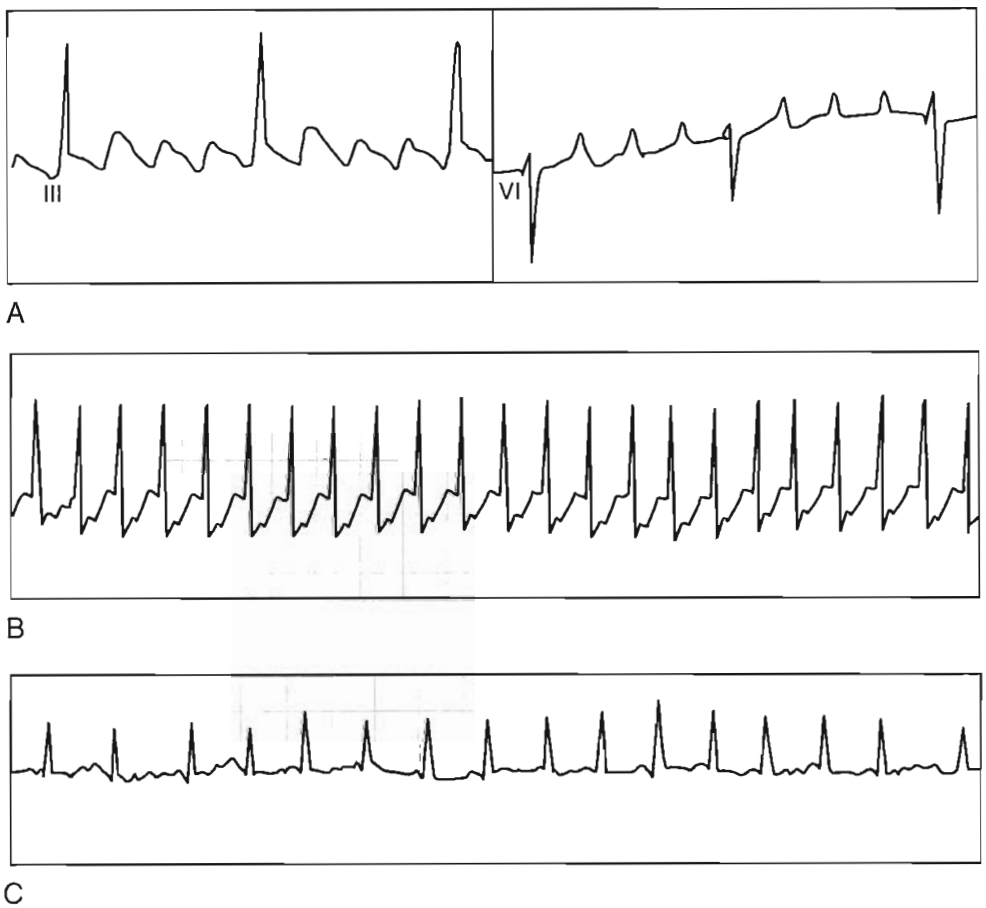

FIGURE 95–7. *A*, Typical counterclockwise atrial flutter. F waves are negative in leads II, III, avF, and V_{5-6} and positive in leads V_{1-2}. *B*, Atrial flutter with 1:1 atrioventricular conduction and a ventricular rate of 270 beats per minute in a patient treated with flecainide. *C*, Atrial fibrillation with fast, uncontrolled ventricular rates.

indication to restore sinus rhythm by either electrical or pharmacologic means. Because atrial fibrillation may be asymptomatic, the "first detected episode" should not be regarded as necessarily the true onset of the arrhythmia, in which case formal anticoagulation (see later) and rate control may be preferential. Persistent or permanent atrial fibrillation should be treated initially by rate control and anticoagulation, when appropriate.

Long-Term Management

Recognition of the pulmonary veins as the source of atrial premature beats or rapid atrial tachycardia that triggers atrial fibrillation or drives the atria prompted the development of ablation techniques that may "cure" the arrhythmia. In symptomatic permanent or persistent atrial fibrillation, AV node ablation and permanent pacing are effective in rate and symptom control. Any patient with first-onset or recurrent atrial fibrillation should be referred to a cardiologist for long-term management.

ACUTE MANAGEMENT

Acute therapy for atrial flutter and atrial fibrillation depends on the clinical presentation. Emergency electrical cardioversion is indicated for patients with hemodynamic collapse and progressively deteriorating left ventricular systolic function.

Direct-Current Cardioversion

Atrial flutter can be converted with DC shock energy as low as 25 to 50 J, but because a 100-J shock is virtually always successful, it should be considered as the initial shock strength. In recent-onset atrial fibrillation, sinus rhythm can be restored by a shock of 100 J, but it is recommended that cardioversion be started with an initial shock energy level of 200 J or greater. In patients with an arrhythmia of unknown duration, in heavier individuals, and in those with chronic obstructive lung disease and pulmonary emphysema, an initial setting of 300 to 360 J is appropriate. Success may occur on the third or subsequent attempt at an intensity that initially proved ineffective. For details, refer to Chapter 210.

Rate Control

Rate control is pertinent to all atrial tachyarrhythmias, particularly if restoration of sinus rhythm is deferred. Intravenous verapamil, diltiazem, and beta blockers can rapidly control the ventricular response rate in atrial fibrillation[2] (see Table 95-2), but the efficacy may be less in atrial flutter. The decrease in the ventricular rate (approximately 20% to 30%), time to maximal effect (20 to 30 minutes), conversion rate (12% to 25%), and adverse reactions (usually hypotension and bradycardia, although left ventricular dysfunction and high-degree heart block may occur) are reportedly similar with both classes of drugs. Beta blockers are preferable if thyrotoxicosis is suspected as a cause of the arrhythmia.

Intravenous digoxin is no longer the treatment of choice when rapid rate control is essential because of the delayed onset of its therapeutic effect (>60 minutes). However, because of its positive inotropic action, digoxin may be safer to use in patients with poor ventricular function and moderately fast ventricular rates. Digoxin may convert flutter to fibrillation, in which rate control is easier to accomplish.

TABLE 95-3. ANTIARRHYTHMIC DRUGS FOR PHARMACOLOGIC CONVERSION OF ATRIAL TACHYARRHYTHMIAS

Drug	Route of Administration	Dose	Potential Adverse Effects
Flecainide	Oral or intravenous	Loading oral dose 200-300 mg or slow injection 1.5-2 mg/kg over 10-20 min; if no response, infusion 1.5 mg/kg for 1 h, then 0.1-0.25 mg/kg over 24 h	Rapidly conducted atrial flutter, possible deterioration of ventricular function in the presence of organic heart disease, monomorphic ventricular tachycardia
Propafenone	Oral or intravenous	Loading oral dose 450-600 mg or 1.5-2 mg/kg over 10-20 min, followed by infusion 5-10 mg/kg if needed	
Ibutilide	Intravenous	1 mg over 10 min; if no response, additional 1 mg	QT prolongation, torsades de pointes, hypotension
Amiodarone	Intravenous (preferably central line)	5-7 mg/kg over 30-60 min, followed by infusion 20 mg/kg for 24 h (total 1200-1800 mg)	Hypotension, bradycardia, QT prolongation, torsades de pointes (?), gastrointestinal upset, constipation, phlebitis
Procainamide	Intravenous	1000 mg over 30 min, followed by 2 mg/min infusion	QRS widening, torsades de pointes, rapid atrial flutter

There is evidence that i.v. amiodarone may be effective in rate control when other AV node blocking agents have no effect on ventricular response or are contraindicated.

Pharmacologic Cardioversion

If the arrhythmia is hemodynamically stable and is of recent onset, pharmacologic cardioversion can be effective.

Flecainide and Propafenone

Pharmacologic cardioversion of atrial fibrillation can be accomplished with the IC class of antiarrhythmic drugs—flecainide and propafenone administered orally as a single dose of 300 and 600 mg, respectively (Table 95-3).[2] Placebo-controlled, randomized studies show an efficacy rate of 60% to 80% between the third and eighth hour after drug ingestion.[9,10] Both oral and i.v. routes of administration are equally effective, although with i.v. injection, restoration of sinus rhythm can be achieved more quickly.

Flecainide is given as a slow i.v. injection of 2 mg/kg over 10 to 30 minutes, up to the maximum dose of 150 mg. Propafenone is administered as a slow i.v. injection of 1.5 to 3 mg/kg, up to 300 to 600 mg. Because these drugs can significantly slow the atrial rate (from 300 to 350 beats/min to 200 beats/min), which may result in 1:1 AV conduction, beta blockers or calcium antagonists with negative dromotropic effects on AV node conduction (verapamil, diltiazem) should be used concomitantly. Other cardiovacular effects include reversible QRS widening and, rarely, left ventricular decompensation. Because of the negative inotropic effect, they are contraindicated in patients with severe structural heart disease and a poor ejection fraction.

Class IC drugs are usually ineffective for the conversion of atrial flutter, because they slow conduction within the reentrant circuit and prolong the flutter cycle length but rarely interrupt the circuit. These drugs pose the risk of increased (e.g., 2:1 or 1:1) AV conduction. Reported efficacy rates are as low as 13% to 40% with i.v. flecainide and propafenone.

Ibutilide

The class III agent ibutilide is administered intravenously as a 10-minute injection of 1 to 2 mg and is particularly effective in terminating atrial flutter, with a success rate of about 60%. Its administration may be associated with excessive QT interval prolongation, however, because of the rapid delayed rectifier potassium current (I_{Kr}) blockade and the risk of torsades de pointes.[11,12] It is less effective in atrial fibrillation. Higher doses of ibutilide administered as two successive infusions of 1 mg are usually required to terminate fibrillation. The advantage of ibutilide is that it may be effective in the conversion of arrhythmias of up to 30 days' duration, but the success rate drops significantly to 20% to 30%. The safety of ibutilide in patients with poor left ventricular function is unknown.

Amiodarone

Amiodarone administered intravenously at a dose of 5 mg/kg for 1 hour, followed by an infusion of 20 mg/kg over 24 hours, is effective in converting both atrial fibrillation and flutter, but the effect is significantly delayed.[13,14] However, because of its ability to control the ventricular rate, a low likelihood of torsades de pointes, and the absence of a negative inotropic effect, amiodarone can be used safely in patients with significant structural heart disease and those who are critically ill.

Procainamide and Sotalol

Procainamide administered as a slow i.v. injection of 1000 mg over 20 to 30 minutes, followed, if necessary, by an infusion of 2 mg/min over 1 hour, converts atrial flutter or fibrillation of less than 48 hours' duration, but its efficacy is limited in longer-lasting arrhythmias.[15] It is less effective than propafenone, flecainide, and ibutilide.

Sotalol is not indicated for the pharmacologic cardioversion of atrial flutter or fibrillation because its efficacy does not exceed 11% to 13%; however, it may satisfactorily control the ventricular rate.

Atrial Pacing

Burst overdrive atrial pacing can terminate atrial flutter in about 80% of cases and is feasible after cardiac surgery, when patients frequently have epicardial atrial pacing wires, or in patients with implantable dual-chamber pacemakers and defibrillators. High-frequency (50 Hz or 3000 beats/min) atrial pacing is available in some of the latest models for the termination of early-onset atrial fibrillation, but its efficacy has not yet been established. Atrial burst overdrive pacing may induce sustained atrial fibrillation, although short periods of fibrillation often precede conversion to sinus rhythm.

ANTICOAGULATION

Anticoagulation is imperative if the arrhythmia persists for more than 24 to 48 hours or if its duration is unknown.

TABLE 95–4. RISK STRATIFICATION AND INDICATIONS FOR ANTICOAGULATION IN ATRIAL FIBRILLATION AND FLUTTER

Risk of Stroke	Definition	Therapy
Low (1%/yr)	Age <65 yr; ejection fraction ≥0.50; no stroke or transient ischemic attack, hypertension, heart failure, or valvular heart disease	Aspirin 325 mg
Low to moderate (1.5%/yr)	Age 65-75 yr; no risk factors	Aspirin 325 mg
Moderate to high (2.5%/yr)	Age 65-75 yr and either diabetes or coronary heart disease	Warfarin (INR 2.0-3.0)
High (6%/yr)	Age <75 yr and hypertension, heart failure, or ejection fraction <0.50 Age >75 yr, particularly women, even in the absence of risk factors	Warfarin (INR 2.0-3.0)
Very high (10%/yr)	Age >75 yr and hypertension, heart failure, or ejection fraction <0.50 Any age with a history of stroke or transient ischemic attack or valvular heart disease	Warfarin (INR 2.0-3.0)

INR, International Normalized Ratio.
Modified from Straus SE, Majumdar SR, McAlister FA: New evidence for stroke prevention: Scientific review. JAMA 2002;288:1388-1395.

Atrial flutter and atrial fibrillation pose similar risks of thromboembolism, and the same criteria for anticoagulation should be applied in patients with either arrhythmia. In hemodynamically stable arrhythmias of more than 48 hours' or of unknown duration, rate control and 3 weeks' anticoagulation with warfarin (International Normalized Ratio 2.0 to 3.0) should be considered before any intervention (electrical or pharmacologic cardioversion, catheter ablation).[16]

TRANSESOPHAGEAL ECHOCARDIOGRAPHY–GUIDED CARDIOVERSION

If, for any reason, deferral of cardioversion is not indicated, the transesophageal echocardiography–guided approach, with short-term anticoagulation with low-molecular-weight heparin, is a safe and effective alternative.[17] It may be clinically beneficial in patients with recent-onset arrhythmias or in individuals at high risk of bleeding complications during prolonged anticoagulation therapy.[18] Compared with unfractionated heparin, low-molecular-weight heparin therapy does not involve prolonged i.v. administration or laboratory monitoring and therefore has the potential to greatly simplify cardioversion-related anticoagulation therapy in low-risk individuals. Post-cardioversion anticoagulation should be considered if thromboembolic risk factors are present (Table 95-4).[16,19]

ATRIAL TACHYCARDIA

MECHANISM

The mechanism of atrial tachycardia is attributed to enhanced automaticity, triggered activity, or intra-atrial reentry. Macroreentrant atrial tachycardia often occurs after surgery for congenital heart disease. Focal atrial tachycardia typically originates along the crista terminalis in the right atrium, in the pulmonary veins in the left atrium, or around one of the atrial appendages.

ELECTROCARDIOGRAPHIC PRESENTATION

The heart rate varies from 120 to 250 beats per minute, P waves precede the QRS complex, and PP intervals are regular (see Fig. 95-5*B*). The PR interval is linked to the rate of tachycardia and is longer than in sinus rhythm at the same rate. P wave morphology is usually different from that during sinus rhythm and depends on the site of origin. Left atrial tachycardia presents with the negative P waves in leads I, avL, V_5, and V_6. Automatic atrial tachycardia may present as an incessant variety, leading to tachycardia-induced cardiomyopathy.

ATRIAL TACHYCARDIA WITH ATRIOVENTRICULAR BLOCK

Tachycardia with AV block occurs commonly in patients with organic heart disease, and in 50% to 75% of cases, it is due to digitalis toxicity (Fig. 95-8). Digoxin-specific antibody fragments (Digibind) are available for the reversal of life-threatening overdosage.

MULTIFOCAL ATRIAL TACHYCARDIA

This tachycardia presents as rapid, irregular atrial activity with discrete P waves of varying morphology and is considered a transitional rhythm between atrial tachycardia and fibrillation. However, it may occur in patients with chronic severe pulmonary disease as a result of theophylline or beta agonist overdose. Elimination of the causative factor may reduce the need for antiarrhythmic therapy. Intravenous verapamil can accomplish rate control.

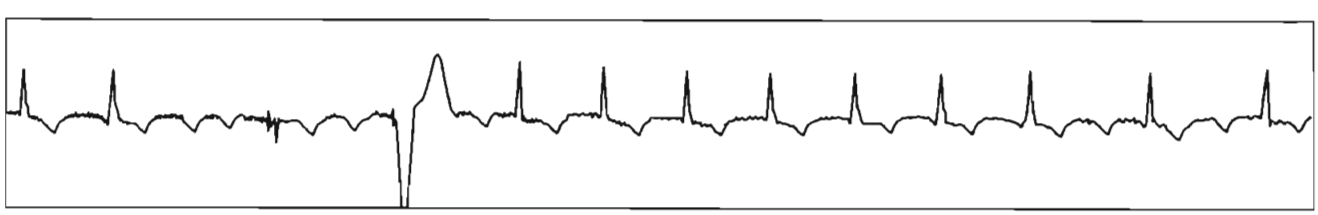

FIGURE 95–8. Atrial tachycardia with varying atrioventricular block as a result of digitalis toxicity.

ACUTE MANAGEMENT

DC cardioversion converts atrial tachycardia based on the reentry mechanism or triggered activity, but it may not terminate automatic tachycardia. Similarly, atrial overdrive pacing may slow the tachycardia rate but seldom suppresses the automatic focus.

It is generally accepted that beta blockers and calcium antagonists, particularly verapamil, can either terminate the tachycardia or produce rate control. Adenosine can terminate atrial tachycardia, but the most common response to adenosine is to create AV block and thereby reveal the unaffected tachycardia (see Fig. 95-5*B*, *C*).

Flecainide, propafenone, sotalol, and amiodarone are effective in converting the arrhythmia. If tachycardia occurs as a result of digitalis intoxication, therapy includes the cessation of digoxin and i.v. administration of potassium.

LONG-TERM MANAGEMENT

Patients with atrial tachycardia should be referred to a cardiologist, because the arrhythmogenic focus can be found and ablated in up to 86% cases.

INAPPROPRIATE SINUS TACHYCARDIA

Inappropriate sinus tachycardia is a persistent increase in resting heart rate unrelated to or out of proportion with the level of physical or emotional stress. It is found predominantly in women and is not uncommon in health professionals. Sinus tachycardia due to intrinsic sinus node abnormalities, such as enhanced automaticity, or abnormal autonomic regulation of the heart, with excess sympathetic and reduced parasympathetic input, is extremely rare. The usual therapy is beta blockers. In general, sinus tachycardia is a secondary phenomenon, and the underlying causes should be actively investigated. Depending on the clinical setting, acute causes include fever, hypotension, infection, anemia, thyrotoxicosis, hypovolemia, acute heart failure, acute pulmonary embolism, and shock. Sinus tachycardia may be associated with the abuse of drugs, such as amphetamines.

ANNOTATED REFERENCES

Albers GW, Dalen JE, Laupacis A, et al: Antithrombotic therapy in atrial fibrillation. Chest 2001;119(1 Suppl):194S-206S.

This paper focuses on the prevention of stroke in nonrheumatic atrial fibrillation and flutter and provides expert recommendations regarding risk stratification, anticoagulation strategies, cardioversion (including transesophageal echocardiography–guided cardioversion), and long-term management of patients at risk of thromboembolism. It contains a complete review of the evidence base for anticoagulation in atrial fibrillation.

Blomström-Lundvist C, Scheiman MM, Aliot EM, et al: ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to develop guidelines for the management of patients with supraventricular arrhythmias). J Am Coll Cardiol 2003;42:1493-1531.

These practice guidelines describe a range of generally accepted approaches to the diagnosis and management of supraventricular tachyarrhythmias (excluding atrial fibrillation) and provide insight into the multiple mechanisms defined by electrophysiologic studies, with a focus on both acute and long-term therapies.

Camm AJ: Atrial fibrillation: Is there a role for low-molecular-weight heparin? Clin Cardiol 2001;24(3 Suppl):115-119.

This review paper summarizes evidence emerging from clinical studies that clearly supports both the use of transesophageal echocardiography–based cardioversion protocols and the introduction of low-molecular-weight heparin for anticoagulation in atrial fibrillation. Clinical settings in which low-molecular-weight heparin may offer advantages over unfractionated heparin and warfarin are discussed.

Fuster V, Rydén LE, Asinger RV, et al: Task force report: ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. Eur Heart J 2001;22:1852-1923.

These guidelines incorporate a comprehensive review of the latest information about the classification, epidemiology, mechanisms, and clinical presentations of atrial fibrillation. Practical approaches to acute and long-term management of this arrhythmia are discussed at length. An extensive list of references covers various aspects of atrial fibrillation.

Mehta D, Wafa S, Ward DE, Camm AJ: Relative efficacy of various physical manoeuvres in the termination of junctional tachycardia. Lancet 1988; 1:1181-1185.

This paper compares the ability of four vagotonic physical maneuvers to terminate paroxysmal supraventricular tachycardias that involve the AV node as a part of their reentrant circuits. It shows that these tachycardias can be terminated without resorting to pharmacologic therapy in more than half of patients. The paper provides a detailed methodologic description and explains the physiologic effects of vagotonic maneuvers.

Chapter 96

VENTRICULAR ARRHYTHMIAS

Raúl J. Gazmuri • Prabhakaran Gopalakrishnan

KEY POINTS

1. **Hereditary and acquired abnormalities in cardiac ion channels** can alter the action potential and predispose to ventricular tachyarrhythmias, especially the torsades de pointes type.
2. Ventricular arrhythmias are the result of **abnormalities in impulse generation (automaticity and triggered activity) and impulse conduction (reentry).**
3. Proper management of ventricular tachyarrhythmias requires the **assessment of precipitating and maintaining conditions**; often, the removal of these conditions is all that is needed.
4. **A long QT interval in the baseline electrocardiogram** should prompt a diligent search for possible drugs and metabolic conditions involved.
5. **Ventricular tachyarrhythmias in critically ill patients** are often precipitated by cardiac and respiratory processes.
6. **Atrioventricular dissociation is a reliable sign that a wide-complex tachycardia is ventricular**; this may be evident on the surface 12-lead electrocardiogram or after analyzing an esophageal lead.
7. **Direct-current synchronized cardioversion should be considered first-line treatment** in patients with ventricular tachycardia who are hemodynamically unstable or have heart failure.

Abnormalities in impulse generation and conduction leading to arrhythmic events are frequent in critically ill patients. They may result from primary cardiac events or may be secondary to a myriad of acute or acute-on-chronic conditions. The presence or anticipation of an arrhythmic event is frequently a reason for hospital admission to a unit with capability to continuously monitor the electrocardiogram (ECG) and with personnel proficient in the recognition and management of life-threatening arrhythmias (i.e., ICUs and telemetry units).

Abnormalities originating in atrial tissue and in pulmonary veins are considered supraventricular. They may compromise cardiac and hemodynamic function by means of an excessive heart rate or disruption of ventricular filling; yet, in the absence of accessory conduction pathways—bypassing the atrioventricular (AV) node—supraventricular arrhythmias are rarely life-threatening and can often be managed by nonemergent pharmacologic or mechanical means. In contrast, abnormalities originating in ventricular structures pose substantial risk of developing into life-threatening arrhythmias (e.g., ventricular tachycardia and ventricular fibrillation) that require immediate intervention to avert or reverse death.

In this chapter, ventricular arrhythmias that develop in critically ill patients are discussed, with primary focus on mechanisms, predisposing conditions, incidence, diagnosis, and acute clinical management. The technical aspects of electrical cardioversion and defibrillation are discussed in Chapter 210.

NORMAL ELECTROPHYSIOLOGY

ANATOMIC SYNOPSIS

The electrical impulse of the heart originates in the sinoatrial (SA) node, located high on the right atrium near its junction with the superior vena cava. The impulse then propagates through muscle fibers and specialized internodal pathways (composed of Purkinje-type fibers) to converge on the AV node, located in the interatrial septum near the tricuspid valve and the opening of the coronary sinus (Fig. 96-1). From the AV node, the impulse travels through the bundle of His, its left and right branches, and the Purkinje system to simultaneously activate the right and left ventricles. A ring of fibrous tissue interposed between the atria and the ventricles precludes spread of the electrical impulse through the muscle fibers. The AV node functions as a relay and filter, limiting the number of impulses that can be transmitted to the ventricles, thus preventing 1:1 conduction under conditions of very rapid atrial activation (i.e., atrial flutter, rate ≈300 cycles/sec; atrial fibrillation, rate ≈350 to 600 cycles/sec).

ACTION POTENTIAL AND PACEMAKER ACTIVITY

Action potential is the result of rapid depolarization and repolarization subsequent to changes in ion currents across the plasma cell membrane of polarized cells. The changes in ion currents result from a coordinated sequence of opening and closing of channels that regulate mainly the influx of sodium ions (Na^+) and calcium ions (Ca^{++}) (inward currents) and the efflux of potassium ions (K^+) (outward currents).[1-4] The action potential serves to propagate the electrical impulse throughout the conduction system and muscle fibers and to signal contractile activity.

The characteristics of the action potential vary, contingent on the type of cell. Cells from the Purkinje system and from atrial and ventricular muscle have a stable resting potential at approximately −90 mV (inside negative). This is largely

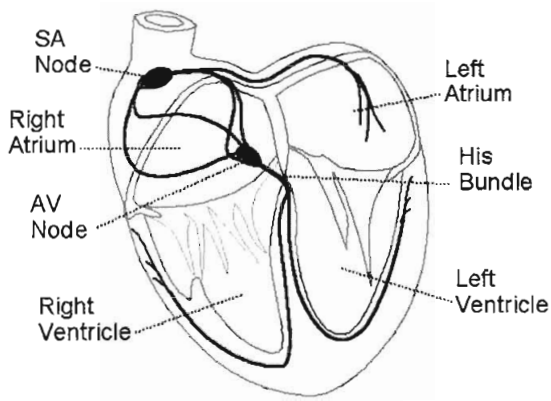

FIGURE 96–1. Conduction system of the heart. AV, atrioventricular; SA, sinoatrial.

the result of a K^+ current known as the inward rectifier (I_{K1}), which "anchors" the membrane potential to a voltage close to the equilibrium potential of K^+.[3] I_{K1} is turned off during depolarization (inward rectification) and then on during repolarization (see later). The arrival of an impulse that depolarizes the plasma membrane to between –70 and –80 mV (threshold potential) is needed for fast voltage-gated Na^+ channels to open and trigger an action potential.[4] The rapid Na^+ influx creates a current (I_{Na}) that drives the membrane potential toward the equilibrium potential of Na^+, causing further depolarization and reversal of the membrane potential to approximately +20 mV (overshoot). This phase is known as phase 0 of the action potential and ushers into a four-phase repolarization (Fig. 96-2). Phase 1 is the initial early repolarization (action potential notch) and results from rapid inactivation of Na^+ channels (inner gate) and the opening of K^+ channels carrying a transient outward

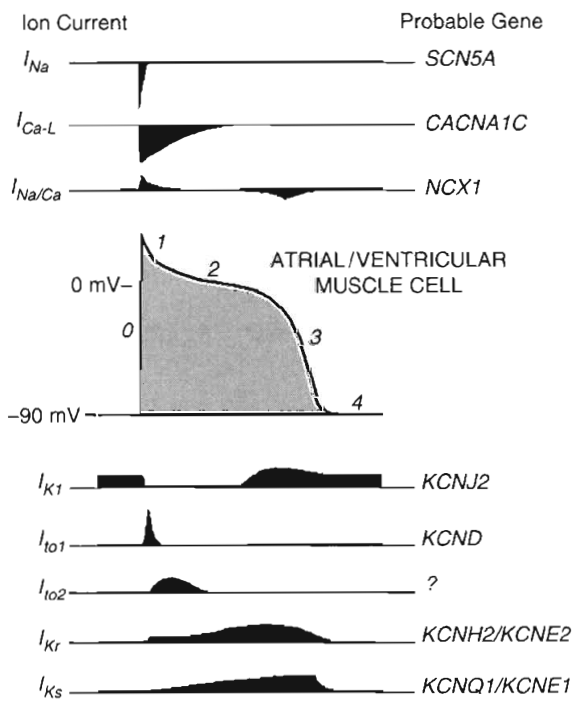

FIGURE 96–2. Action potential of a cardiac muscle cell depicting the main underlying inward and outward currents and their respective gene products. The distinctive phases of the action potential are numbered.

current (I_{to}). These channels turn on rapidly after depolarization and then quickly inactivate.[5-7] Because I_{to} is expressed in the subepicardial and midmyocardial regions but not in the subendocardial region, it contributes to the inhomogeneity of repolarization.[8] I_{to} has two components: one that is voltage-gated (I_{to1}) and one—less well characterized—that is presumably activated by changes in cytosolic Ca^{++} (I_{to2}).[6,7,9] Phase 2 is the plateau phase of the action potential and results mainly from a Ca^{++} current carried by the slow and prolonged opening of L-type voltage-gated Ca^{++} channels ($I_{Ca\text{-}L}$).[10,11] Opening of these channels begins during phase 0 at a membrane potential of –30 to –40 mV. These channels are inactivated in response to increases in cytosolic Ca^{++} and are strongly regulated by neurotransmitters. Phase 3 corresponds to late repolarization and follows the closing of Ca^{++} channels, along with the opening of K^+ channels, with slow activation kinetics carrying currents known as delayed rectifiers (I_K). These are the main repolarizing currents and have two components carried by distinct gene products: a rapid component (I_{Kr}) and a slow component (I_{Ks}).[12,13] Both are implicated in the heritable forms of long QT syndrome (see later).[14] In addition, opening of I_{K1} contributes to repolarization. Phase 4 represents the return to resting membrane potential and the interval during which ionic balance is restituted, largely through the action of the Na^+-K^+ pump.

Cells of the SA and AV nodes lack voltage-gated Na^+ channels, and phase 0 is carried by L-type Ca^{++} channels ($I_{Ca\text{-}L}$).[15] Because of their slower opening kinetics (relative to Na^+ channels), they give rise to a slanted phase 0 and in part determine the lower conduction velocity of the SA and AV nodes (≈50 cm/sec) compared with the His-Purkinje system (≈400 cm sec^{-1}) and muscle cells (≈100 cm sec^{-1}). SA and AV node cells also have pacemaker activity and slowly depolarize during phase 4 to a threshold potential of approximately –40 mV. The slow depolarization is called prepotential or pacemaker potential and involves a background Na^+ current ($I_{Na\text{-}B}$), a decay of K^+ currents, the opening of T-type voltage-gated Ca^{++} channels ($I_{Ca\text{-}T}$) at a potential between the thresholds for I_{Na} and $I_{Ca\text{-}L}$, and the opening of L-type Ca^{++} channels, unleashing phase 0. Cells of the His-Purkinje system have latent prepotential activity and can become active when SA or AV node activity is depressed or their impulse is blocked. Atrial and ventricular muscle cells exhibit prepotential activity only under abnormal circumstances (see later).

The preceding description is succinct and oversimplified. Various other ion channels, antiporters, pumps, and receptors play important roles in specific physiologic states and disease processes. For example, there is a nonselective cationic channel that is gated at resting potential by intracellular Ca^{++} and produces an inward Na^+ current (I_{NS}).[16] This current may contribute to delayed afterdepolarizations following Ca^{++} release by the sarcoplasmic reticulum. $I_{K(ATP)}$ is a K^+ current carried through metabolically regulated channels that are inhibited by adenosine triphosphate (ATP) and opened under conditions of ischemia and hypoxia. $I_{K(ATP)}$ is the main contributor to the shortening of the action potential duration[17] and the characteristic ST segment elevation observed in the surface electrocardiogram[18] during ischemia.

The sarcolemmal Na^+-Ca^{++} exchanger is another important modulator of the action potential. Because it exchanges one Ca^{++} for three Na^+, it is electrogenic and generates a current ($I_{Na/Ca}$) whose direction is determined by the Na^+ and Ca^{++} gradients and the membrane potential.[19,20] In settings in which there is cytosolic Ca^{++} overload (e.g., ischemia and

reperfusion, digitalis toxicity), Ca^{++} may trigger Ca^{++} release from the sarcoplasmic reticulum during phase 4, which in turn prompts reverse-mode operation of the Na^{+}-Ca^{++} exchanger, causing an inwardly directed $I_{Na/Ca}$ (Na^{+} influx). This current contributes to the generation of delayed afterdepolarizations and triggered arrhythmias (see later).

Adrenergic receptors also play important roles in modulating the action potential by modifying channel activity.[21-23] For example, stimulation of beta-adrenergic receptors increases the activity of L-type Ca^{++} channels (leading to increases in $I_{Ca\text{-}L}$ and contractility). Beta-adrenergic receptor stimulation can also activate K^{+} channels, shortening repolarization and the duration of the action potential.[24] $Alpha_1$-adrenergic receptors exert actions via G protein on the Na^{+}-K^{+} pump, K^{+} channels, and phospholipase C and can alter impulse initiation and repolarization. $Alpha_1$-adrenergic stimulation has been linked to triggered rhythms via early and delayed afterdepolarizations and the development of abnormal automatic rhythms in the setting of ischemia and reperfusion.[25,26]

Alteration in the proteins forming these various channels—mostly genetic, but also acquired—may distort the normal action potential, yielding distinctive electrocardiographic patterns (e.g., long QT syndrome, Brugada's syndrome) that are associated with increased risk of ventricular tachyarrhythmias.

MECHANISMS OF VENTRICULAR TACHYARRHYTHMIAS

The mechanisms by which ventricular tachyarrhythmias develop encompass abnormalities in impulse generation and abnormalities in impulse conduction. Both mechanisms often coexist and orchestrate the initiation and maintenance of ventricular tachyarrhythmias. Identification of the arrhythmogenic mechanism is important, because therapeutic strategies may be designed to target the so-called vulnerable parameter responsible for the genesis or maintenance of the arrhythmia.[27-29]

ABNORMALITIES IN IMPULSE GENERATION

Abnormalities in impulse generation are generally the result of automaticity (ectopic pacemaker activity) or triggered activity. Automaticity may result from enhanced normal automaticity in cells of the conduction system whose pacemaker potential is normally under overdrive suppression, or from the development of abnormal automaticity in muscle cells that normally do not exhibit pacemaker potential. Triggered activity refers to arrhythmias that arise from afterdepolarizations.

Enhanced normal automaticity occurs when cells from the AV node or His-Purkinje system fire at rates that escape the overdrive suppression of the SA node. This phenomenon may result from effects on phase 4 prepotentials that favor the earlier development of action potentials (i.e., less maximal polarization, faster depolarization, or lower threshold potential) or from shortening of the action potential duration, with an earlier return to phase 4. Enhanced normal automaticity is usually the result of adrenergic stimulation.

Abnormal automaticity refers to the generation of impulses in fibers that are partially depolarized as a result of a pathologic process, such as ischemia. Under these conditions, the reduction in the resting membrane potential (less negative; to −70 or even −50 mV) shifts the balance during phase 4 toward depolarizing currents.[30] Through this mechanism, automaticity can developed in atrial and ventricular muscle cells, and the firing conditions of specialized tissues other than the SA node can be altered. Examples of abnormal automaticity include accelerated idioventricular rhythms and some ventricular tachycardias that develop 24 to 72 hours after acute myocardial infarction.[31,32]

Triggered activity refers to action potentials that result from afterdepolarizations, which are alterations in membrane potential that occur during repolarization without intervening external triggers or cell-to-cell interactions.[33] Afterdepolarizations that develop during phase 2, phase 3, or early phase 4 are called early afterdepolarizations and are characterized by transient retardations in repolarization, with or without upturn of the membrane potential (Fig. 96-3). When the upturn is of a magnitude sufficient to reach the threshold, an extra action potential is triggered before the cycle is over. Early afterdepolarizations are typically associated with conditions that prolong the action potential duration, such as decreased inactivation of fast I_{Na} (i.e., long QT3 syndrome) or decreased outward K^{+} currents (i.e., I_{Ks} in long QT1 and I_{Kr} in long QT2 syndromes), prompting Ca^{++} entry through L-type Ca^{++} channels.[34] The development of early afterdepolarizations in this setting is thought to trigger torsades de pointes. Early afterdepolarizations are also associated with increased sympathetic tone, use of catecholamines, hypoxia, acidosis, and bradycardia. Afterdepolarizations that occur in late phase 4 are called delayed afterdepolarizations and are characterized by low-amplitude depolarizations that may reach threshold and trigger an action potential (see Fig. 96-3). The main underlying abnormality is intracellular Ca^{++} overload, promoting Ca^{++} release from the sarcoplasmic reticulum[34] and depolarizing currents (i.e., inward $I_{Na/Ca}$ currents). Delayed afterdepolarizations are classically associated with digitalis toxicity; however, many other conditions that favor cytosolic Ca^{++} overload can produce them, such as myocardial stretch, hypertrophy, catecholamines, ischemia, and reperfusion. Increased expression of Na^{+}-Ca^{++} exchanger, along with abnormalities in the ryanodine receptor, has been shown to predispose to delayed afterdepolarizations in the setting of heart failure.

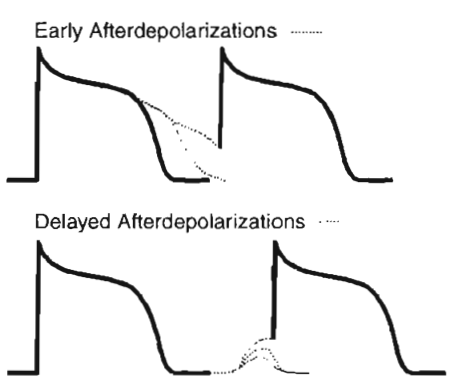

FIGURE 96–3. Afterdepolarizations *(dotted lines)*. Early afterdepolarizations are retardations in repolarization, with prolongation in the action potential duration *(upper figure)*. Delayed afterdepolarizations represent spontaneous depolarizations that occur after repolarization is over *(lower figure)*. Afterdepolarizations that reach threshold trigger an action potential.

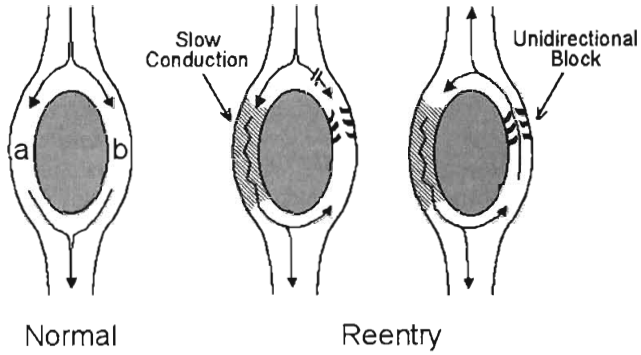

FIGURE 96–4. Ring model of reentry.

ABNORMALITIES IN IMPULSE CONDUCTION (REENTRY)

Abnormalities in impulse conduction leading to reentry account for the vast majority of sustained ventricular tachyarrhythmias. Reentry is a phenomenon in which a normally propagating impulse reenters previously excited tissue after its refractory period is over, and excites it again. Reentry can continue to repeat and establish a tachyarrhythmia. Several forms of reentry have been described, including circus movement reentry, phase 2 reentry, and reflection.[35]

Circus Movement

Circus movement is the most widely studied mechanism and encompasses four distinct models: ring, leading circle, figure of eight, and spiral wave.

The ring model is the simplest and illustrates the basic mechanism of reentry (Fig. 96-4).[36] This model requires two anatomically contiguous paths in specialized tissue or in muscle fibers separated by a central area of unexcitable tissue. One of these paths (*b* in Fig. 96-4) must exhibit a zone of unidirectional block, allowing the impulse to propagate in only one direction. The alternative path (*a* in Fig. 96-4) allows the impulse to circumvent the unidirectional block. Conduction through this alternative path should be slow, or refractoriness proximal to the path should be brief, to allow recovery of tissue excitability. Once the impulse reaches the distal end of the alternative path, it propagates in a retrograde manner through the path of unidirectional block to reenter the proximal end of the alternative path. For the cycle to repeat (and establish a reentry tachyarrhythmia), the wavelength of the circling impulse—defined as the product of conduction velocity and the duration of the refractory period—must be shorter than or at least equal to the length of the reentry circuit (path length), enabling its leading edge to find the tissue in an excitable state. Reentry is usually triggered by the arrival of a premature beat that finds the path of unidirectional block in a refractory period. Unidirectional block may result from increased refractoriness associated with either anatomic abnormalities (e.g., fibrosis, accessory pathway, bundle branch) or functional defects (e.g., ischemia, action of drugs). The ring model best applies to tachyarrhythmias that involve AV accessory pathways and the AV node.

The leading circle model is similar to the ring model but does not require anatomic obstacles and can develop in structurally uniform myocardium by a properly timed premature impulse.[37,38] The figure-of-eight model was first described in experimental myocardial infarction. It refers to two reentry circuits moving alongside a functional conduction block (ischemia or infarct) in opposite directions, forming a pretzel-like configuration.[39] The spiral wave model is considered a more complex version of the leading circle model. It involves a core and filaments and is usually described as reentry in two dimensions.[40,41] The spiral wave model has been used to explain the electrocardiographic patterns associated with monomorphic and polymorphic ventricular tachycardias and also ventricular fibrillation. In monomorphic ventricular tachycardias, the spiral wave is thought to be anchored and unable to drift within the myocardium, whereas in polymorphic ventricular tachycardias, such as torsades de pointes, the spiral is thought to drift. In the case of ventricular fibrillation, the spiral wave is believed to break up into multiple rotating spiral waves that are continuously extinguishing and re-creating. However, some authors have proposed a single rapidly shifting spiral, and others have postulated a stationary rotor whose frequency of excitation is exceedingly high, resulting in multiple areas of intermittent block.[42]

Phase 2

Phase 2 reentry refers to the generation of local re-excitation as a result of increased heterogeneity of repolarization. This phenomenon occurs when repolarization is markedly shortened in certain regions of the myocardium, essentially obliterating the action potential plateau (phase 2), but is maintained in others. This creates conditions conducive to local re-excitation, which may precipitate ventricular tachyarrhythmias during myocardial ischemia.[43] During ischemia, action potentials of normal duration alternate with ones of shorter duration, yielding beat-to-beat alternans (temporal dispersion) and site-to-site alternans (spatial dispersion) and promoting regions of conduction block and regions with injury current, leading to reentry and ventricular tachyarrhythmias. The degree of spatial and temporal dispersion progresses along with the duration of ischemia, suggesting that this mechanism may be an important trigger of ventricular tachycardia and ventricular fibrillation during acute myocardial ischemia.[44,45] In the surface electrocardiogram (ECG), dispersion of the action potential duration manifests as T-wave alternans, which is a powerful predictor of ventricular fibrillation.[46]

Reflection

Reflection refers to a back-and-forth propagation of the impulse over the same functionally unexcitable tissue, with recurrent activation of the proximal region as a result of electrotonic currents.[47,48] The area of unexcitable tissue could result from ischemia and lead to extrasystolic activity. Reflection differs from classic reentry, in that the impulse travels along the same pathway in both directions.

PREDISPOSING CONDITIONS

CHANNELOPATHIES

The term "channelopathies" has recently been coined to identify a group of diseases in which there are abnormalities in the proteins that form ion channels.[49,50] These abnormalities distort the normal action potential, primarily accentuating the inherent instability of repolarization and increasing the risk of polymorphic ventricular tachycardia of the torsades de pointes type. The intensivist should be able to promptly identify prolongation of the QT interval in the surface ECG. Channelopathies may be hereditary or acquired.

TABLE 96-1. CONGENITAL LONG QT SYNDROMES

Genetic Type	Gene	Chromosome	Protein
LQT1	*KCNQ1*	11	α subunit, I_{Ks}
LQT2	*HERG*	7	I_{Kr}
LQT3	*SCN5A*	3	α subunit, I_{Na}
LQT4	*ANKB*	4	Ankyrin-B
LQT5*	*KCNE1*	21	β subunit, I_{Ks}
LQT6†	*KCNE2*	21	Membrane protein, I_{Kr}

*KCNQ1 and KCNE1 gene products assemble to form a complete I_{Ks} channel.
†HERG and KCNE2 gene products assemble to form a complete I_{Kr} channel.

The hereditary channelopathies described so far result mainly from mutations in genes that encode for Na^+ and K^+ channels, with the most representative being long QT syndrome.[51-53] This syndrome was first described in 1957 by Jervell and Lange-Nielsen in a group of patients with long QT intervals, episodes of torsades de pointes, and deafness.[54] This syndrome is transmitted by autosomal recessive inheritance and is known as the Jervell and Lange-Nielsen syndrome. In 1963 and 1964, Romano and colleagues[55] and Ward[56] independently reported patients with an almost identical disorder but without deafness, in which the transmission was autosomal dominant (Romano-Ward syndrome). It is now recognized that long QT syndrome results from mutations in at least six genes, leading to distinct types designated LQT1 through LQT6 (Table 96-1). LQT1 is the principal genetic type responsible for both Jervell and Lange-Nielsen and Romano-Ward syndromes and accounts for nearly 50% of all genotyped families. LQT2 accounts for nearly 45%, and LQT3 for about 5%. The remaining types are much less frequent. With the exception of LQT3 and LQT4, these mutations affect K^+ channels, causing decreased activity of either I_{Kr} or I_{Ks} by mechanisms involving loss of function, dominant-negative transmission, or, more rarely, autosomal recessive transmission. LQT4 has recently been linked to a loss-of-function mutation in the *ANKB* gene.[57] This gene encodes ankyrin-B, which is a member of a family of versatile membrane adapters. Ankyrin-B—among other functions—coordinates the opening and closing of calcium, potassium, sodium, and chloride channels. The failure to properly coordinate the opening and closing of ion channels leading to long QT syndrome and arrhythmias illustrates a novel mechanism of arrhythmias. LQT3 stems from a mutation in *SCN5A*, the gene that encodes the α subunit of the fast cardiac Na^+ channel. *SCN5A* mutation leads to incomplete channel inactivation and persistence of I_{Na} during the plateau phase of the action potential.

The common mechanistic thread among long QT syndromes is perturbation of the balance between I_{Na} and I_K during the plateau phase of the action potential, yielding prolongation of repolarization, a reduced rate of $I_{Ca\text{-}L}$ inactivation, late Ca^{++} influx, and early afterdepolarizations, predisposing to torsades de pointes.[58]

The diagnosis is suspected in young individuals who present with syncope or episodes of sudden death, typically during exercise, emotional distress, or exposure to factors that cause prolongation of the QT interval (see later). A family history of unexplained syncope or sudden cardiac death, especially in young kindred, should raise suspicion. Sudden cardiac death occurs in approximately 4% of affected individuals. The diagnosis should be suspected when the corrected QT interval ($QTc = QT_{(msec)}/\sqrt{R-R_{(sec)}}$) exceeds 470 msec in males (normal, <422 msec) and 480 msec in females (normal, <432 msec) in the absence of other conditions that may lengthen the corrected QT interval. In addition, there may be sinus bradycardia with sinus pauses in about one third of individuals (especially in LQT3), QT dispersion, and various T-wave abnormalities (e.g., notched, bifid, biphasic). Factors predisposing to sudden cardiac death include recurrent syncope, survival from cardiac arrest, congenital deafness, female sex, relative bradycardia, corrected QT interval greater than 600 msec, and kinship with a symptomatic patient.[51]

Another important hereditary channelopathy that also results from a mutation in the *SCN5A* gene is Brugada's syndrome.[59-62] In contrast to LQT3, this mutation leads to a loss of function, resulting in accelerated inactivation of I_{Na}; this unbalances the effects of I_{To}, during phase 1, which prompts rapid repolarization and a very short action potential. Because I_{To} is expressed predominantly in the epicardium, the normally depolarized endocardium can re-excite the prematurely repolarized epicardium, leading to phase 2 reentry. Brugada's syndrome was described in 1992 by the Brugadas, who noticed an association between sudden cardiac death and ST segment elevation in V_1 to V_3, with a pattern resembling right bundle branch block in individuals with structurally normal hearts.[59] The ST segment can adopt various shapes, which have been related to the severity of the I_{Na}/I_{To} imbalance, including—in order of increasing severity—saddleback, coved, and triangular shapes.[58] Some authors have proposed that this *SCN5A* defect may be responsible for up to 50% of all sudden deaths in patients with apparently normal hearts, with an even higher incidence in younger individuals (idiopathic ventricular fibrillation).[63] The syndrome can present with the typical ECG pattern; however, patients may have concealed or intermittent forms, which can be unmasked by the administration of Na^+ channel blockers such as ajmaline, flecainide, or procainamide. This test is highly specific and should be considered in all patients who present with a history of syncope of unknown origin or idiopathic ventricular fibrillation. Patients with Brugada's syndrome must be treated with an internal cardioverter defibrillator. Antiarrhythmic agents have not been found to be effective.[62]

Acquired channelopathies may result from a broad spectrum of conditions. Advanced heart failure affects the expression of several ion channels.[64,65] There is down-regulation of I_{To1} and I_{K1}, which prolongs the QT interval; this allows more time for excitation-contraction coupling but predisposes to inhomogeneous repolarization and early afterdepolarizations. In addition, there is up-regulation of Na^+-Ca^{++} exchanger, yielding larger $I_{Na/Ca}$, which predisposes to delayed afterdepolarizations and triggered arrhythmias, especially in the face of cytosolic Ca^{++} overload.

Drugs represent an increasingly important cause of acquired channelopathies that manifest by a prolongation of the QT interval, mostly as a result of decreased activity in I_{Kr},[66] which is the same current responsible for congenital long QT2 syndrome. The list is long and includes antiarrhythmic agents, in which the primary target is ion channels, as well as many other drugs in which prolongation of the QT interval is an unintended effect (Table 96-2).[67] The intensivist should be familiar with this group of medications and capable of recognizing the clinical features of long QT syndrome. The University of Arizona, Health Sciences Center, maintains a complete and up-to-date list of drugs that prolong the QT interval; it is available at www.qtdrugs.org.

TABLE 96–2. DRUGS ASSOCIATED WITH QT PROLONGATION AND RISK OF TORSADES DE POINTES

Antiarrhythmic Agents

Amiodarone
Disopyramide
Ibutilide
Procainamide
Quinidine
Sotalol

Antibiotics

Clarithromycin
Erythromycin
Gatifloxacin
Halofantrine
Pentamidine
Sparfloxacin

Antipsychotic Agents

Chlorpromazine
Haloperidol
Mesoridazine
Pimozide
Thioridazine

Tricyclic Antidepressants

Amitriptyline
Clomipramine
Desipramine
Doxepin
Imipramine

Nonsedating Antihistamines

Astemizole
Terfenadine

Opiate Agonists

Levomethadyl
Methadone

Enterokinetic/Antinausea Agents

Cisapride
Domperidone
Droperidol

OTHER CONDITIONS

The QT interval may also be prolonged by electrolyte abnormalities, cocaine abuse, organophosphorus compound poisoning, subarachnoid hemorrhage, stroke, myocardial ischemia, fasting using liquid-protein-modified diets, autonomic neuropathy, and human immunodeficiency virus disease.[68-72] Some of these conditions are discussed below.

Electrolyte Abnormalities

Electrolyte abnormalities rarely precipitate but often contribute to the development of ventricular tachyarrhythmias, mostly in relation to abnormalities in serum K^+, Mg^{++}, and Ca^{2+}.[73]

Abnormalities in serum K^+ are among the most common electrolyte abnormalities in critically ill patients. Hypokalemia (serum $K^+ < 3.5$ mM) decreases the resting membrane potential (making it more negative), rendering cells less excitable and lowering the firing rate of pacemaker cells. Hypokalemia also prolongs the QT interval and flattens the T wave.[14] This effect is explained by the fact that conductivity of I_{Kr} is proportional to the square root of external K^+. Thus, at lower K^+, I_{Kr} is reduced, prolonging repolarization. This effect is more pronounced in cells from the midmyocardial region (which have a greater I_{Kr}/I_{Ks} ratio). Hypokalemia can develop in various settings, including the use of thiazide and loop diuretics, diabetic ketoacidosis, gastrointestinal fluid losses, alcohol abuse, hypomagnesemia, administration of insulin, and beta-receptor agonist stimulation. Hyperkalemia (serum $K^+ > 5.5$ mM) exerts opposite effects. It lowers the resting membrane potential (making it less negative), rendering cells more excitable; however, with severe hyperkalemia, the rate of rise of phase 0 is reduced, slowing conduction velocity and leading—at very high potassium levels—to widespread blocks (widening of the P wave and QRS interval). Rapidly rising serum K^+ can precipitate ventricular fibrillation, probably as a result of reentry that follows areas of conduction block. Hyperkalemia, by increasing I_{Kr}, accelerates repolarization and shortens the action potential duration, yielding the characteristic peaked and tall T waves. Prompt treatment of these defects is important to avert life-threatening events.

Magnesium plays an important electrophysiologic role. Mg^{++} is a cofactor for the Na^+-K^+ pump and hence is important in maintaining the integrity of intracellular K^+ and the resting membrane potential. Mg^{++} also modulates the effects of various K^+ and Ca^{++} channels. Hypomagnesemia is associated with prolongation of the QT interval and increased risk of ventricular arrhythmias. This effect could be mediated in part through other electrolyte deficits, because hypomagnesemia is associated with hypokalemia and hypocalcemia.

Serum calcium is also important. Hypocalcemia increases the QT interval, predisposing to ventricular tachycardias. Hypercalcemia exerts the opposite effects, reducing the QT interval. Changes in intracellular calcium contribute to arrhythmias associated with acute ischemia and reperfusion and may be important in the genesis of ventricular tachycardia induced by exercise and by digitalis.

Hypothermia

Moderate (32°C to 35°C) and severe (<32°C) hypothermia can also predispose to ventricular tachyarrhythmias by causing prolongation of the QT interval, along with QT dispersion.[74] Typically, patients with hypothermia develop J waves (also known as Osborn waves) in the 12-lead ECG, which reflects accentuation of the inhomogeneity of repolarization caused by the predominant distribution of I_{To} in subepicardial and midmyocardial regions.[75] Accentuation of the action potential notch in the epicardium but not in the endocardium is responsible for the voltage gradient that manifests in the surface ECG as a J wave. Hypothermia may be complicated by the ingestion of drugs and the presence of electrolyte abnormalities that further increase the risk of ventricular tachyarrhythmias.

Arrhythmogenic Right Ventricular Cardiomyopathy

This disorder is characterized by progressive replacement of the normal right ventricular muscle cells by fibrous tissue and fat.[76] The condition may be familial, with autosomal

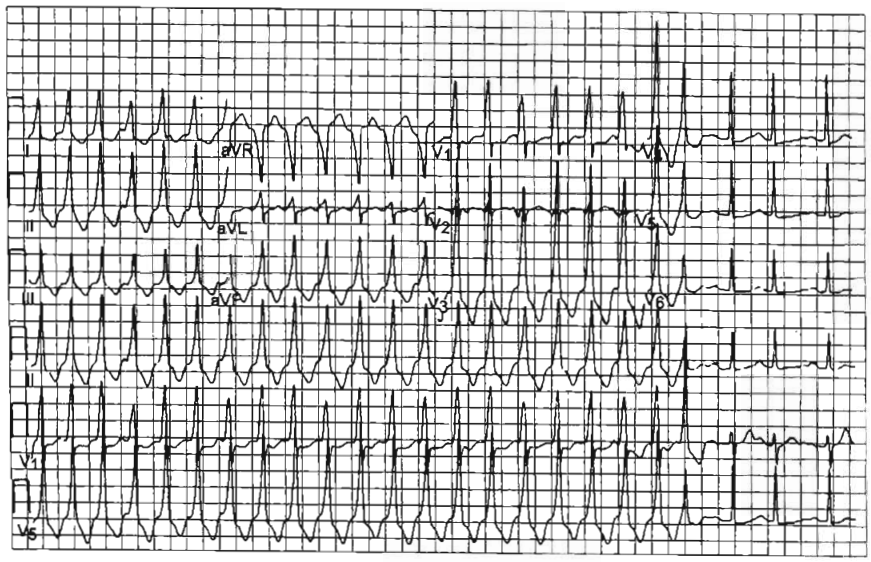

FIGURE 96–5. Representative monomorphic ventricular tachycardia with atrioventricular (AV) dissociation (P waves are best seen in V_1). The tachycardia ends into a sinus rhythm with first-degree AV block preceded by one fusion beat. (From Murphy JG [ed]: Mayo Clinic Cardiology Review, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2000, p 657.)

dominant inheritance.[77] Patients present with palpitations, syncope, and sometimes sudden death. It is considered an important cause of sudden death in subjects younger than 35 years, especially when related to exercise.[78,79] The ECG is abnormal in 90% of cases, showing T-wave inversions beyond lead V_1 and epsilon waves in leads V_1 to V_3. The QRS complex may be widened (>110 msec), with complete or incomplete right bundle branch block morphology. There are ventricular premature beats with left bundle branch configuration.

CLINICAL DIAGNOSIS

Ventricular ectopic activity is suspected whenever wide QRS complexes dissociated from atrial activity appear in the ECG. Various types of ventricular arrhythmias can develop in critically ill patients, with different prognostic implications and management.

Premature ventricular contractions (PVCs) are isolated ventricular ectopic beats that may be found in normal, healthy individuals. However, they often accompany cardiac conditions (ischemia, cardiomyopathy, valvular heart disease), use of stimulants (caffeine, cocaine, alcohol, ephedrine, pseudoephedrine), electrolyte abnormalities (hypokalemia, hyperkalemia, hypomagnesemia), hypoxemia, catecholamine discharge, and medications (tricyclic antidepressants, antipsychotic medications, digoxin, flecainide, sotalol, quinidine). The ECG demonstrates a wide QRS complex with a bizarre axis, a T wave with polarity opposite to the QRS, and a full compensatory pause. PVCs usually do not produce symptoms.

Ventricular tachycardia is defined as three or more consecutive ectopic beats that originate below the AV node, with a rate that typically exceeds 100 beats per minute and often ranges between 130 and 170 beats per minute. Ventricular tachycardias usually have QRS complexes of 120 msec or longer and are therefore classified as wide-complex tachycardias. However, wide-complex tachycardias can also be supraventricular when the impulse originates above the bifurcation of the bundle of His but is conducted with aberrancy (see later).[80] Ventricular tachycardias are classified as monomorphic if all QRS complexes have similar morphology and polymorphic if they have variable morphology.

Monomorphic ventricular tachycardias are the most common form and are usually associated with structural heart disease, such as previous myocardial infarction and, less commonly, cardiomyopathy. The reentrant circuit can be small (microentry) or large (macroentry) and can be located in different regions of the myocardium, contingent on the infarcted sites. The mechanism is usually reentry operating within or around the damaged myocardium. A representative 12-lead ECG is shown in Figure 96-5.

Polymorphic ventricular tachycardias have irregular rhythms, usually compromise hemodynamic function, and may quickly degenerate into ventricular fibrillation. Variation in QRS morphology represents changes in the electrical axis. One special form of polymorphic ventricular tachycardia is torsades de pointes. This is a descriptive term denoting a rotating electrical axis in which the complexes rotate 180 degrees along an imaginary axis ("twisting points"); it is typically associated with long QT syndrome. Representative tracings are shown in Figure 96-6.

Ventricular tachycardias are considered sustained if they last 30 seconds or longer and nonsustained if they last less than 30 seconds. Most sustained ventricular tachycardias present with palpitations, chest discomfort, and weakness or with more severe symptoms such as dizziness, angina, syncope, seizures, and even sudden cardiac death.[81] On physical examination, the rhythm is usually regular. Hypotension may accompany the episode, especially in patients with underlying heart disease. Examination of the jugular veins may show cannon A waves, indicative of AV dissociation. Variability in S_1 occurrence and intensity and variations in blood pressure are also findings consistent with AV dissociation.

In nonemergency settings, a standard 12-lead ECG should be obtained to determine whether a wide-complex tachycardia is present and whether it is monomorphic or polymorphic. If monomorphic, the possibility of supraventricular tachycardia with aberrancy should be considered, although most wide-complex tachycardias are ventricular. The presence of shock, heart failure, or cardiac arrest favors ventricular tachycardia, and treatment should not be delayed.

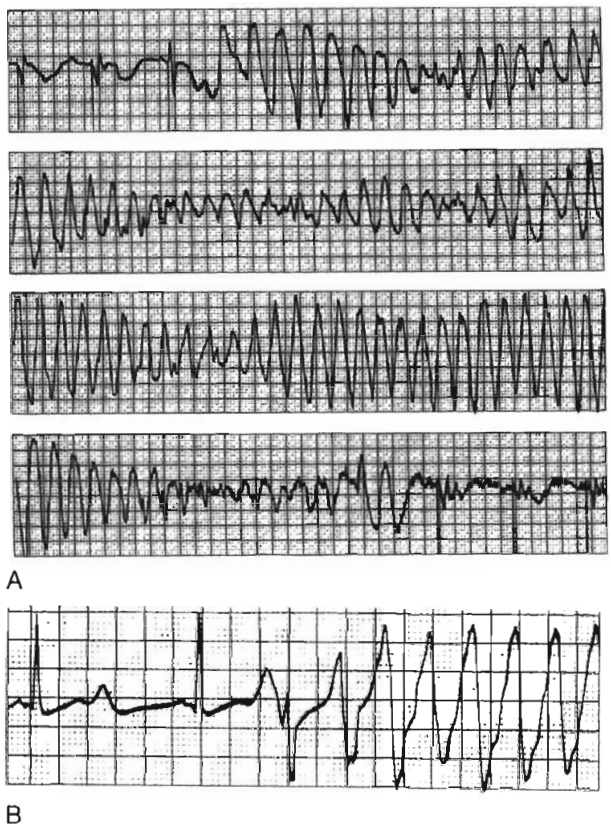

FIGURE 96–6. Torsades de pointes. *A*, A patient with a demand ventricular pacemaker developed QT prolongation (≈640 msec, seen during paced rhythm) after treatment with amiodarone for recurrent ventricular tachycardia. An episode of torsades de pointes developed that spontaneously terminated with resumption of a paced ventricular rhythm. *B*, Tracing from a young boy with congenital long QT syndrome and marked prolongation of the QTU interval (≈600 msec). TU alternans is noted before a late premature complex occurring on the downslope of the TU wave initiates an episode of ventricular tachycardia. (From Braunwald E, Zipes D, Libby P [eds]: Heart Disease: A Textbook of Cardiovascular Medicine, 6th ed. Philadelphia, WB Saunders, 2001, p 868.)

Supraventricular tachycardia with aberrancy (in a stable patient) should be suspected whenever there is a history of previous aberrant rhythms, accessory pathways, and baseline or rate-induced bundle branch block. The ECG should be carefully examined for evidence of AV dissociation, which is specific for ventricular tachycardia.[82] If P waves are not visualized in V_1 or in any of the other standard leads, a Lewis lead (arm electrode positioned on the parasternal area) or an esophageal lead can be used.[83] AV dissociation is indicated by P waves and QRS complexes that present at different and uncoupled rates. Other manifestations of dissociation include captured beats (narrow QRS conducted beats) and fusion beats (merge of ectopic with conducted beats).

Other ECG clues include regularity of the RR interval, which can be altered in supraventricular tachycardia but usually not in monomorphic ventricular tachycardia, and a QRS duration greater than 160 msec; however, the QRS duration can be shorter (110 to 114 msec) in instances of fascicular tachycardia. With respect to axis and morphology, the QRS in V_1 is usually predominantly positive (right bundle branch block morphology) or predominantly negative (left bundle branch block morphology). Occasionally, the QRS in V_1 has two peaks, leading to an RSr′ pattern that is known as a "rabbit ear." In this instance, a taller "left ear" favors ventricular tachycardia, whereas a taller "right ear" is noncontributory. The T waves are characteristically large and opposite for the main QRS deflection. Additional ECG criteria and algorithms are available to help differentiate ventricular from supraventricular tachycardia.[84-87] A widely accepted four-step algorithm developed by Brugada is shown in Figure 96-7.[85] A similar algorithm that incorporates pertinent clinical information can be found at http://www.anaesthetist.com/icu/organs/heart/ecg/wct.htm#step0.

Some special forms of ventricular tachycardia tend to be mistaken for supraventricular tachycardia with aberrancy.[88] These include bundle branch reentrant tachycardia, in which the impulse travels down the right bundle branch, across the interventricular septum, and up the left bundle branch.[89,90] The morphology resembles supraventricular tachycardia with left bundle branch block and is common among patients with nonischemic dilated cardiomyopathy.[91] Right ventricular outflow tract tachycardia is another condition caused by triggered activity from delayed afterdepolarizations that most commonly originate in the right ventricular outflow tract.[92] The tachycardia usually presents with left bundle branch block morphology and right axis deviation. Right ventricular outflow tract tachycardias occur in structurally normal hearts, typically in young individuals, and are responsive to verapamil or adenosine.[93] Finally, there are fascicular tachycardias that originate from either fascicle of the left bundle branch. They occur in structurally normal hearts, mimic supraventricular tachycardia with aberrancy, and are responsive to beta blockers and verapamil.[94]

Accelerated idioventricular rhythm is a form of automatic ventricular arrhythmia and is characterized by the presence of regularly wide QRS complexes with a rate between 50 and 120 beats per minute. It is often, but not always, slightly faster than the underlying sinus rhythm. Accelerated idioventricular rhythm is an electrocardiographic diagnosis and does not produce symptoms. Identifying this rhythm is important because it usually indicates underlying myocardial ischemia, and the treatments for ventricular tachycardia may not apply.

Ventricular fibrillation is defined as the abrupt onset of irregular waveforms of varying contour, duration, and amplitude without identifiable QRS and T waves. Ventricular tachycardia or supraventricular tachycardias that conduct through accessory pathways (e.g., Wolff-Parkinson-White syndrome) may be the initiating rhythm that degenerates into ventricular fibrillation. Ventricular fibrillation (and pulseless ventricular tachycardia) causes immediate cessation of blood flow, precipitating unconsciousness within seconds. Generalized seizures and agonal breathing may follow, which should not distract from the primary diagnosis and the emergency treatment of cardiac arrest.

INCIDENCE IN THE CRITICAL CARE SETTING

The incidence of ventricular arrhythmias in critically ill patients is difficult to ascertain with precision and varies in relation to the underlying condition, predisposing factors, structural abnormalities, and triggering events, as well as the method of detection.[95,96] Artucio and Pereira, using a chart review, reported in 1990 a 78% incidence for all types of brady- and tachyarrhythmias of atrial and ventricular origin in 2820 patients admitted to a general-purpose ICU over 12 years.[95] The incidence of ventricular tachyarrhythmias for the entire group was 22%, with the highest incidence in

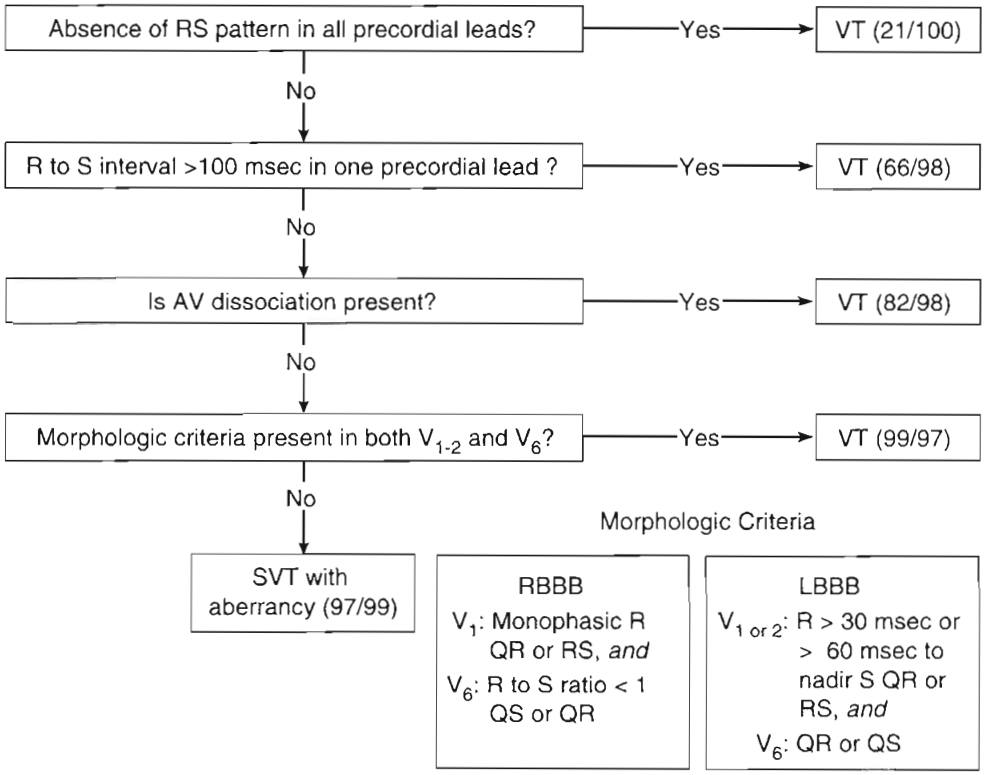

FIGURE 96–7. Four-step Brugada algorithm for the diagnosis of wide-complex tachycardia. Ventricular tachycardia is diagnosed whenever an answer is positive within each successive steps: in step 1, when an RS complex cannot be identified in any precordial lead; in step 2, when the longest RS complex (beginning of R to nadir of S) in a precordial lead exceeds 100 msec; in step 3, when there is atrioventricular (AV) dissociation; and in step 4, when the morphologic criteria for tachycardia with right bundle branch block (RBBB) or left bundle branch block (LBBB) morphology are met. In parentheses are the sensitivity and specificity reported in the original report based on 554 wide-complex tachycardias.[85] VT, ventricular tachycardia. SVT, supraventricular tachycardia.

patients with cardiovascular (460 of 1767; 26%) and respiratory (64 of 339; 19%) conditions and the lowest in patients with multiple trauma (7 of 107; 7%). Conditions such as sepsis, neurologic disorders, and intoxication had an intermediate incidence. Ventricular fibrillation occurred in 119 patients, representing 4% of the entire group and 19% of the subset with ventricular tachyarrhythmias. More recently, Reinelt and colleagues—using more restricted criteria (in which PVCs, couplets, and triplets were not included)—reported an overall incidence of cardiac arrhythmias of 18% (133 of 756 consecutive admissions) in a medical-coronary ICU.[96] The incidence of ventricular tachyarrhythmias for the entire group was 9% (65 of 756 patients); monomorphic ventricular tachycardia was the most common (54 of 65), followed by ventricular fibrillation (6 of 65) and polymorphic ventricular tachycardia (5 of 65). Factors present during the arrhythmic episodes included hypokalemia (10%), hypomagnesemia (12%), sedation (60%), mechanical ventilation (77%), and administration of catecholamines such as norepinephrine, epinephrine, and dobutamine (75%). In 23% of the episodes there was a history of previous myocardial infarction, and in 40%, a history of recent myocardial infarction. Fifty-two percent of the episodes occurred during a postoperative period, and 35% while a pulmonary artery catheter was in place. The presence of arrhythmias was associated with an increased length of stay and lower survival. However, fatal arrhythmic events occurred in only two patients, suggesting that arrhythmias were an indicator of severity rather than a cause of poor outcome.

Special consideration should be given to patients admitted for the evaluation of an acute coronary syndrome. Before the advent of thrombolysis in the 1980s, the incidence of ventricular tachycardia ranged between 3% and 39%.[97] With the widespread use of thrombolysis, the incidence has decreased.[98] This is thought to reflect less ventricular dysfunction and dilatation as a result of successful reperfusion. For similar reasons, ventricular tachycardia is less frequent in patients with non–ST segment elevation (<1%) than in those with ST segment elevation (≈4%) myocardial infarction.[98]

Episodes of ventricular tachycardia have different implications, depending on whether they occur early or late in the course of myocardial infarction and whether they are sustained or nonsustained. Early is usually defined as the initial 48 hours after the onset of symptoms, although some authors use a 12-hour cutoff.[99] Early nonsustained ventricular tachycardias are relatively common, with an incidence between 9% and 12%.[100,101] They reflect electrical instability during the acute ischemic event but have little prognostic implication.[102] Early sustained ventricular tachycardias occur in less than 2% of patients,[103] but they identify a population with a poorer prognosis.[98]

Late ventricular tachycardias coincide with the phase of myocardial healing and may signal the presence of persistent ischemia, left ventricle dysfunction, or electrophysiologic instability.[99] Nonsustained ventricular tachycardias occur in approximately 6% of patients.[53,104] Sustained ventricular tachycardias occur in approximately 1% and convey a worse prognosis than do nonsustained episodes.[98,105]

One particularly arrhythmogenic period is during reperfusion after thrombolysis.[53,100] There are frequent PVCs and episodes of nonsustained ventricular tachycardia but rarely episodes of sustained ventricular tachycardia or ventricular fibrillation.[106] Accelerated idioventricular rhythm is also common, with an incidence as high as 50% to 75%. It occurs within 24 hours after the start of thrombolysis and then subsides.[106,107]

ACUTE MANAGEMENT

PVCs and episodes of nonsustained ventricular tachycardia have little immediate hemodynamic significance. Management should focus on identifying and removing contributing factors.

The risk of degenerating into sustained ventricular tachyarrhythmias is low when PVCs occur with a frequency of less than 30 per hour but increases as PVCs occur with greater frequency, are multifocal, present in pairs or triplets, or exhibit the R-on-T phenomenon. Acute antiarrhythmic drug therapy is typically not required. Treatment of nonsustained ventricular tachycardia that persists after the episode of critical illness should take into account the underlying cardiac substrate and may involve a thorough assessment of mechanical and electrical function. In general, asymptomatic patients without structural heart disease require no specific therapy.

The management of sustained ventricular tachyarrhythmias requires a dynamic approach in which therapeutic interventions often parallel and occasionally precede diagnostic evaluation. This is particularly true in instances of ventricular fibrillation and pulseless ventricular tachycardia, when delivery of unsynchronized electrical shocks and advanced life support cannot be delayed. In less urgent situations (or after reestablishment of cardiac activity), treatment should focus on identifying and removing precipitating and maintaining factors, paying close attention to (1) hemodynamic and respiratory abnormalities, (2) endogenous or exogenous adrenergic states, (3) acid-base and electrolyte imbalances, (4) presence of proarrhythmic agents, and (5) mechanical stimulation of cardiac structures. Not infrequently, treatment of these factors alone terminates the arrhythmic episode (e.g., repositioning of a pulmonary artery catheter, reversal of myocardial ischemia, discontinuation of drugs that prolong the QT interval, correction of electrolyte imbalances, discontinuation of sympathomimetic agents).

Specific antiarrhythmic interventions should take into consideration the type of rhythm and the degree of hemodynamic stability (discussed next).

MONOMORPHIC VENTRICULAR TACHYCARDIA

Antiarrhythmic agents and direct-current synchronized cardioversion are acceptable first-line options. Among the antiarrhythmic agents, lidocaine was previously recommended as the best diagnostic and therapeutic intervention. The initial diagnosis is often wide-complex tachycardia, and it was believed that lidocaine would be effective if the tachycardia was ventricular but not if it was supraventricular. However, more recent studies have demonstrated that lidocaine does not consistently terminate monomorphic ventricular tachycardia and is less effective than procainamide, sotalol, and probably amiodarone.[108-111] The 2000 international guidelines favor procainamide and sotalol (class IIa) over amiodarone and lidocaine (class IIb).[112,113] However, amiodarone is gaining popularity as a first-line drug for a wide variety of supraventricular and ventricular tachyarrhythmias.[114-117] In patients with impaired left ventricular function (ejection fraction <40%), amiodarone and lidocaine may be considered first-line antiarrhythmic agents because they have fewer antiinotropic effects. Lidocaine should also be considered when myocardial ischemia is the substrate for ventricular tachyarrhythmias.

Addition of a second antiarrhythmic agent is discouraged because their proarrhythmic effects are compounded. Thus, a single agent should be used and proceed to direct-current synchronized electrical cardioversion if optimal dosing fails. Electrical cardioversion is a highly effective and accepted intervention and should be considered first-line treatment in patients who are unstable or in those who have borderline blood pressure that could be further decreased by the vasodilator and anti-inotropic effects of most antiarrhythmic agents.

POLYMORPHIC VENTRICULAR TACHYCARDIA

The treatment of polymorphic ventricular tachycardia should aim at prompt restoration of a sinus rhythm with emergency electrical cardioversion if necessary. However, substantial effort should be directed at identifying and correcting associated precipitating and maintaining factors. Polymorphic ventricular tachycardia of the torsades de pointes type usually occurs in the setting of bradycardia and prolonged QT interval. The mainstay of management includes discontinuation of drugs that prolong the QT interval and correction of electrolyte abnormalities. In the setting of congenital long QT syndrome, beta blockers (or sympathetic interruption), pacing, and implantation of an internal cardioverter defibrillator device should be considered. In the acquired forms of long QT syndrome, intravenous magnesium, overdrive pacing (or isoproterenol, when pacing is not immediately available), and beta blockers after pacing are recommended interventions. Isoproterenol is contraindicated in congenital long QT syndrome because it can precipitate torsades de pointes.

Polymorphic ventricular tachycardia not of the torsades de pointes type is not responsive to magnesium. Ischemia should be suspected and treated accordingly. Use of beta blockers, including sotalol, and amiodarone is recommended. An algorithm for the treatment of stable monomorphic and polymorphic ventricular tachycardia is shown in Figure 96-8.[118]

VENTRICULAR FIBRILLATION AND PULSELESS VENTRICULAR TACHYCARDIA

The probability of survival after ventricular fibrillation and pulseless ventricular tachycardia is inversely related to the time elapsed between the onset of the arrhythmia and the delivery of electrical shocks.[119,120] Recent studies have shown that immediate defibrillation is highly effective and is associated with high survival rates when the duration of untreated ventricular fibrillation is short (<4 minutes).[121,122] With more protracted untreated ventricular fibrillation, mounting evidence from animal and human studies indicates that a period of closed-chest resuscitation before attempting defibrillation improves outcome.[121,123-125] For defibrillation, current evidence favors biphasic waveforms using nonescalating energy levels as low as 150 J (in contrast to the traditional 200-, 300-, 360-J sequence recommended when using monophasic waveforms).[126-128] For patients with shock-refractory ventricular fibrillation or pulseless ventricular tachycardia, use of amiodarone has been shown to facilitate the restoration of cardiac activity.[129,130]

Electrical storm is a rather uncommon but highly lethal phenomenon defined as recurrent episodes of ventricular fibrillation, occurring mainly in the course of an acute myocardial infarction. Conventional antiarrhythmic drug therapy—including lidocaine and procainamide—often fails to secure a stable sinus rhythm. The underlying mechanism seems to be excessive (and probably unbalanced) sympathetic activity. Recent studies have shown that outcome can be dramatically improved by sympathetic blockade

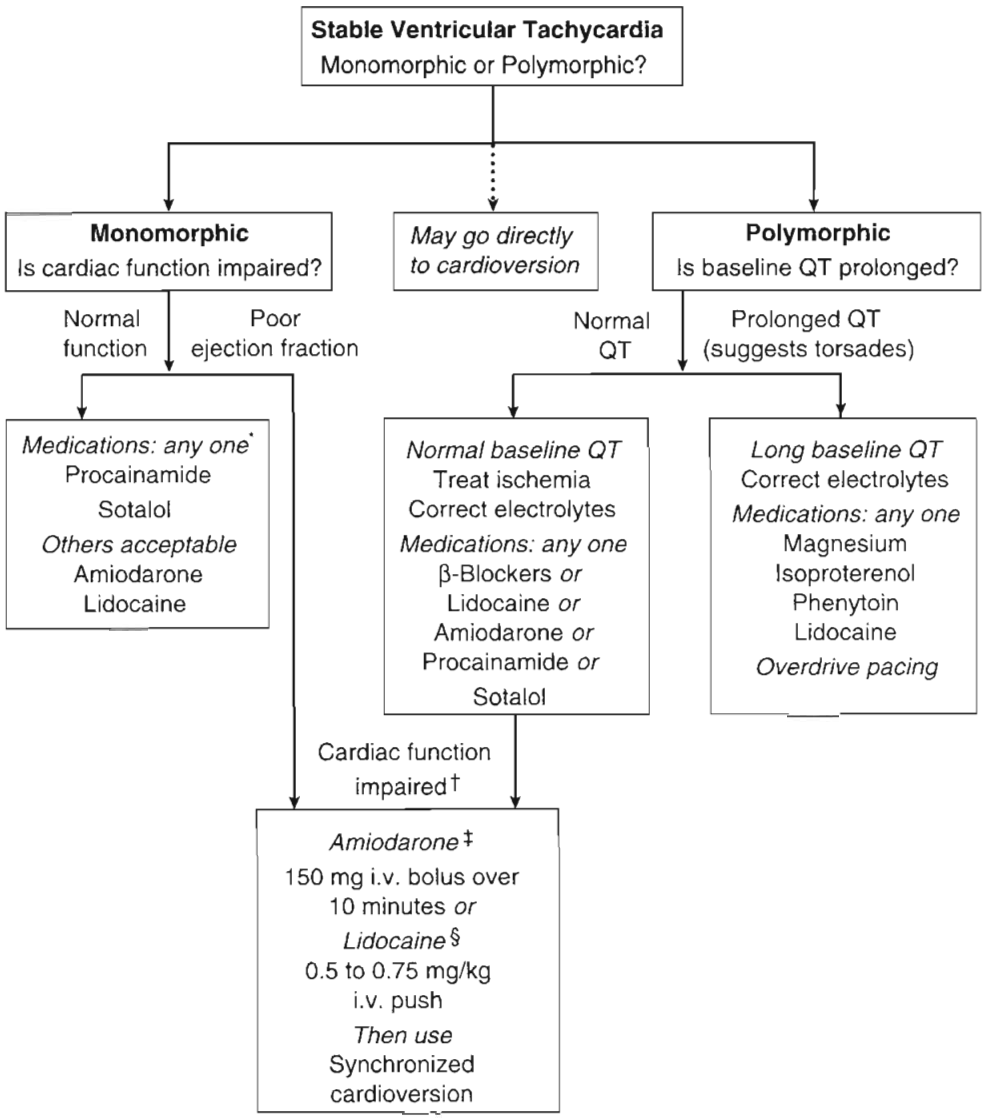

FIGURE 96–8. Algorithm for managing stable monomorphic or polymorphic ventricular tachycardia according to "Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care" (Circulation 2000;102:I158-I165).
*Use only one agent to avoid proarrhythmic effects.
†Ejection fraction <40% or clinical manifestations of congestive heart failure.
‡For amiodarone, give 150-mg bolus over 10 minutes and repeat dose if necessary every 10 to 15 minutes *or* infuse 360 mg over 6 hours (1 mg/min) followed by 540 mg over 18 hours (0.5 mg/min) to a maximal total cumulative dose of 2.2 g in 24 hours.
§For lidocaine, give 0.5 to 0.75 mg/kg i.v. push and repeat dose if necessary every 5 to 10 minutes, followed by an infusion of 1 to 4 mg/min to a maximum of 3 mg/kg per hour.

using intravenous beta blockers or stellate ganglionic blockade.[131]

CONCLUSION

Ventricular tachyarrhythmias are important and prevalent manifestations of cardiac and extracardiac abnormalities in critically ill patients. In addition to the traditional assessment based on ECGs and hemodynamic manifestations, understanding and recognition of the processes that affect ion channels, pumps, exchangers, and signaling mechanisms are important for proper management. There is also increased awareness that mutations affecting cardiac channels are prevalent and clinically relevant. The intensivist should be alert and prepared to identify them and provide the necessary initial treatment and an appropriate referral. The initial enthusiasm for antiarrhythmic agents has diminished as the proarrhythmic effects of various compounds have become evident. Some drugs are no longer recommended as first-line agents, whereas others have become components of accepted algorithms. More emphasis is currently being place on understanding arrhythmogenic mechanisms and on correcting the precipitating and maintaining factors.

ACKNOWLEDGMENTS

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The Sicilian gambit: A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. Circulation 1991;84:1831-1851.

This article provides an expanded classification of antiarrhythmic agents that takes into account their complexity and multiplicity of actions.

Chapter 97

CONDUCTION DISTURBANCES AND CARDIAC PACEMAKERS

Jason Knight • John Sarko

KEY POINTS

CONDUCTION DISTURBANCES

1. Atrioventricular (AV) node block is most often caused by medications, increased parasympathetic tone, or ischemia. Except when infarction permanently damages a portion of the conduction pathway, such blocks are usually reversible. Infranodal blocks, however, are rarely caused by physiologic abnormalities.
2. First-degree AV node block and Wenckebach block typically do not require treatment. Type II second-degree heart block and complete heart block usually do require treatment.
3. Therapy for AV block consists of atropine, adrenergic agents, Digibind (if appropriate), and pacing.
4. Bradyarrhythmias are common after cardiac surgery and may require temporary pacing, but a decision to place a permanent pacemaker should not be made until 5 to 7 days after surgery.

PACEMAKERS

1. A cardiologist or electrophysiologist should be consulted when a pacemaker or cardioverter-defibrillator malfunction is suspected.
2. Placing a magnet over the pacemaker disables the sensing mechanism, causing the pacemaker to fire at its preprogrammed rate, regardless of the underlying intrinsic rhythm.
3. Magnetic resonance imaging may be safe in a pacemaker patient if the unit is programmed to an asynchronous mode and the patient is watched carefully.
4. Failure to sense occurs when the pacemaker generates output regardless of the patient's underlying rhythm; this is rarely an urgent problem.
5. Failure to pace is noted when a pacemaker spike is not seen when expected (after the lower rate-limiting interval has been exceeded); this can be devastating for a pacemaker-dependent patient, and temporary pacing may be required.
6. Failure to capture occurs when a pacemaker fires as expected but fails to depolarize the myocardium. This complication may require temporary pacing.

CONDUCTION DISTURBANCES

Bradyarrhythmias and conduction blocks are common in the ICU. A broad range of clinical presentations and pathologic findings occurs in this group of arrhythmias. Some bradyarrhythmias are benign and asymptomatic and do not require treatment. Other atrioventricular (AV) blocks and arrhythmias are life threatening and warrant immediate intervention.

NORMAL CARDIAC CONDUCTION

Normal depolarization and impulse conduction are central to maintaining cardiac output. Two types of cells are found in the heart: (1) cells responsible for impulse generation and conduction, and (2) cells responsible for contraction. Depolarization of the myocardium begins in the sinoatrial (SA) node. The SA node is located in the posterior and superior portion of the right atrium and is innervated by the sympathetic and parasympathetic nervous systems.

The impulse is generated by a specialized group of cells with the ability to depolarize spontaneously. The initial depolarization of the SA node is not seen on the electrocardiogram (ECG). The P wave is generated when the impulse spreads throughout the atria. There is no specific conduction system in the atria to convey the SA node impulse to the AV node.[1] The impulse is transmitted by depolarization of adjacent atrial myofibrils. Approximately halfway through the P wave, the impulse reaches the AV node. The second half of the P wave is due to left atrial depolarization.

In a normal heart, the atria and the ventricles are electrically isolated from each other, except at the AV node. The AV node is located in the atrial septum near the apex of the triangle of Koch. The AV node is innervated by the sympathetic and parasympathetic nervous systems. Conduction through the AV node accounts for the majority of the PR interval. After emerging from the AV node, the impulse is conducted through the bundle of His. From there, the impulse travels down the right and left bundle branches and their fascicles to the Purkinje network, which causes ventricular contraction.

FAILURE OF IMPULSE CONDUCTION

Failure of conduction can occur anywhere along the conduction pathway. AV node block is most often caused by medications, increased parasympathetic tone, or ischemia. AV node blocks are usually reversible, except when infarction permanently damages a portion of the conduction pathway. Infranodal blocks are rarely caused by physiologic abnormalities. Structural heart disease and anatomic disruption of the conduction system are the main causes of infranodal heart block. Rare causes of infranodal block include disruption of the bundle of His from aortic valve calcification, Lenègre's disease (idiopathic degeneration of Purkinje fibers), and Chagas' disease.[2]

Once AV block is identified, it is helpful to determine the site of conduction pathology. The anatomic site can be identified in most cases by synthesizing the type of AV block, the width of the QRS complex, and the QRS morphology. When the QRS complex is narrow (<0.12 sec), the site of pathology is most likely supraventricular. When the QRS complex is wide, the most likely site of AV block is infranodal. Bundle branch and fascicular blocks produce various QRS morphologies that may aid in determining the specific anatomic location of pathology.

Clinical Presentation

Syncope and presyncope are the most dramatic symptoms of conduction disturbances; palpitations, dyspnea, angina, and fatigue are seen as well. Many patients are asymptomatic. A significant number of patients develop bradydysrhythmias after an acute myocardial infarction (MI) (Table 97-1).[3]

Diagnostic Evaluation

A high-quality ECG is paramount for the appropriate evaluation of P waves and various intervals. Routine monitoring in the ICU is usually accomplished with a single- or three-lead display at the bedside. The lead chosen should clearly delineate the P waves and QRS complexes. Complex arrhythmias may require Lewis leads, intra-atrial leads, or esophageal ECG monitoring. Calipers significantly aid in the diagnosis of AV blocks and are helpful to "march out" P waves and intervals. Holter or continuous loop monitoring can also be an important tool in the evaluation of AV block.[4] These monitors allow one to evaluate the cardiac conduction system during a patient's activities of daily living. A monitoring period of at least 24 hours is recommended so that both daytime and nighttime activities are included.

TABLE 97–1. INCIDENCE OF BRADYDYSRHYTHMIAS IN ACUTE MYOCARDIAL INFARCTION

Rhythm	Incidence (%)
Any bradydysrhythmia	25-30
Sinus bradycardia	25
Junctional escape rhythm	20
Idioventricular escape rhythm	15
First-degree atrioventricular (AV) node block	15
Second-degree AV block type I	12
Second-degree AV block type II	4
Third-degree block	15
Right bundle branch block	7
Left bundle branch block	5
Left anterior fascicular block	8
Left posterior fascicular block	0.5

SINUS NODE ABNORMALITIES

Sinus Bradycardia

Sinus bradycardia is defined as a sinus rhythm with a heart rate less than 60 beats per minute. Sinus bradycardia is divided into two categories: appropriate and inappropriate. Appropriate bradycardia is seen in young, healthy individuals and endurance athletes; the heart rate increases appropriately with exercise. Pathologic sinus bradycardia does not increase appropriately with exercise. Medications are the most common cause of inappropriate sinus bradycardia; autonomic influences, electrolyte abnormalities, and intrinsic structural disorders are others. In older individuals, sinus bradycardia can result from a decrease in the sinus node firing rate, which is a normal part of the aging process. Ischemia may also increase vagal tone and result in a slower heart rate.

Sinus Arrest

Sinus arrest occurs when the pacemaker cells in the SA node fail to depolarize. Pauses of less than 3 seconds may be seen in up to 11% of normal individuals and should not cause concern.[5] There is a higher incidence of sinus pause in athletes. Pauses longer than 3 seconds are usually considered pathologic and should be evaluated.

SA exit block and sinus arrest appear similar on ECGs, but they should be distinguished, if possible. The duration of the pause in exit block is a multiple of the PP interval. High-grade exit block cannot be distinguished from sinus arrest. The treatment is the same for both conditions.[6]

Noninvasive testing includes ECG, carotid sinus massage, and a tilt table test. Carotid sinus massage is useful to diagnose carotid sinus hypersensitivity. Risks of carotid sinus massage include transient ischemic attack and stroke, and the test should not be performed on patients with carotid bruits. The tilt table test is helpful to determine whether syncopal episodes are due to autonomic dysfunction. Invasive diagnostic testing of the SA node can also be performed, although this is rarely necessary.

The treatment of sinus node dysfunction can be temporary or permanent. Atropine or an isoproterenol drip can be used in the ICU as a bridge to permanent pacemaker placement. Temporary pacing is indicated for patients who fail to respond to medical therapy.

Carotid Sinus Hypersensitivity

Carotid sinus hypersensitivity is diagnosed when ventricular asystole greater than 3 seconds' duration (usually due to a sinus pause or arrest) or a drop in systolic blood pressure greater than 50 mm Hg occurs in response to carotid massage. If symptoms occur, a 30 mm Hg drop in systolic blood pressure defines a positive response. Treatment is permanent pacing in symptomatic patients only.[7]

Postsurgical Bradydysrhythmias

Bradyarrhythmias are common after cardiac surgery. Valve surgery and septal myectomy can cause significant damage to the conduction system. Prolonged ischemia during heart transplantation may also result in sinus node or conduction system damage. The decision to place a permanent pacer should not be made until 5 to 7 days postoperatively, however, because the bradyarrhythmia may be temporary. Medication administered during surgery or reversible ischemia is often implicated. Pacing is required in 2% to 3%

TABLE 97–2. CAUSES OF ATRIOVENTRICULAR NODE DYSFUNCTION

Drugs
Digoxin
Beta blockers
Certain calcium channel blockers
Membrane-active antidysrhythmic drugs
Primary cardiac disease
Ischemic heart disease
Idiopathic fibrosis of the conduction system
Congenital heart disease
Calcific valvular disease
Cardiomyopathy
Metabolic
Hyperkalemia
Hypermagnesemia
Infiltrative disease
Infectious/inflammatory disease
Collagen vascular disease
Endocrine
Addison's disease
Trauma
Radiation
Tumors
Neurally mediated
Carotid sinus syndrome
Vasovagal syndrome
Neuromyopathic disorders

Adapted from Wolbrette DL, Naccarelli GV: Bradycardias: Sinus nodal dysfunction and atrioventricular conduction disturbances. In Topol EJ (ed): Textbook of Cardiovascular Medicine. Philadelphia, Lippincott-Raven, 1998, p 1655.

of patients with valve surgery and approximately 10% of patients with transplants.[8]

ATRIOVENTRICULAR NODE DYSFUNCTION

There are many causes and several manifestations of AV node dysfunction. Table 97-2 lists the causes of AV node abnormalities.

First-Degree Atrioventricular Block

First-degree AV block is characterized by a prolonged PR interval greater than 0.20 second in adults and 0.18 second in children who are not taking medications that can prolong the PR interval (Fig. 97-1). All the P waves are conducted to the ventricles, and the PR interval is typically fixed. Potential causes of first-degree AV block include delayed conduction through the atria from the SA node to the AV node, a delay in AV node conduction, or prolonged infranodal conduction.

Conduction delays from the SA node to the AV node are typically due to structural causes, such as right atrial enlargement or an ostium primum atrial septal defect. A delay in AV node impulse conduction is the most common

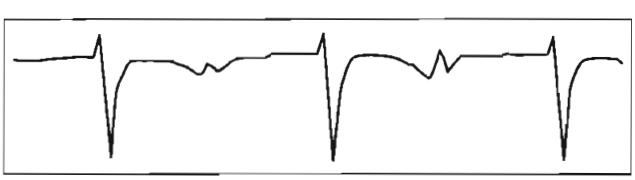

FIGURE 97–1. Electrocardiogram from a patient with first-degree atrioventricular block. The PR interval is approximately 0.34 second. All the P waves are being conducted to the ventricles. The PR interval is constant.

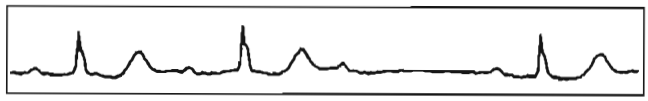

FIGURE 97–2. Electrocardiogram rhythm strip from a patient with second-degree atrioventricular block type I. Note the progressive prolongation of the PR interval until a failure of conduction occurs. Also note the reciprocal RP shortening. The pattern of conduction is 3:2.

cause of first-degree AV block. Patients with delayed conduction in the AV node often have a PR interval greater than 0.30 second. Infranodal causes of first-degree AV block are rare and are typically associated with a wide QRS complex due to disease in the fascicles or the bundle of His. First-degree AV block can also occur when each of these conduction times is at the upper limit of normal and summate to produce an overall prolongation of the PR interval.[7]

First-degree AV block is typically benign and asymptomatic. It can be seen in 0.5% of young adults without heart disease. In older people, first-degree block is most often the result of idiopathic degenerative disease. A prolonged PR interval is often an incidental finding when an ECG is ordered for other reasons. It rarely warrants further workup or treatment.

Second-Degree Atrioventricular Block Type I

Second-degree AV block type I, or a Wenckebach (or Mobitz type I) rhythm, is defined by a progressive prolongation of the PR interval with each successive beat, with eventual failure of a P wave to conduct to the ventricles (Fig. 97-2). This results in a dropped beat and failure of the ventricles to depolarize. The P waves occur at regular intervals. As the PR interval lengthens, the RR interval becomes shorter, which eventually results in decremental conduction. There is a reciprocal relationship between the RP interval and the PR interval.

The pathophysiology of second-degree AV block type I is similar to that of first-degree AV block, except that intra-atrial block is usually not a cause. For all practical purposes, second-degree AV block type I is caused by a block in AV node conduction. The QRS complex is generally narrow.

QRS complexes are typically grouped in twos, threes, fours, and so on. Group beating is characteristic of Wenckebach rhythms. The rhythm is described by recording the number of P waves and QRS complexes involved in the pattern of block (e.g., 4:3 or 3:2). During a dropped beat, a P wave is observed with no corresponding QRS complex. Second-degree AV block type I is a stable rhythm and has a much better prognosis than does a Mobitz type II rhythm. If the Wenckebach rhythm is due to medication, resolution of the block can be monitored with an ECG. Once the medication is discontinued, a shortening of the PR interval and a lengthening of the RP interval, with a corresponding improvement in AV node conduction, may be observed.

Second-Degree Atrioventricular Block Type II

Second-degree AV block type II (or Mobitz type II block) is characterized by a sudden nonconducted P wave without a change in the PR interval. A P wave with no corresponding QRS complex is observed on the ECG (Fig. 97-3). This is an inherently unstable rhythm, and serious pathology may be present. In contrast to the Mobitz type I rhythm, type II is described as a high degree of AV block, with P wave–to–QRS ratios of 3:1 and 4:1. A Mobitz type II rhythm is almost

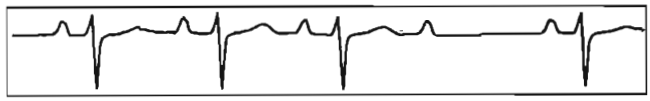

FIGURE 97–3. This electrocardiogram demonstrates second-degree atrioventricular block type II. The PR interval is constant before and after the blocked P waves. The QRS complex is widened.

always due to an infranodal conduction disturbance. The conducted QRS complexes are often wide, and a bundle branch block pattern is often observed. Second-degree AV block can result from anterior wall MI. Type II second-degree AV block can progress to complete heart block.

2:1 Atrioventricular Block

When conduction of every other P wave is blocked, 2:1 AV block is present. The PR interval of the conducted beat remains fixed. QRS complexes are regular and occur at half the atrial rate. 2:1 AV block can be caused by a Mobitz I (usually with a narrow QRS complex) or Mobitz II (with a wide QRS complex) rhythm, and the two entities are difficult to distinguish.

Third-Degree Atrioventricular Block

Third-degree AV block is characterized by complete AV dissociation. There is no conduction of the atrial signal through to the ventricle, so the atrial and ventricular systems operate independently. On ECGs, the P waves "march through" and are not associated with ventricular contraction. The PR intervals are irregular. The ventricular complexes may be junctional (narrow QRS complex; rate 40 to 60) or ventricular (wide QRS complex; rate <40). Depending on the escape heart rate, patients may present with tachypnea, dyspnea on exertion, fatigue, cyanosis, or syncope (Fig. 97-4).

Third-degree block can be divided into congenital and acquired causes. Sixty percent of patients with congenital heart block are female. Patients with congenital third-degree block often have an escape rhythm with an adequate rate.[9] Acquired third-degree block occurs most frequently in the seventh decade of life and usually requires permanent pacing; these patients are often male. Specific causes include medications, ischemia, progression from Mobitz type II rhythm, and infarction. Acute MI results in third-degree heart block in 14% of patients with inferior wall infarcts and 2% of patients with anterior infarcts. Third-degree block is usually observed within 24 hours after an MI. Third-degree block as a complication of inferior MI is usually temporary and may require only temporary pacing. Complete heart block as a result of anterior MI usually requires a permanent pacer.

Treatment involves correction of underlying disorders and immediate transcutaneous or transvenous pacing in unstable patients. If the primary cause cannot be medically managed, permanent pacing is required.

Diagnostic Pitfalls

Determining the degree of AV node block is usually straightforward if an adequate ECG has been obtained. There are circumstances, however, in which one may be misled to an incorrect diagnosis.

Third-degree block is occasionally misdiagnosed as second-degree block type II if there appears to be a constant PR interval. This may occur for short periods on an isolated rhythm strip. The clinician must therefore examine a strip for an appropriate length of time to make the correct diagnosis. Vagal maneuvers can also be attempted and may identify a second-degree AV block that is really a third-degree AV block.

With isorhythmic AV dissociation, the P waves and QRS complexes occur at a similar rate. The P waves may never "march out" long enough to determine whether they are all conducting. Interventions such as vagal maneuvers to change the P-QRS relationship may aid in diagnosis.

When second-degree AV block is fixed (2:1, 3:1, 4:1), some P waves may be concealed during the repolarization phase of the ECG. This may occur in acute MI or with ischemia. Vagal maneuvers and examination of multiple leads may be necessary to correctly identify the AV block.

When complete AV dissociation occurs with accelerated junctional or ventricular rhythms, it is possible that some of the atrial impulses would be conducted if the heart rate were slower. It is best to designate these rhythms as complex AV dissociation.

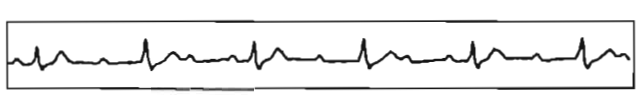

FIGURE 97–4. Complete heart block. The PR intervals are irregular, because the ventricles and atria represent two independent sources of depolarization.

Therapy

Medical therapy for AV block consists of atropine, adrenergic agents, Digibind (if appropriate), and pacing. Atropine decreases vagal tone and is useful for hypervagotonia but not AV node ischemia. It is more useful in inferior wall MI than anterior wall MI. Atropine will not improve third-degree AV block or a Mobitz type II block if the pathology is below the AV node, and it is ineffective in heart transplant patients. Atropine should be used with caution in patients with Mobitz type II rhythms, because a paradoxical decrease in heart rate can occur.

Digibind should be used in symptomatic patients with digoxin-induced AV block. The number of vials of Digibind required is approximately equal to the patient's weight (in kilograms) times the digoxin serum level (in ng/mL) divided by 100.

PACEMAKERS

Although pacemakers are reliable, patients occasionally present with abnormalities in one or more pacemaker functions that may impact their current illnesses. Intensivists can expect to encounter patients with pacemakers routinely, and it is helpful to be familiar with the basics of their functions and malfunctions.

The North American Society of Pacing and Electrophysiology and the British Pacing and Electrophysiology Group created a code consisting of five letters to describe pacemaker functions, known as the NBG pacemaker code (Table 97-3).[10] The first three letters describe the antibradycardia functions, the fourth describes the programmability of rate responsiveness, and the fifth describes any antitachycardia functions. A pacemaker may carry one classification (e.g., DDD) but be capable of several modes of function, depending on how it is programmed. Indications for permanent pacing were updated by the American College of Cardiology in 2002.[11]

TABLE 97–3. NBG PACEMAKER CODE

Position	I	II	III	IV	V
Category	Chamber paced	Chamber sensed	Response to sensing	Rate modulation or programmability	Antitachycardia functions
Letters used	A = atria V = ventricular	A = atria V = ventricular	T = triggered I = inhibited	R = rate modulation P = simple programmable (rate or output)	P = pacing S = shock
	D = dual (A + V)	D = dual (A + V)	D = dual (T + I)	M = multiprogrammable O = none	D = dual (P + S)

From Bernstein AD, Camm AJ, Fletcher AD: The NASPE/BPEG generic pacemaker code for antibradyarrhythmia and adaptive rate pacing and antitachycardia devices. Pacing Clin Electrophysiol 1987;10:794-798.

The pacemaker itself consists of two components: a pulse generator, and wire leads connecting the generator to the heart. The pulse generator consists of a lithium-based battery and the circuitry to detect and analyze the cardiac rhythm and produce the output. The battery can last more than 10 years, depending on the type of programming, and at the end of its life it shows a gradual rate decrease, not an abrupt drop-off.[12]

Pacemakers also contain a reed switch that can be used to assess the pacemaker's pacing ability. When an external magnet is placed over the pulse generator, the reed switch closes, disabling the sensing mechanism. The unit then fires asynchronously, without regard for the patient's underlying rhythm. The pacing rate is unique to each model and manufacturer, and the magnet-programmed rate can vary, depending on whether the battery is at the beginning or end of its life or at a time of elective replacement.

Each patient is given a card when a pacemaker is implanted that describes the manufacturer, model, and pacing parameters. The pacemaker itself also contains a radiopaque code, visible on x-ray, that identifies the unit. Pacemakers can be interrogated with a manufacturer-specific program that retrieves ECG information about the unit that can help assess its functioning. An electrophysiologist should be consulted when a malfunction is suspected.

Two types of lead systems exist: unipolar and bipolar. Bipolar leads are considered standard, unless patient-specific factors warrant the use of a unipolar lead. Unipolar programming uses the lead in the endocardium as the cathode and the pacemaker unit itself as the anode. Because voltage in a unipolar lead is detected over a greater distance, the pacing spike is larger than with bipolar lead programming. Leads can be attached to the endocardium by active fixation (screwed into the myocardium) or passive fixation (held in place by fins). Passive fixation is associated with a greater incidence of dislodgment and perforation.[13]

Assessment of pacemaker function requires knowledge of its parameters. A pacing spike must be present on the ECG to properly evaluate the unit. If one is not present, a magnet can be placed over it and an ECG recorded. This can then be used with the clinical situation and prior ECG to determine its function.

Every pacer is programmed to fire after a maximum period in which no activity has been detected. This is called the lower rate-limiting interval, and it is the time between two consecutive paced beats. The escape interval is the time between a native complex and the following pacemaker spike. A slight delay beyond the lower rate-limiting interval can be programmed into the pacemaker when it senses a native QRS complex. This is an attempt to permit the heart to generate its own output and thus function in a more physiologic manner; this is called rate hysteresis, and it is found most often in ventricular demand pacemakers.[14] Dual chamber pacers have an interval programmed between atrial and ventricular spikes, called the AV interval, which functions basically as the PR interval. The interval between a ventricular spike and the next atrial pacing spike is the ventriculoatrial interval. The AV and ventriculoatrial intervals sum to equal the lower rate-limiting interval.

COMPLICATIONS

Failure to Sense (Undersensing)

Undersensing occurs when the pacemaker generates output regardless of the patient's underlying rhythm (Fig. 97-5). A spike is seen at an interval earlier than the lower rate-limiting interval. Pacemaker output then competes with the patient's own intrinsic rhythm. Although ventricular pacing can present a problem when the threshold for ventricular capture has been altered (e.g., by ischemia), and atrial pacing can produce atrial fibrillation, these are rarely urgent problems.[15]

Specific causes of failure to sense are listed in Table 97-4. Blanking is not a true cause; rather, it is an instance of functional undersensing in dual chamber pacemakers. To prevent a pacemaker-induced tachycardia, a 12- to 125-msec period of inactivity is programmed into the ventricular component after an atrial complex. If an intrinsic QRS complex occurs during this period, it will not be sensed. Scar tissue does not conduct impulses as easily as normal myocardium does, so sensing may not occur. Most pulse generators begin asynchronous pacing at a critical point at the end of their life and will not sense intrinsic activity. Defibrillation can damage the unit; placing the defibrillator pad in an anteroposterior position may help. The unit should be observed closely after shocks are delivered.

Failure to Pace (Generate Output)

This complication is noted when a pacemaker spike is not seen after the lower rate-limiting interval has been exceeded

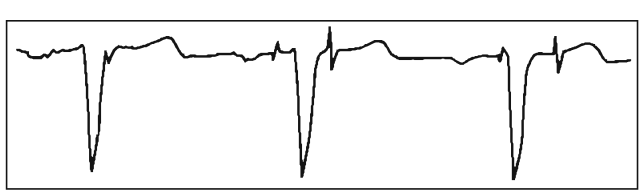

FIGURE 97–5. Failure to sense. Atrial and ventricular pacing spikes are seen around the intrinsic QRS complexes. Pacemaker activity does not lead to capture.

TABLE 97–4. CAUSES OF UNDERSENSING

Cause	Treatment
Lead fracture	Replace lead
Lead dislodgment	Reposition lead or increase sensitivity
Insulation defect in pacing lead	Replace lead
Magnet interrogation	Remove magnet
Blanking	Decrease ventricular refractory period
Amplitude of P wave or QRS complex too low to be sensed	Increase sensitivity
Myocardial fibrosis	Increase sensitivity or reposition lead
Myocardial perforation	Increase sensitivity or reposition lead
End of battery life	Replace battery
Acute myocardial infarction	Treat myocardial infarction
Electrolyte disturbance	Correct electrolytes
Antidysrhythmic drugs	Increase sensitivity, change drug
Magnetic resonance imaging	Reprogram to VOO, AOO, or DOO mode
Defibrillation	Place defibrillator pads as far from pacemaker unit as possible, place in anteroposterior position
Complexes occurring in pacemaker's refractory period	None, or use new generator with shorter refractory period

TABLE 97–5. CAUSES OF FAILURE TO PACE

Cause	Treatment
Lead fracture, loose connection, or insulation defect	Adjust or replace leads
Battery depletion	Replace battery
Pulse generator failure	Replace pulse generator
Cross-talk	Program a blanking period or safety pacing
Electromagnetic oversensing	
Sensing P or T or U waves	Decrease sensitivity, or advance tip deeper into right ventricle
Myopotential sensing	Decrease sensitivity, or use bipolar sensing
Electrocautery	Decrease sensitivity, or electrically isolate patient
Extracorporeal shock wave lithotripsy	Decrease sensitivity, or use minimal equipment necessary
Transcutaneous electrical nerve stimulator (TENS)	Decrease sensitivity, stop TENS unit
Magnetic resonance imaging	Program to DOO, VOO, or AOO mode

(except when hysteresis has been programmed; Fig. 97-6). Oversensing occurs when stimuli are erroneously sensed as pacemaker output. As a result, the expected, proper output is inhibited; this can be continuous or intermittent. Failure to pace can be a devastating complication for a pacemaker-dependent patient. It is important to determine whether output is truly occurring or not. A 12-lead ECG should be done, because spikes may be too small to be seen in a specific lead. Several causes are possible (Table 97-5).

Cross-talk is not a true malfunction of the pacemaker, but it can lead to an inhibition of activity. In a dual chamber system, the output of one chamber is sensed as the output of the other, and no pacemaker spike is generated; this occurs more often in unipolar leads. This problem is corrected by programming a blanking period. For a brief period after the atrial output (12 to 25 msec), the ventricular component is inhibited from firing. A second protection against cross-talk is to program the unit to fire depending on when in the AV interval the stimulus is detected. If it occurs immediately after the blanking period, a "safety" spike is generated, because it is assumed that it is impossible to differentiate cross-talk from a native QRS complex.

Failure to Capture

This complication occurs when a pacemaker fires as expected but fails to depolarize the myocardium. A pacer spike is seen on the ECG, but no QRS complex immediately follows it (Fig. 97-7). This can be dangerous for a pacemaker-dependent patient and may require temporary pacing until the problem is fixed. Most cases are due to problems with the lead-tissue interface, although isolated problems in the leads or the myocardium can also occur (Table 97-6).[13,16]

When a lead is placed into the myocardium, tissue fibrosis occurs over the first 4 to 6 weeks. Because scar tissue does not conduct as well as normal myocardium, the output voltage may need to be increased. Twiddler's syndrome is seen when a patient fidgets with the generator and ends up pulling the leads from their attachments to the myocardium. It is confirmed by chest x-ray. The pacemaker is replaced and fixed tightly to the underlying fascia. Perforation of the ventricle typically occurs shortly after the leads are placed and is confirmed by a chest x-ray showing the tip of the lead outside the heart. It is suggested by a change in pacing to a right bundle branch pattern, failure to capture, contraction of the diaphragm or intercostal muscles with pacing, or development of a pericardial friction rub. Provided the patient is not anticoagulated, the perforation is usually well tolerated.[14] Echocardiography can assess for the presence of pericardial effusion or tamponade. Repositioning of the lead is typically performed in the operating room after any coagulopathy has been reversed.

An increased threshold for capture can also be caused by myocardial ischemia, metabolic abnormalities, or certain drugs. Definitive treatment involves correcting the underlying disorder.

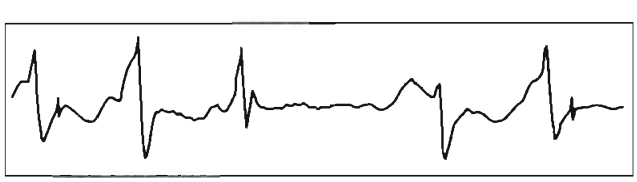

FIGURE 97–6. Failure to pace. An unduly long interval passes after the third QRS complex before another beat occurs. The pacemaker should have fired before this intrinsic beat.

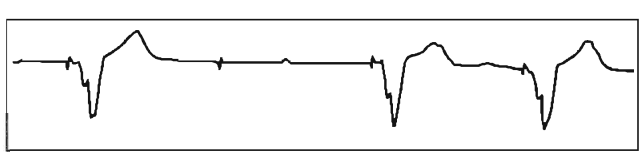

FIGURE 97–7. Failure to capture. After the first QRS complex, a small pacemaker spike occurs that does not result in depolarization of the ventricle. A nonconducted P wave follows, and then a pacemaker spike with capture occurs.

TABLE 97-6. CAUSES OF FAILURE TO CAPTURE

Cause	Treatment
Lead dislodgment from endocardial surface	Repair lead
Twiddler's syndrome	Fix unit to chest wall
Lead fracture or break in insulation	Replace lead
Improperly or inadequately programmed voltage	Reprogram voltage
Battery failure	Replace battery
Cardiac perforation	Reposition lead (in operating room) or increase voltage
Increased threshold for capture	
Fibrosis or scar tissue at contact site	Increase voltage or reposition lead
Myocardial ischemia	Treat ischemia
Metabolic	Treat abnormality
Hyperkalemia	
Hypercarbia	
Hypoxemia	
Hypothyroidism	
Drugs	Remove drug and replace with another
Beta blockers	
Class Ia antidysrhythmics	
Verapamil	
Flecainide	

When assessing for failure to capture, a distinction must be made between pseudofusion and fusion beats. A pseudofusion beat occurs when the pacemaker fires at the same time that an intrinsic beat occurs. The pacemaker output does not depolarize the myocardium, and instead, the pacemaker spike simply deforms the native QRS complex. It is an example of failure to capture. A fusion beat occurs when both the native complex and the pacemaker spike depolarize the myocardium, resulting in a QRS complex that is a hybrid of the two.

Other Problems

Pacemaker-mediated tachycardia, also called endless loop or pacemaker reentrant tachycardia, is a complication of dual chamber units. A premature atrial contraction or premature ventricular contraction that travels in a retrograde manner into the atria is sensed by the atrial component of the pacemaker, which induces the ventricular component to fire. The resulting ventricular depolarization reenters the atria, and the cycle continues. An upper rate limit is programmed into the pacemaker, so the tachycardia will not exceed this rate. A tachycardia paced by atrial and ventricular spikes is seen. Application of a magnet terminates the dysrhythmia; adenosine may not reliably block it.[17] A blanking period must be programmed.

Pacemaker syndrome is seen when only the ventricle is paced. Patients present with lethargy, syncope, dizziness, weakness, fatigue, palpitations, or congestive heart failure. It occurs because of an inability to raise the heart rate with exercise and because of the loss of AV synchrony. Dual chamber pacing is required to correct this.

The diagnosis of MI in a patient with a functioning pacemaker is difficult. Criteria similar to those in patients with left bundle branch block have been proposed, but sensitivity and specificity are lower.[15]

Advanced Cardiac Life Support protocols are not contraindicated by the presence of a pacemaker. Defibrillator pads should be kept as far away from the pulse generator as possible to minimize any damage to the unit.

Examination by magnetic resonance imaging has been considered contraindicated because of the interaction between the strong magnetic field and the pulse generator. Increased pacing rates, decreased rates, and pacing at the magnet rate have all been seen. However, programming the pacemaker to an asynchronous mode (AOO, VOO, or DOO) and close monitoring of the patient, along with the use of lower magnetic fields, may allow safe imaging.[18,19]

TEMPORARY PACING

Temporary cardiac pacing may be required for emergent or elective reasons. In general, any patient with bradycardia causing symptoms or hemodynamic instability that is unresponsive to atropine ought to be considered for temporary pacing (Table 97-7).[20] In most cases, this occurs after acute MI,[20,21] but certain drug poisonings may benefit from pacing,[22,23] and some interventions may, because of underlying disease, predispose a patient to significant bradycardia.

MODES OF PACING

Several modes of temporary pacing are available. Transcutaneous pacing involves placing the pacing pads on either the chest wall and back (the usual locations) or in an anterolateral position (especially if external defibrillation may be required). The negative electrode is placed over the apex of the heart. This is the easiest mode to use, but it is uncomfortable for a conscious patient and may require analgesia or sedation.

Transvenous pacing is usually well tolerated by patients but requires a high degree of skill to correctly place the pacing electrode in the right ventricle. Therefore, the American College of Physicians and the American College of Cardiology recommend that only physicians formally trained in their use place these electrodes.[24] The right internal jugular vein approach is best because of its more direct

TABLE 97-7. INDICATIONS FOR TEMPORARY CARDIAC PACING

Drug toxicity
Beta blocker
Calcium channel blocker
Digitalis-induced dysrhythmia (when direct-current cardioversion is contraindicated)
Hyperkalemia with bradycardia or asystole
Hypothermia (transcutaneous pacing only)
Symptomatic bradycardia (including hemodynamic compromise, syncope, or ventricular ectopy in response to bradycardia) not responsive to atropine
Pacemaker malfunction with symptoms
Alternating BBB (after MI)
RBBB with alternating LAFB or LPFB (after MI not known to be old)
RBBB with LAFB or LPFB, or LBBB with first-degree heart block, not known to be old
Mobitz type II heart block
Asystole
LBBB not known to be old
Recurrent sinus pauses >3 sec not responsive to atropine
RBBB with first-degree heart block
Possibly helpful: bifascicular block or RBBB of unknown age

BBB, bundle branch block; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LPFB, left posterior fascicular block; MI, myocardial infarction; RBBB, right bundle branch block.

route to the heart; the left subclavian vein approach can also be used but should be avoided, if possible, because it is a preferred site for placement of a permanent pacemaker.[20]

Transesophageal pacing allows pacing of either the atria or the ventricles, but it is not a commonly used modality. Transthoracic pacing, in which leads are placed percutaneously into the ventricular myocardium, is also possible but is fraught with complications, including pericardial tamponade, pneumothorax, visceral injury, and coronary artery laceration. Pacing leads placed during open heart surgery can also be used.

Pacing threshold should be determined, and the pacing energy should then be set at two to three times this minimum output. Thresholds should be checked daily.

ANNOTATED REFERENCES

American College of Cardiology: ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: Summary article. Circulation 2002;106:2145-2161.

This guideline revises the indications for implantable pacemakers and cardioverter-defibrillators.

Bernstein AD, Camm AJ, Fletcher AD: The NASPE/BPEG generic pacemaker code for antibradyarrhythmia and adaptive rate pacing and antitachycardia devices. Pacing Clin Electrophysiol 1987;10:794-798.

The system for describing pacemakers is introduced and discussed in this article.

Sommer T, Valhous C, Lauch G, et al: MR imaging and cardiac pacemakers: In-vitro and in-vivo studies in 51 patients at 0.5 T. Radiology 2000;215:869-879.

This study of several dozen pacemakers and patients with pacemakers suggests that magnetic resonance imaging is safe when performed under optimal conditions of asynchronous programming of the pacemaker, continuous patient monitoring, and low magnetic field strength.

Chapter 98

SUDDEN CARDIAC DEATH: IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

Michael McCready • Derek V. Exner

KEY POINTS

1. The implantable cardioverter-defibrillator (ICD) has a rapidly expanding role in the treatment of ventricular tachyarrhythmias. A general familiarity with its function, malfunction, and associated clinical problems is required of all acute care practitioners.
2. Current ICDs use nonthoracotomy leads and are often implanted subpectorally; all devices have pacemaker (ventricular, dual chamber, or biventricular) functions and advanced antitachyarrhythmia therapies, including low-energy cardioversion, antitachycardia pacing, and defibrillation.
3. Large clinical trials of ICDs demonstrate that device-based therapy is superior to medication-based approaches for preventing sudden death, particularly in patients with left ventricular systolic dysfunction and coronary artery disease.
4. Pacing malfunctions that may occur include oversensing, undersensing, failure to capture, and paced tachycardias. Chest radiographs to assess lead position and device interrogation can help define the cause of abnormal device behavior or lead failure.
5. ICD system infection is associated with high morbidity and mortality. Patients with unexplained fever, systemic inflammation, proven bacteremia, or pulmonary embolism should undergo careful examination of the pulse generator pocket and echocardiography to assess for lead vegetations.
6. Single ICD shocks are common, and multiple repetitive shocks can occur. It is important to distinguish appropriate from inappropriate shocks and identify possible precipitants of ventricular arrhythmias, such as exercise, myocardial ischemia, medication noncompliance, or electrolyte disturbance. If necessary, magnet application can suspend the tachyarrhythmia therapies to prevent repetitive shocks.
7. Important medical interventions that may affect ICD function in the ICU include surgical electrocautery, magnetic resonance imaging, external cardioversion-defibrillation, cardiopulmonary resuscitation, insertion of pulmonary artery catheters, and use of antiarrhythmic drugs.
8. Disabling ICD functions should be performed only after considering and thoroughly discussing the medical, ethical, and legal implications.

Since its initial development in the 1970s[1] and its introduction to clinical practice in the 1980s,[2] the implantable cardioverter-defibrillator (ICD) has revolutionized the management of patients with life-threatening ventricular arrhythmias. The effectiveness of these devices in preventing death due to ventricular tachycardia (VT) or ventricular fibrillation (VF) has been demonstrated in several large, well-conducted, randomized, controlled trials.[3-8] Far from being a "last resort," as previously conceived, device-based treatment of recurrent VT or VF is the initial treatment of choice for many patients who have experienced or are at high risk for experiencing these rhythm disturbances.[9] Device complexity makes a detailed understanding of ICD technology challenging for practitioners who are not electrophysiologists, but a general understanding of these devices and their associated clinical problems is increasingly important as device-based therapy becomes more widespread.

EPIDEMIOLOGY OF SUDDEN CARDIAC DEATH

Sudden cardiac death, arbitrarily defined as death from a cardiac cause occurring within 1 hour of symptom onset or without preceding symptoms,[10] is a major public health problem accounting for 450,000 deaths annually in the United States.[11] Out-of-hospital cardiac arrest carries a dismal prognosis, with reported rates of survival to hospital admission of 5% to 10% and minimal improvement in survival rates over the past several decades.[12] This poor outcome occurs in spite of public health efforts to improve public recognition of cardiac symptoms and shorten the time to therapy by means of bystander cardiopulmonary resuscitation (CPR) and better access to emergency medical services.[13] Among patients who survive to hospital admission, mortality and morbidity remain exceedingly high,[14,15] highlighting the need for preventive efforts.

A significant proportion of sudden cardiac deaths are due to a treatable arrhythmia such as VT or VF,[13,16] with the remainder being due to pulseless electrical activity or asystole. In autopsy studies, a majority of sudden cardiac death victims have pathologically apparent structural heart disease, particularly coronary atherosclerosis.[17] In many cases, recent unstable coronary disease can be demonstrated by pathologic evidence of recent plaque rupture, with or without thrombosis.[18] In cases in which cardiac monitoring was in place at the time of death, arrhythmia is commonly present.[19]

A significant proportion of sudden cardiac death occurs in patients without previously identified cardiac disease.[15,20] Currently, there is no feasible means of screening the population at large to identify all individuals who are at risk for

this catastrophic event. Prediction and prevention strategies have therefore focused on identifying patients whose other clinical characteristics place them at particularly high risk for sudden cardiac death.[21,22] From the public health perspective, the most important conditions that predispose to a high risk of sudden cardiac death include cardiovascular risk factors, coronary artery disease, and left ventricular (LV) dysfunction of ischemic and nonischemic causes. Other conditions that predispose to sudden cardiac death in which the ICD has a role are listed in Table 98-1.

Sudden death is estimated to represent approximately 50% of all deaths due to chronic heart failure.[21,23] The majority of these are due to ventricular tachyarrhythmias,[19] but a significant proportion appear due to bradycardia.[24] Among the factors that predict sudden cardiac death, severity of LV systolic dysfunction and age are by far the strongest predictors.[25-27] For this reason, large clinical trials of ICD therapy have focused on patients with LV dysfunction, coronary disease, and spontaneous or inducible ventricular arrhythmias.[28]

PREVENTION OF TACHYARRHYTHMIC SUDDEN CARDIAC DEATH: NONDEVICE THERAPY

Before development of the ICD, antiarrhythmic drugs were the cornerstone of treatment and prevention of recurrent VT and VF. However, it is now recognized that these drugs are intrinsically hazardous owing to arrhythmogenicity and other adverse effects.[29-34] Currently, antiarrhythmic drugs retain a primary role in patients with a relatively low risk of sudden cardiac death. Among higher-risk patients, antiarrhythmic drugs are often used as adjuncts to ICD therapy.

An empirical approach to drug therapy has been extensively evaluated but remains controversial. Although class IC antiarrhythmic drugs, including encainide, flecainide, and moricizine, are effective for the suppression of ventricular ectopy, they were shown to significantly increase mortality in the landmark Cardiac Arrhythmia Suppression Trials.[30,31] D-Sotalol, which has class III antiarrhythmic properties, was evaluated in a randomized, controlled trial and, similar to class IC agents, was found to increase mortality.[35] The L-isomer that confers the beta-blocking effect may attenuate this hazard.[36] Another study demonstrated the relative safety of dofetilide, a class III agent, in patients with symptomatic heart failure and LV dysfunction, in that mortality was not increased when therapy was initiated in the hospital.[37]

TABLE 98–1. CAUSES OF VENTRICULAR ARRHYTHMIAS

Structural Disease
Left ventricular dysfunction
Coronary artery disease and acute myocardial infarction
Coronary artery anomalies
Hypertrophic cardiomyopathy
Arrhythmogenic right ventricular dysplasia
Primary Electrophysiologic Defects
Wolff-Parkinson-White syndrome
"Idiopathic" ventricular tachycardia or fibrillation
Catecholamine-sensitive polymorphic ventricular tachycardia
Long QT syndrome (congenital or acquired)
Brugada syndrome

Amiodarone remains the only reasonable empirical choice for arrhythmia prevention in patients with heart failure or LV dysfunction. Several trials have shown decreased risk of death among patients treated with amiodarone after myocardial infarction.[33,38] Among patients at risk for arrhythmic death, a meta-analysis of controlled trials showed a reduction in total, cardiac, and sudden cardiac deaths with amiodarone therapy.[39] In patients with heart failure, empiric amiodarone does not increase the risk of death (in contrast to class IC agents).[29,40]

Guided approaches to antiarrhythmic drug choice have also been evaluated.[41] The noninvasive approach uses serial ambulatory cardiac monitoring and assesses the arrhythmia's response to specific drug choices. An invasive approach is similar but uses serial programmed electrical stimulation to evaluate the effect of selected drugs on the inducibility of VT or VF. Both approaches have been evaluated and can predict response to medical treatment reasonably well.[42-44]

Both empirical and guided therapies are limited by high recurrence rates of VT and VF and medication-related adverse events.[34,45,46] For example, although amiodarone is the most effective antiarrhythmic drug for preventing the recurrence of VT and VF, a substantial proportion of patients (>20%) treated with amiodarone are unable to continue therapy in the long term owing to cumulative side effects, recurrent arrhythmia prompting a change in therapy, or death.[34,47]

Medications other than antiarrhythmic drugs have also been evaluated. Beta blockers clearly reduce the risk of death among patients with recent myocardial infarction[48,49] and LV dysfunction,[50-52] and it appears that approximately 50% of this decreased risk is due to reductions in sudden death.[49] Beta blockers have been shown to suppress ventricular arrhythmias among patients at elevated risk[53,54] and may reduce death when used as primary antiarrhythmic therapy.[55] Use of HMG-CoA reductase inhibitors ("statins") has been associated with a lower risk of sudden death compared with nonuse in several studies.[56,57] However, prospective randomized confirmation of this finding is lacking. Trials of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with heart failure and coronary disease have shown reductions in the risk of sudden cardiac death in these populations.[58] Omega-3 fatty acids ("fish oils") appear to reduce the risk of sudden cardiac death in epidemiologic studies[36,59] and in prospective randomized trials.[60] Mechanisms, magnitude of benefit, and interactions with other potential therapies require further evaluation.

Catheter ablation and surgery are often effective in preventing recurrent VT in patients who are difficult to treat by other means. Both techniques attempt to damage or "ablate" involved myocardial tissue to interrupt reentrant VT circuits, thus preventing the development of sustained arrhythmias. In the past, VT surgery was considered a primary form of therapy in experienced centers, as it could offer a cure to patients with few other therapeutic options.[61-64] Currently, VT surgery has a limited role owing to very high operative morbidity and mortality and improved nonsurgical approaches. Catheter ablation is a developing technique whereby intracardiac catheters are used to induce VT, map the pathologic circuits, and, using radiofrequency energy or direct-current shock, ablate small areas of tissue to interrupt the circuit.[65,66] Although this technique may carry a lower procedural risk than open surgical approaches, a substantial number of patients have recurrent ventricular arrhythmias,[64,67]

and experience in most centers is limited. VT related to ischemic heart disease is especially difficult to manage with catheter ablative procedures,[67,68] owing to multiple pathologic intracardiac circuits.

Revascularization is of primary importance in patients with coronary artery disease and malignant ventricular arrhythmias. One study evaluated the role of ICD in patients undergoing coronary artery bypass grafting and showed no benefit in this population.[69] Until recently this was the only clearly negative trial evaluating the role of ICDs in the primary prevention of death in patients at risk for VT or VF. Other studies have demonstrated an association between coronary artery bypass grafting and decreased risk of sudden death.[70-72] A recent randomized trial of ICD therapy early following myocardial infarction (DINAMIT) also found no difference in mortality with usual medical care versus an ICD (see Table 98-4).

Several lifestyle factors have been associated with lower risks of sudden death. Tobacco avoidance, exercise, moderate alcohol consumption,[73] and a diet rich in fish[59] have all been shown to be protective, and lifestyle modification programs may prevent sudden cardiac death.[74,75]

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

DEVICE BASICS

The ICD is composed of two parts: the pulse generator and the leads. The generator consists of batteries; a capacitor for charging and discharging ("shocking"); electronic circuits that monitor, analyze, and guide treatment of arrhythmias; and information storage capabilities. Additional capabilities are available in current devices.

The pulse generators of early devices were large (approximately 250 cm^3) and required surgical implantation in the abdomen. Leads were large (150 to 180 cm^2) epicardial pads placed via a thoracotomy. Separate epicardial screw-in sensing leads were also required. Implantation was associated with significant perioperative morbidity and mortality. Rhythm analysis was rudimentary and relatively insensitive. Only medium- or high-energy shock therapy was available. Data storage capacity was limited to information regarding the number of shocks. When intracardiac electrogram storage and analysis became available, it was apparent that inappropriate shocks, predominantly for atrial fibrillation, were common.[76,77]

The initial primary purpose of the ICD was to detect VT and VF and terminate these arrhythmias with effective defibrillation. Reports of early experiences suggested a substantially lower annual mortality among ICD recipients versus similar historical comparative groups.[78] More recent refinements in ICD technology have improved the safety and tolerability of the devices substantially, but effective defibrillation remains the crucial, lifesaving feature.

Current devices are much smaller, allowing subpectoral or subcutaneous implantation. Using nonthoracotomy lead systems, implantation methods are identical to permanent pacemaker implantation. Local anesthetic with mild sedation is used for implantation; heavy sedation or a brief general anesthetic is needed to test defibrillation thresholds. Operative mortality for nonthoracotomy systems is less than 0.5%.[79] The greatest intraoperative risk is related to the induction of VF and the resulting hemodynamic compromise. Particularly in patients with severe LV dysfunction, the hemodynamic effects of even brief spells of VF can be persistent and detrimental.[80] Obesity or cachexia, limited vascular access, pulmonary hypertension, anticoagulation or bleeding disorders, and vascular or cardiac anomalies may increase the technical challenge of implantation. Tricuspid valve prosthesis or significant tricuspid valvular disease may preclude use of endocardial lead systems. Features of current devices are listed in Table 98-2. Common procedural risks are listed in Table 98-3.

THERAPEUTIC FUNCTIONS

Bradycardia and Pacing

Patients with significant heart failure commonly have symptomatic bradycardia due to conduction disturbances, inadequate chronotropic responses, and medications that induce bradycardia.[24] Further, postcardioversion and postshock bradycardia is common among ICD patients. To meet these

TABLE 98–2. FEATURES OF CURRENT IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

Size	30-80 cm^3
Weight	70-150 g
Batteries	Low-resistance lithium or silver vanadium for charging defibrillation capacitor; separate battery for pacing functions
Leads	Steroid-eluting, silicone- or polyurethane-coated, 4-9 Fr. (1.3 to 3 mm) caliber, depending on type; ports for ventricular, atrial, left ventricular (coronary sinus), and superior vena cava leads
Output, charge	30-40 J, 750-800 V
Battery life	4-10 yr, depending on manufacturer, device, and use
Arrhythmia detection	Rate-based; enhanced ventricular tachycardia detection features vary by device and manufacturer
Arrhythmia management	Defibrillation with biphasic waveform, low-energy cardioversion, antitachycardia pacing features; atrial therapies, including antitachycardia pacing and cardioversion; bradycardic ventricular and dual chamber pacing; biventricular pacing
Storage capabilities	Device and lead identification, implantation date, physician contact; arrhythmia event data, including date and time, onset, heart rate, therapies delivered, shock counters, rate histograms, electrograms, marker channel; pacemaker functions, including pacing thresholds, lead impedances, R and P wave amplitude, percent pacing, heart failure diagnostic information
Programmable functions	Pacing parameters, tachyarrhythmic therapies, tiered therapy algorithms; many other refined programmed functions vary by manufacturer

TABLE 98–3. RISKS OF CARDIOVERTER-DEFIBRILLATOR IMPLANTATION

Anesthetic risk
Risk of fibrillation or defibrillation
Atrial and ventricular arrhythmias
Bleeding
Embolism (thrombus, air)
Vessel or organ injury
Cardiac injury or pericardial tamponade
Infection

needs, all current ICDs have pacing capabilities. Devices are available with ventricular, dual chamber, or biventricular pacing modalities.

Although ventricular and dual chamber pacemakers are frequently indicated for ICD patients, there are concerns about the potential adverse effects of right ventricular pacing. One major trial showed that atrioventricular sequential pacing at a rate of 70 beats per minute was associated with higher rates of heart failure, hospitalization, or death when compared with backup ventricular pacing at 40 beats per minute.[81] This effect was ascribed to the untoward hemodynamic effects of right ventricular pacing. Other studies have supported this finding.[82] Further, pacing can precipitate ventricular tachyarrhythmias in some patients.[83] Thus, the pacemaker backup rate should be turned down to the lowest acceptable rate in patients with LV dysfunction.

Biventricular pacing, or resynchronization therapy, is a new pacing modality incorporated into some devices. Biventricular pacing is not intended to treat bradycardia per se; instead, it coordinates synchronous left and right ventricular contraction.[84] In the presence of left bundle branch block or right ventricular pacing, the interventricular septum moves rightward during systole. This decreases the contribution of septal contraction to LV output, leading to less efficient LV systolic function. Biventricular pacing coordinates left and right ventricular contraction to minimize this effect. The left ventricle is approached through the venous system (coronary sinus) using specially designed catheters to allow epicardial LV pacing.

Several recent studies evaluated biventricular pacing in patients with advanced symptomatic heart failure and significant intraventricular conduction delay.[85-87] Results suggest improvements in symptoms, exercise tolerance, and quality of life[88] among a significant proportion of these selected patients. A survival benefit has also been recently demonstrated (see Table 98-4).[89]

Tachyarrhythmia Detection

The primary methods of detecting sustained VT are assessment of ventricular rate and duration of the tachycardia. Therapy is delivered for persistent heart rates exceeding a cutoff that is manually programmed. Different algorithms can be programmed for different rates (discussed later). The major limitation of an exclusively rate-based rhythm analysis is that tachycardias other than VT (e.g., supraventricular tachycardia) cannot be distinguished by rate alone.

Enhanced arrhythmia detection features in current dual chamber systems enable highly sensitive and specific detection of VT and VF, decreasing the occurrence of inappropriate therapies.[90-95] Onset criteria allow the distinction between sinus tachycardia, which generally has a gradual onset, and VT, which is abrupt. Rate stability criteria distinguish irregular atrial fibrillation from VT. Devices also use the intracardiac electrogram to identify VT. Analysis of QRS width and slew rate (steepness of up- or downstroke of QRS) and comparison of QRS morphology during tachycardia with that during sinus rhythm aid further. Dual chamber devices use atrial lead sensing to evaluate the relationship between ventricular and atrial activity to distinguish supraventricular tachycardia from VT.[94]

Tachyarrhythmic Therapies: Tiered Therapy Algorithms

Using the methods outlined previously, the ICD detects arrhythmias and administers therapies as programmed. In contrast to early devices, current ICDs can deliver therapies other than defibrillation, including lower-energy cardioversion and antitachycardia pacing. Several devices also have atrial antitachycardia and cardioversion features, whose clinical benefit remains to be proved.[96,97] In a tiered therapy algorithm (Fig. 98-1), different "zones" of detection are programmed.

High-energy defibrillation is the primary and most important function of the ICD. It is the only effective therapy for VF or very rapid VT. The other available therapies are intended to abort hemodynamically tolerated VT to obviate a painful, high-energy shock.

If the ICD detects a ventricular rhythm in the VF zone, the battery charges the capacitor, which then discharges, or "shocks," if a second rhythm analysis confirms ongoing VF. Current is transmitted between the right ventricular lead and either the device itself ("active" or "hot" can) or other electrodes or coils.[98] The current passes through ventricular myocardium and depolarizes a proportion of myocytes with an energy of 27 to 35 J, depending on the manufacturer and configuration. This depolarized mass of myocardium interrupts the fibrillating electrical wave fronts and terminates VF. If defibrillation is ineffective, the device reinstates a diagnostic algorithm to detect ongoing VF. If VF is detected, the capacitor recharges, discharges, and continues this cycle of behavior until another rhythm is detected or the therapies are exhausted (4 to 6 consecutive high-energy shocks).

The major limitation of high-energy shocks is the associated discomfort experienced if the patient remains conscious during the arrhythmia. Most patients report that shocks are very painful, and fear, embarrassment, or other unpleasant emotions may be associated with the shock.[99] Quality of life is significantly impaired in patients who receive ICD shocks, although it is not known whether this impairment is due to the shock itself or the health condition necessitating the shock.[100,101]

Low-energy cardioversion is an established method of terminating hemodynamically tolerated VT, with a success rate greater than 80%.[102,103] When the device detects a rhythm in the slow VT zone, the capacitor is charged and a lower-energy shock is delivered, synchronized to the R wave. Energy outputs of 0.1 to 5 J can terminate some VTs. Patient discomfort increases substantially with increased output, particularly above 0.5 to 1 J. Above 5 to 10 J, no benefit is gained with low-energy cardioversion versus defibrillation in terms of patient comfort, although avoidance of high-energy output may prevent long-term device dysfunction[104,105] and prolong battery life. The other major risks of low-energy cardioversion are acceleration of the tachycardia rate, which occurs in up to 10% of cases, and delay of definitive therapy.[103] Less commonly, cardioversion can cause the rhythm to degenerate to polymorphic VT or VF, necessitating defibrillation.

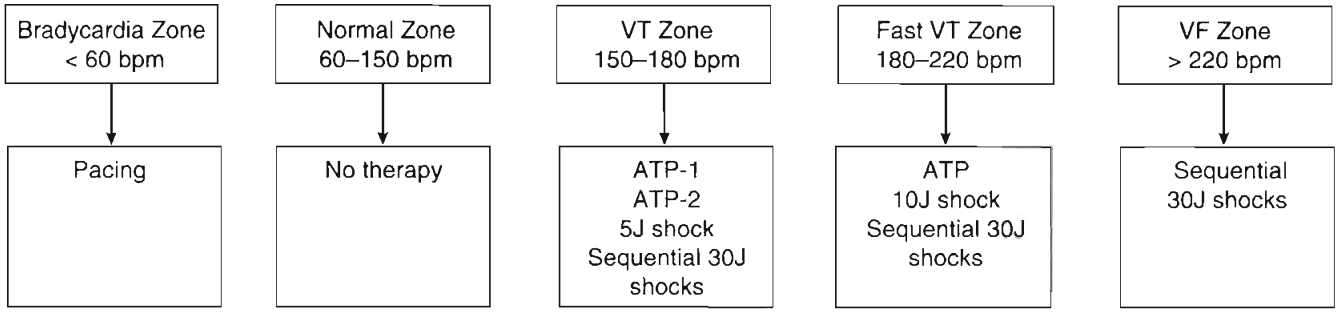

FIGURE 98-1. Example of a tiered therapy algorithm. ATP, antitachycardia pacing; bpm, beats per minute; VF, ventricular fibrillation; VT, ventricular tachycardia.

Antitachycardia pacing, when effective, is ideal therapy for terminating hemodynamically tolerated VT. Antitachycardia pacing is painless, although awareness of palpitations can occur. Antitachycardia pacing is usually the initial therapy attempted for episodes of VT, because success rates are similar to those obtained with low-energy cardioversion; up to 90% of VTs can be terminated with pacing.[106-108]

Antitachycardia pacing is more complex than defibrillation or cardioversion. The principle is to deliver pacing stimulation to the ventricle to gain control over the reentrant circuit that is perpetuating the tachycardia (overdrive suppression). If pacing is effective in entering the VT circuit, when pacing is terminated, the patient's native or paced control over ventricular depolarization is restored. In order to enter the circuit, pacing must occur in the excitatory gap when the ventricle is not refractory to stimulation, and the device must pace at a rate faster than the VT rate. Rates with a cycle length between 70% and 90% of the VT cycle length (i.e., approximately 10% to 40% faster) are most effective in terminating the tachycardia.[106,109] There are numerous pacing techniques intended to improve entry into the circuit and termination of the tachycardia. No standard nomenclature is shared by manufacturers to describe antitachycardia pacing algorithms, but each method employs several comparatively simple principles. Burst pacing delivers a series of several beats at a fixed cycle length. Ramp pacing progressively shortens cycle length (i.e., accelerates). Adaptive therapy modes allow pacing at differing rates, depending on the VT rate. Scanning allows the device to introduce pacing at varying points in the VT cycle. In the setting of slow VT, the device delivers several different antitachycardia pacing protocols in an attempt to terminate the tachycardia.

Atrial therapies incorporated in many newer devices include antitachycardia pacing and cardioversion. Their effectiveness in preventing and terminating atrial arrhythmias has been demonstrated,[97,110,111] but the clinical value of this approach remains controversial, except in selected patients in whom such therapies have proved individually beneficial and tolerable. Currently, it is rare to implant a device to treat atrial arrhythmias solely, but this is occasionally done in highly symptomatic patients who are intolerant of medical therapy.

CLINICAL TRIALS

As discussed earlier, prevention of sudden cardiac death has focused on a population of patients with LV dysfunction and heart failure, a large group that has been shown to be at high risk for arrhythmic death. In North America and western Europe, the majority of these patients have ischemic heart disease, although a substantial minority have nonischemic cardiomyopathy. Until recently, trials that enrolled only patients with nonischemic causes have shown neutral results related to mortality.[40,112,113] Three large recent trials indicate that ICD therapy reduces the risk of death versus amiodarone or best medical therapy (SCID-HEFT DEFINITE) (see Table 98-4).

Thirteen (n>100) randomized, controlled trials assessing the efficacy of ICD therapy have been completed (Table 98-4).[3,4,6,7,69,112-115] Three large trials assessed the role of ICD therapy as secondary prevention of sudden cardiac death among patients with ischemic LV dysfunction and sustained, hemodynamically significant ventricular arrhythmias.[3,4,114] The largest of these trials (Antiarrhythmics versus Implantable Defibrillators, or AVID) randomized 1016 patients with symptomatic VT or VF and LV dysfunction (LV ejection fraction < 0.40) to therapy with ICD versus antiarrhythmic drugs (82.4% amiodarone).[4] This study was stopped before completion of enrollment because of a statistically significant survival benefit (11.3% absolute risk reduction at 3 years) of the ICD. The Canadian Implantable Defibrillator Study (CIDS)[114] and the Cardiac Arrest Study Hamburg (CASH)[3] demonstrated trends toward decreased mortality, but these findings were not statistically significant. Meta-analysis of these three randomized trials supported data consistency, with a significant relative reduction in mortality risk of 28% (95% confidence interval 13% to 40%).[116]

The ten major primary prevention trials assessed the role of ICD therapy among patients at risk for but without clinically sustained VT or VF.[6-8,69] Although inclusion criteria varied somewhat, enrollment in these trials focused on patients with LV dysfunction. Similar to the secondary prevention trials, results of the primary prevention trials were consistent. Mortality reductions in the primary and secondary prevention trials have demonstrated similar results (Table 98-4). From these studies it is clear ICD therapy reduces annual mortality by 2% to 7% in most patient groups. These studies also indicate that patients with both ischemic and nonischemic etiologies of LV dysfunction benefit from ICD therapy and that amiodarone has a limited role in the prevention of sudden death in patients with heart failure.

All but two of the primary prevention trials demonstrated a mortality benefit from ICD therapy (Table 98-4). As previously discussed, routine aggressive coronary artery revascularization was likely responsible for the lack of benefit from routine ICD therapy in the CABG-Patch Trial.[69] This inference is supported by a lower than anticipated mortality rate in that trial and the fact that the ICD resulted in a significantly lower rate of arrhythmic death.[71] ICD therapy also did not

reduce the risk of death in DINAMIT (see Table 98-4). Similar to CABG-Patch, the proportion of arrhythmic deaths to the total deaths in DINAMIT was also lower than anticipated.[72] It is not clear whether the lack of benefit from the ICD in DINAMIT reflects the influence of altered cardiac anatomic and electrical structure (remodeling) that occur in the initial three months following myocardial infarction or other factors. The lack of benefit from ICD therapy in these two trials illustrates that when considering a patient for an ICD, careful thought must be given to the long-term risk of arrhythmic death and the competing modes of death. As the rate of arrhythmic death is reduced, the impact of the ICD is significantly lessened.

A marked increase in the number of ICDs is anticipated to occur based on the results of recent trials (see Table 98-4). Issues of cost and identifying those patients most likely and least likely to benefit (risk stratification) from ICD therapy await the results on ongoing studies. It is worth emphasizing that ICD therapy is costly,[117,118] and the magnitude of benefit is sensitive to baseline risk.[119] Studies to date have assessed ICD therapy in relatively high-risk populations, but even within these populations, risk appears to vary substantially. For example, in AVID, no benefit was observed among the subgroup of patients with an LV ejection fraction greater than 0.35.[26] Whether ICD therapy is appropriate in lower-risk high-risk patients, particularly those with relatively preserved LV ejection fraction, remains to be determined. Further studies will aid in determining whether ICD therapy in such patients provides (1) no benefit, (2) a small but excessively costly benefit, (3) a small but clinically important benefit, or (4) excessive hazard.

DEVICE-RELATED ISSUES AMONG PATIENTS IN INTENSIVE CARE

DEVICE INTERROGATION

Device interrogation is performed by placing an analyzing header directly over the generator. Devices from different manufacturers require brand-specific programmers. ICD patients are provided with device information and contact telephone numbers so that device type can be determined in the event of an emergency. If this information is unavailable, an overpenetrated chest x-ray will reveal identifying markers on the pulse generator. Interrogation of the device determines the manufacturer, model, settings, recorded events, and battery and lead parameters. Implanting centers generally provide around-the-clock interrogation and reprogramming. In smaller facilities, if emergent device interrogation or reprogramming is required and a programming computer is available, the device manufacturer can provide guidance remotely and advise about the use of magnets for suspending therapies. It is worth reemphasizing that the application of a magnet will suspend detection of VT and VF by ICD. In contrast, a magnet results in reversion to a "safe pacing mode" when applied to a pacemaker.

LEAD FAILURE

Lead failure due to dislodgment, fracture, or insulation breach occurs in 5% to 10% of patients, and lead replacement is usually required.[120-122] Risk of lead failure is higher with a subclavian route compared with a cephalic vein approach, owing to the compressive effects of the clavicle and first rib on the subclavian vein.[121] The majority of lead-related complications are asymptomatic, but symptomatic device malfunctions, including inappropriate shocks and failure to deliver therapy, have been reported. Increased defibrillation thresholds can occur in the absence of lead defects or dislodgment and are thought to be due to myocardial fibrosis at the point of contact of the defibrillation lead. Frequent shocks appear to exacerbate this response. Steroid-eluting leads attenuate the inflammatory-fibrotic myocardial response and the associated increase in thresholds.

PACING FUNCTION PROBLEMS

Oversensing occurs when the pacemaker detects electrical activity that is not due to chamber depolarization. It is suspected when the heart rate falls below the programmed lower pacing rate limit or when surface lead channels or intracardiac electrograms appear "noisy." This activity may be due to electrical activity in another cardiac chamber (far-field sensing), T-wave sensing, myopotentials from pectoral muscles, or electromagnetic interference. In this situation, the device fails to pace appropriately. Oversensing can be corrected by increasing sensing thresholds, switching from a unipolar to a bipolar pacing mode, avoiding electromagnetic interference, or either repositioning or replacing the lead.

Undersensing occurs when the device fails to detect chamber depolarizations. This is usually detected as extra pacing spikes, with or without associated capture. Undersensing may be due to poor lead contact with the myocardium, defects of the lead insulation or coil, myocardial infarction, or device malfunction. Chest x-ray to assess lead position and integrity as well as device interrogation to assess lead impedance are required.

Failure to capture occurs when pacemaker spikes do not effect ventricular depolarization. This may occur because the ventricle is refractory, insufficient energy is delivered, or the lead contact is inadequate. Chest x-ray and pacemaker interrogation are required to assess lead position and pacing thresholds.

Paced tachycardias can occur. This is due to either inappropriate tracking of atrial tachyarrhythmias or pacemaker-mediated (endless loop) tachycardia by a dual chamber device. Atrial tachycardias such as atrial fibrillation or atrial flutter may be sensed by a dual chamber pacemaker, and the ventricle may be paced at inappropriately rapid rates. This is treated by pharmacologic management of the atrial arrhythmia, decreasing the upper pacing rate of the ventricle, or turning on the mode-switching function, if available. Pacemaker-mediated tachycardia occurs with dual chamber devices but is less common than in the past because of automatic recognition and prevention algorithms. When ventricular pacing is associated with ventricle-to-atrium conduction, an endless loop of ventricular pacing, ventricle-to-atrium conduction, atrial sensing, and ventricular pacing can develop. Reprogramming to prevent immediate postventricular event detection of atrial events or prolonging the postventricular atrial refractory period ameliorates pacemaker-mediated tachycardia.

INFECTION

Infections involving ICDs have been reported to occur in up to 1% to 16% of patients.[123-125] This is a devastating complication carrying substantial morbidity; early mortality has been reported to be as high as 10%.[126,127] *Staphylococcus epidermidis*

TABLE 98–4. RANDOMIZED STUDIES OF IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS (ICDs)

Trial and Year of Publication	Sample Size (*n*)	Treatment Arms	Patient Characteristics	Mortality Benefit (Annualized Absolute Risk Reduction)	Comments
Cardiac Arrest Survivors (Secondary Prevention)					
AVID[4] 1997	1016	ICD vs amiodarone	Mixed etiologies (81% CAD) LVEF ≤ 0.40	4%	Largest secondary prevention trial Quality-of-life assessment showed neutral effects of ICD
CIDS[114] 2000	659	ICD vs amiodarone	Mixed causes (80%-90% CAD)	2%	Result trends similar to AVID Quality-of-life assessment showed possible benefit of ICD
CASH[3] 2000	288	ICD vs amiodarone vs metoprolol	Mixed etiologies (75% CAD)	2%	Propafenone arm discontinued due to increased mortality Metoprolol and amiodarone performed similarly
Patients at High Risk of Sudden Death (Primary Prevention)					
MADIT[115] 1996	196	ICD vs no ICD	100% CAD LVEF ≤ 0.35 Inducible, nonsuppressible VT	5%	First study to demonstrate benefit of strategy of primary prevention
MADIT II[6] 2002	1232	ICD vs no ICD	100% CAD LVEF ≤ 0.30	3%	Largest primary prevention trial in patients wth CAD
CABG-Patch[69] 1997	900	ICD vs no ICD	100% CAD undergoing CABG LVEF ≤ 0.35 Abnormal signal-averaged ECG	None	Revascularization in both groups may have attenuated the benefits of ICD therapy
COMPANION[113] (2004)	1520	ICD + CRT vs Pacemaker + CRT vs no device	Mixed etiologies (54% to 59% CAD) LVEF ≤ 0.35 Highly symptomatic heart failure	7% ICD + CRT 4% Pacemaker + CRT	CRT lowers the risk of death The combination of an ICD + CRT resulted in the lowest risk of death CRT also improved quality of life
DEFINITE[112] (2004)	458	ICD vs no ICD	Heart failure not related to CAD LVEF ≤ 0.35 Symptomatic heart failure	3%	Largest primary prevention trial in non-CAD Extends the results of previous trials in patients with CAD
SCD-HeFT[40] (2004)	2521	ICD vs amiodarone vs placebo	Mixed etiologies (52% CAD) LVEF ≤ 0.35 Symptomatic heart failure	2%	Largest primary prevention trial ICD significantly reduced the risk of death Amiodarone had no impact on mortality
DINAMIT[72] (2004)	674	ICD vs no ICD	Early following myocardial infarction LVEF ≤ 0.35 Abnormal heart rate variability	None	A reduction in arrhythmic death (2%) but an unexplained increase in non-sudden death (2.5%) was observed with ICD therapy ICD therapy is not efficacious early after myocardial infarction, possibly due to changes in underlying substrate and risk of non-sudden death

AVID, Antiarrhythmics Versus Implantable Defibrillators; CABG-Patch, Coronary Artery Bypass Graft—Patch Trial; CAD, coronary artery disease; CASH, Cardiac Arrest Study Hamburg; CIDS, Canadian Implantable Defibrillator Study; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CRT, cardiac resynchronization therapy; DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT, Defibrillator in Acute Myocardial Infarction; LVEF, left ventricular ejection fraction; MADIT, Multicenter Automatic Defibrillator Trial; SCD-HeFT, Sudden Cardiac Death Heart Failure Trial.

and *Staphylococcus aureus* cause the majority of infections, although any pathogenic bacteria or fungus can theoretically seed the device. Infection in the first several months following implantation usually results from bacterial contamination with skin colonizers introduced during or immediately after the implantation procedure.[128] Late device infections (>1 year after implantation) are equally common,[129] and primary sources of bacteremia other than the ICD are usually implicated.[130-132]

Diagnosis of device infection is often challenging. Clinical suspicion must be high in patients with an implanted device who present with fever, weight loss, fatigue, systemic inflammation, or pulmonary embolism.[127,133] All ICD or pacemaker patients with fever of uncertain cause should undergo careful examination of the generator pocket site for signs of inflammation, and blood cultures should be performed. In all patients with proven bacteremia or fungemia, transthoracic and transesophageal echocardiography may be helpful.[134]

Treatment of confirmed ICD system infection requires extraction of all device components, a prolonged (e.g., 2 to 6 weeks) intensive antibiotic course, and reimplantation.[129] The optimal duration of antibiotic therapy is uncertain, and timing of reimplantation in patients at high risk for life-threatening arrhythmias or those who are pacemaker dependent must be individualized. When infection is suspected but unconfirmed, a trial of prolonged antibiotic therapy and close clinical vigilance for relapse may obviate system extraction. The risk of occult lead infection among patients with staphylococcal bacteremia is high,[134,135] and consideration should be given to extraction,[135] especially if relapse of infection occurs.

Current guidelines do not mandate antibiotic prophylaxis for pacemaker or ICD insertion,[136] but current evidence supports peri-implantation antistaphylococcal antibiotic prophylaxis.[137] Endocarditis prophylaxis for subsequent invasive procedures in patients with ICDs and pacemakers who have no other indications remains controversial and is not universally recommended.[136]

ARRHYTHMIAS AND ANTIARRHYTHMIC DRUGS

Patients with ICDs are at high risk for atrial and ventricular tachyarrhythmias. Management of these arrhythmias generally does not differ from the usual therapy for patients without ICDs. Indeed, more liberal use of rate-slowing and proarrhythmic medications is often permissible, owing to the protective effect of backup pacemaking and defibrillation. Observing device behavior during arrhythmias is important, because it may influence management decisions. For example, if rapid ventricular pacing is observed in a patient with rapidly conducted atrial fibrillation, it is likely that the device is undertaking an antitachycardia pacing algorithm for termination of VT. Urgent slowing of the ventricular rate may prevent escalation of therapy and inappropriate shocks. In patients with atrial or ventricular tachyarrhythmias, device-based termination with overdrive suppressive pacing should not be overlooked as a therapeutic option. Failure of the device to detect and treat ventricular and regular atrial arrhythmias may be solved by simply reprogramming the device by a practitioner familiar with its features.

ICD patients often receive additional antiarrhythmic therapy to prevent device-provided therapies[138] and to improve patient tolerance of these arrhythmias. Amiodarone[138] and sotalol[139,140] may decrease the frequency of VT and VF and thus decrease the need for defibrillation therapies, avoiding patient discomfort. Dofetilide does not appear to decrease the frequency of ventricular arrhythmias and may cause torsades de pointes.[141] Class I antiarrhythmic drugs, though avoided in general, are occasionally used in ICD patients to decrease occurrences of VT. Amiodarone often decreases the VT rate, which may limit the hemodynamic effects of the rhythm and facilitate pace termination. However, decreasing the VT rate can have several deleterious effects. The device may fail to detect the slower ventricular arrhythmia and may require reprogramming. Negative chronotropic and atrioventricular node blocking effects may lead to increased pacing, which can contribute to battery depletion and untoward hemodynamic effects in some patients.

Antiarrhythmic drug therapy has the potential to increase defibrillation thresholds. Class I drugs, except propafenone,[142] and chronic amiodarone use[143] have this effect, which may be clinically important in patients whose defibrillation threshold is close to the maximum output of the device. Acutely, in a monitored hospital setting, raising the defibrillation threshold may not be clinically important. However, if amiodarone therapy is initiated, consideration should be given to follow-up testing of device function.[47]

CARDIAC ARREST AND DIRECT-CURRENT CARDIOVERSION

Cardiopulmonary resuscitation and transthoracic direct-current cardioversion involve particular issues for patients with ICDs.[144,145] In principle, given the dire circumstances surrounding cardiac arrest, the presence of an ICD should not be a distraction; resuscitation should proceed as usual, but the potential for device-related problems should be recognized. Cardiac compressions theoretically increase the risk of lead dislodgment leading to asystole in pacemaker-dependent patients. Elective transthoracic cardioversion or emergent defibrillation exposes the device to potentially damaging high voltage.[146] Contemporary devices have incorporated elements that shunt energy away from the pulse generator. As a result, a circuit can develop, causing thermal damage at the lead-tissue interface and raise pacing and defibrillation thresholds.[147] Inadvertent reprogramming has been reported as well. Transient elevations in thresholds are common; however, failure to capture following cardiac arrest or cardioversion should prompt immediate assessment for lead dislodgment or potentially permanent lead failure. Direct-current cardioversion-defibrillation paddles should be placed as far from the pulse generator as possible in an anteroposterior position, and the lowest effective energy should be used.[144,145] The potential for electromagnetic interference due to transthoracic defibrillation should be recognized, and the device should be defunctioned by applying a magnet if inappropriate device defibrillations occur.

For elective cardioversion, there are several special considerations.[144] Thought should be given to attempting programmed cardioversion through the device rather than externally. If external cardioversion is necessary, a device programmer should be available in the room for immediate assessment of abnormal device function. Given the potential for a transient increase in capture threshold, the practitioner should be prepared to externally pace if necessary. Pacing and sensing thresholds should be checked immediately after a successful cardioversion and then again in 24 hours if feasible. The local device clinic should be contacted before attempting elective cardioversion, if possible, to ensure that immediate assistance is available and to identify any device peculiarities in advance.

EVALUATION AFTER A SHOCK

Most ICD patients experience a shock within 2 years of implantation,[148] and most isolated appropriate device

therapies do not require a change in treatment, although addition or increase of a beta blocker, amiodarone, or sotalol may be considered. Symptoms and patient-perceived device behavior before the shock should be assessed. The presence of presyncope, syncope, or palpitations suggests that the shock was due to arrhythmia and was not spurious. It is important to identify precipitants of arrhythmia, such as exercise, angina, noncompliance with medications, or symptoms of worsening heart failure. Unstable myocardial ischemia and electrolyte disturbances should be excluded and treated. Diagnosis of ischemic events after a shock is challenging, because pacing, antitachycardia pacing, and shocks can cause nonspecific abnormalities of the ST segments,[149] and cardiac markers are often transiently elevated.[150]

In addition to baseline clinical parameters, the initial assessment of a patient after a shock includes device interrogation. Patients' memory of the sequence of events can be inaccurate, and interrogation provides information about the heart rate and rhythm before therapy initiation, therapy attempts, rhythm response to therapy, and definitive therapy, including number of shocks. Such information is crucial for evaluating the appropriateness of the shock and possible precipitating events, and it allows tailored programming of the device.

MULTIPLE SHOCKS AND ELECTRICAL STORM

Multiple, repetitive shocks can occur in 10% to 20% of ICD patients.[148,151,152] When these occur, it is crucial to rapidly determine whether such therapies are appropriate. Frequent shocks are often highly psychologically distressing[153] and can result in a syndrome similar to post-traumatic stress disorder.[154] Sedation with benzodiazepines improves patient comfort and may ameliorate catecholamine-dependent arrhythmias.[155] If the shocks are inappropriate, tachyarrhythmia detection should be disabled by magnet application. Urgent device reprogramming and therapy directed at the underlying condition (e.g., atrial tachyarrhythmias) are required. Frequent, repetitive appropriate therapies (electrical storm) are ominous and have been shown to predict an increased risk of nonsudden death in the next several months.[151] Recurrent VT or VF is most appropriately treated with beta blockade alone[156] or in combination with intravenous amiodarone,[148] and sedation with benzodiazepines may be beneficial. Additionally, deterioration in underlying conditions, including heart failure and myocardial ischemia, may precipitate electrical storm[148] and may require intensification of directed therapy.

ELECTROMAGNETIC INTERFERENCE

Several environmental and medical sources of electromagnetic interference can affect device functioning (Table 98-5).[144,157] Noise (electromagnetic interference) can be interpreted as rapid cardiac activity resulting in inhibition of pacing functions or spurious antitachycardia therapies. Noise reversion algorithms prevent prolonged inhibition of pacing by activating an asynchronous pacing mode when prolonged noise is detected; however, asynchronous pacing can have adverse hemodynamic effects and can initiate ventricular arrhythmias.

MAGNETIC RESONANCE IMAGING

The functioning of ICDs can be adversely affected by magnetic resonance imaging (MRI) techniques and can create artifacts that limit image quality. There are several major potential risks of exposure to clinically relevant magnetic field strengths (0.2 to 3 T).[144,158] Magnetic force induces significant device torque, which can cause motion of the pulse generator, resulting in local pain, tissue damage, or device dislodgment.[159,160] Electromagnetic interference can precipitate rapid pacing or inadvertent therapies or interfere with sensing functions, leading to therapy inhibition. ICDs are more sensitive to inhibition of pacing than pacemakers are. Lead heating is well described, but its clinical significance is not known. Theoretically, heating of the lead tip can cause local tissue damage, myocardial perforation, or scar and increase sensing and pacing thresholds.[158] In addition to the risk to the patient, the presence of any foreign body with ferromagnetic properties can create imaging artifacts, limiting the diagnostic value of MRI scanning in the area of the pulse generator or leads.

The absolute risk of adverse events in routine clinical situations is unknown, because there are no large-scale studies. With current technology, the presence of an ICD or implanted pacemaker is considered a contraindication to MRI. In the rare case in which a patient is foreseen to require an implantable device but also requires an MRI, implantation may be deferred if the potential diagnostic benefit of MRI in the near future outweighs the risk of delaying device implantation. In situations in which the diagnostic value of MRI is considered essential to the care of an ICD patient, scanning should be considered only after appropriately planning for the risks; a team prepared to address potentially life-threatening traumatic complications must be present to immediately attend to the patient.

SURGERY

With careful planning, most, if not all, surgical procedures can be safely performed in ICD patients. ICD patients have a high burden of cardiovascular morbidity, and perioperative cardiac events (ischemia, heart failure, arrhythmias) are relatively common. Adherence to established guidelines for perioperative assessment,[145] appropriate consultation, and anticipation of potential complications may reduce complications. The greatest risks related to the device itself are malfunction due to electromagnetic interference, arrhythmia precipitation due to catecholaminergic surge, and increased defibrillation thresholds due to anesthetic agents.[145] Strategies to prevent complications from electromagnetic interference are listed in Table 98-5.

DISEASE PROGRESSION AND END-OF-LIFE ISSUES

Many ICD patients inevitably develop end-stage heart failure due to underlying disease progression, possibly exacerbated by the presence of the ICD.[6] Upgrading of an existing ICD system to include resynchronization should be considered. When standard therapies are exhausted, heart transplantation may be an option. In patients who are not transplant candidates, a symptom-directed palliative approach is undertaken. When patients indicate a desire for permanent defunctioning of the ICD, possible reversible transient precipitants, such as depression or other mood disturbances, should be sensitively explored. In many cases, deterioration in health, such as an exacerbation of heart failure, causes frustration, and patients may feel that treatments are futile.

TABLE 98–5. SOURCES OF ELECTROMAGNETIC INTERFERENCE

Source	Potential Problems	Preventive Measures
Imaging techniques (MRI)[144]	Device motion Lead heating Oversensing Reprogramming	MRI contraindicated If unavoidable, program to asynchronous pacing mode and defunction ATP therapies; resuscitation team must be available during imaging
Surgical procedures involving electrosurgical (electrocautery) techniques[144,145,161]	Oversensing Spurious antitachyarrhythmia therapies	Use alternative cutting and hemostatic techniques Use bipolar electrocautery if working within 10 cm of the device and/or leads. Preoperative reprogramming (decrease sensitivity, asynchronous pacing, or noise reversion mode) Provide internal or external alternative pacing system for pacemaker-dependent patients Peripheral monitoring (e.g., pulse oximeter) Place ground pad on leg to direct current away from pulse generator Use brief bursts with pauses of at least 10 sec; use lowest power output possible and do not use near pulse generator Assess and reprogram device immediately after procedure
Muscle and nerve stimulators (including spinal, peripheral, and transcutaneous)	Oversensing	Test stimulator functioning and interrogate device's sensed activity and response before use
Radiotherapy	Cumulative dose-dependent pulse generator damage Prolonged charge time Battery depletion	Minimize dose Shield device Check device functioning after sessions
Temporary intracardiac foreign bodies (including pulmonary artery catheters, temporary pacemakers, and instruments used in percutaneous coronary interventions)	Lead dislodgment	Avoid these manipulations with recently implanted devices Use fluoroscopy or echocardiographic guidance if necessary
Environmental (including cellular telephones, security systems [retail and airport], electrical equipment [including household appliances])[162]	Usually not problematic in an inpatient setting Possible interference with device sensing functions	Proscribe cell phone use in monitored areas Observe for unusual device behavior (rapid pacing, pacing inhibition, shocks) during use of electrical equipment near patient Awareness of potential for interaction
Other medical procedures (e.g., radiofrequency ablation, percutaneous coronary interventions, extracorporeal shock wave lithotripsy)[144]	Several case reports of interaction with devices	Device interrogation following exposure

ATP, antitachycardia pacing; MRI, magnetic resonance imaging.

Psychosocial support and discussion of the goals of therapy often clarify patients' motivations and desires. In truly terminal patients or in those who are clear and firm about their desire to discontinue ICD therapy, device defunctioning (which remains reversible) should be undertaken after full discussion of the medical, ethical, and legal ramifications. Disabling pacing functions is more challenging, particularly in those who are pacemaker dependent. This should be undertaken only after extensive discussion with the patient and family and should be performed in accordance with local policies.

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Chapter 99
SEVERE HEART FAILURE

Michael D. Sosin • Gregory Y.H. Lip

KEY POINTS

1. Severe heart failure is a common emergency presentation associated with a high rate of mortality and a high rate of morbidity among survivors.
2. Ischemic heart disease is the most common underlying cause in the Western world, although the cause may differ between ethnic groups. Severe heart failure may be the first presentation of ischemic heart disease. Other common causes are hypertensive heart disease and dilated cardiomyopathy.
3. The diagnosis of heart failure is not always straightforward—it may be confused with asthma or chronic airway disease. Classic examination findings of heart failure are not sensitive or specific and require confirmation by the early use of investigations such as echocardiography.
4. Assessment for B type natriuretic peptide may be a useful method of ruling out heart failure in the acutely breathless patient but is not sufficiently sensitive to diagnose heart failure without additional investigations.
5. Initial therapy for an episode of severe heart failure should involve diuretic therapy, and a single dose of intravenous diamorphine can be considered. In patients with preserved systolic blood pressure, an infusion of vasodilator or recombinant brain natriuretic protein (nesiritide) may be considered. In patients with hypotension, inotropic agents can be considered, although studies suggest increased risk of mortality with such agents.
6. Patients who do not show evidence of improvement, or whose condition deteriorates, should be considered for additional support such as intra-aortic balloon counterpulsation or assisted ventilation early. Patients with cardiogenic shock due to ischemic heart disease should be considered for revascularization.
7. Once stabilized, patients must be established on appropriate secondary preventative therapy, including angiotensin-converting enzyme inhibitors and beta-blockers. Long-term follow-up is best provided by a specialist heart failure clinic.

Heart failure is a very common condition,[1] with high mortality and morbidity rates. Data from the Framingham heart study suggest that at 40 years of age, the lifetime risk for congestive heart failure is 21.0% (95% CI, 18.7-23.2%) for men and 20.3% (95% CI, 18.2-22.5%) for women.[2] Heart failure is increasing in prevalence,[3] partly due to improvements in treatment, so it is likely that severe heart failure will be seen more and more frequently in emergency departments throughout the world. Patients with severe heart failure often present in extremis, and their condition may deteriorate rapidly, so a sound knowledge of immediate treatment is vital for critical care and emergency physicians. Such patients often respond rapidly to appropriate treatment, making this a very satisfying condition to treat. However, it is important to note that outlook remains poor despite initial clinical improvement.

In this chapter, we will discuss causes, presentation, investigation, treatment, and prognosis of severe heart failure, including new developments in the investigation and management of this common, serious condition.

ETIOLOGY

Ischemic heart disease is the most common cause of heart failure, commonly related to previous myocardial infarction.[4] Although epidemiologic surveys such as the Framingham study suggest a high prevalence of hypertension as the "cause" of heart failure, it is likely that associated ischemic heart disease or arrhythmias also contribute. Other studies have demonstrated similar findings (Table 99-1).

It should be pointed out that epidemiologic studies such as the Framingham study have been carried out in almost exclusively white populations—etiologic factors may have different relative importance in other ethnic groups. For example, in Afro-Caribbeans, hypertension is the predominant etiologic factor, whereas in Indo-Asians, coronary artery disease and diabetes are common. It is important to note that different causes may coexist in the same patient.

ISCHEMIC HEART DISEASE

Ischemic heart disease is the most common cause of heart failure in the Western world. Many patients presenting with severe heart failure will give a history of previous myocardial infarction. However, an episode of severe heart failure may also be the first manifestation of ischemic heart disease, either due to massive myocardial infarction causing cardiogenic shock[5] or as a result of previous silent (or unreported) episodes of ischemia/infarction. It is therefore important to exclude myocardial infarction in all patients presenting with severe heart failure. Additionally, once the patient is stabilized, adequate secondary preventative strategies are vital to prevent

TABLE 99–1. EPIDEMIOLOGIC STUDIES OF ETIOLOGY OF HEART FAILURE

Etiology	Teerlink et al (31 Studies 1989-90) (%)	Framingham Heart Study* (%)		Hillingdon Study(%)
		Men	Women	
Ischemic	50	59	48	36
Nonischemic:	50	41	52	64
Hypertension	4	70	78	14
Idiopathic	18	0	0	0
Valvar	4	22	31	7
Other	10	7	7	10
Unknown	13	0	0	34

Because of rounding, totals may not equal 100%.
*Total exceeds 100% as coronary artery disease and hypertension were not considered as mutually exclusive causes.
Data from Lip GYH, Beevers DG: ABC of heart failure: Aetiology. BMJ 2000; 320:104-107.

TABLE 99–2. FINAL DIAGNOSES IN 1230 PATIENTS WITH INITIALLY UNEXPLAINED CARDIOMYOPATHY

Diagnosis	Number	Percentage
Idiopathic dilated cardiomyopathy	616	50
Myocarditis	111	9
Ischemic heart disease	91	7
Infiltrative cardiomyopathy	59	5
Peripartum cardiomyopathy	51	4
Hypertension	49	4
Human immunodeficiency virus infection	45	4
Connective tissue disease	39	3
Substance abuse	37	3
Familial	25	2
Valvular disease	19	1.5
Doxorubicin therapy	15	1
Endocrine disorder	11	1
Others	62	5.5

Data from Felker GM, et al: Underlying causes and long term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 2000;342:1077-1084.

further ischemia or infarction. Some patients with ischemic cardiomyopathy may show evidence of "hibernation" of segments of myocardium,[6] and cardiac function in these patients may improve with revascularization (see later).

HYPERTENSIVE HEART DISEASE

Hypertension causes a significant proportion of cases of heart failure. An episode of severe heart failure may be the first presentation of hypertension—such patients have had unrecognized severe hypertension for many years. The onset of heart failure may result in a previously raised blood pressure becoming normal or even low, which can make the diagnosis difficult in a patient with previously undiagnosed hypertension. Electrocardiography and echocardiography may show evidence of left ventricular hypertrophy. Patients with hypertension also commonly have diastolic dysfunction as a cause for heart failure. In this situation, systolic contraction is normal or minimally impaired but the main abnormality is in diastolic relaxation and ventricular compliance.[7] The incidence of diastolic abnormalities increases with age, and while the mortality rate associated with diastolic heart failure appears to be lower than that of systolic heart failure, it is still significant. To date, the ideal method of defining abnormal diastolic function has not been clearly ascertained.

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy is defined as left ventricular dysfunction of unknown cause. It is therefore a diagnosis of exclusion, and a firm diagnosis of dilated cardiomyopathy can only be made in the presence of a normal coronary angiogram. Intensive investigation of patients with a label of dilated cardiomyopathy may yield a definite cause in as many as 50% of cases (Table 99-2).

Dilated cardiomyopathy can manifest at any age, and, because heart failure may be perceived as a disease of the elderly, this can often result in misdiagnosis in younger patients.

VALVULAR HEART DISEASE

Structural Valve Disease

Valvular heart disease was, in previous years, a leading cause of heart failure in the Western world. Owing to the rise in ischemic heart disease, and the decrease in rheumatic fever, it is now less often the primary cause of an episode of severe heart failure. However, it is important not to discount significant valve disease in patients presenting with severe heart failure and to remember that signs may be difficult to elucidate in the acutely ill patient. Because all patients with severe heart failure should undergo echocardiography soon after admission, most if not all cases of significant valve disease should be detected. As noted earlier, after extensive myocardial infarction, acute mitral regurgitation can develop, causing sudden onset severe heart failure days after a patient's initial presentation with chest pain.

Functional Valve Disease

Patients with heart failure of any cause with dilatation of the left ventricle and mitral valve ring can develop functional mitral regurgitation. This further reduces left ventricular performance, and, in selected patients, mitral valve repair or replacement may be indicated.

DIABETES

In addition to the role of diabetes as a risk factor for the development of ischemic heart disease and resultant heart failure, there is evidence for a distinct diabetic cardiomyopathy.[8] Recognition of diabetes is important in the patient presenting with heart failure, as there is a growing body of evidence that rigorous control of blood glucose (using dextrose/insulin/potassium infusion, GIK) may improve outcome in cardiovascular disease,[9] although studies so far have not been directed specifically at patients with heart failure. All patients presenting with heart failure should be screened for diabetes, both for this reason and so that appropriate secondary prevention can be instituted.

OTHER POSSIBLE CAUSES OR EXACERBATING FACTORS

Patients with severe heart failure often have additional medical problems complicating management. Patients with a long history of stable heart failure may develop severe symptoms

due to deliberate or accidental omission of medications, intercurrent infection, or the development of atrial fibrillation. Patients with heart failure tolerate anemia poorly. It is vital to consider and treat such exacerbating conditions where appropriate.

PRESENTATIONS OF SEVERE HEART FAILURE

Severe heart failure can manifest in several ways. The patient may or may not have a previous history of heart failure, or precipitating conditions such as angina or hypertension. It is important to note that gradual onset heart failure can easily be mistaken for asthma, and patients presenting to an emergency department may well have been given a diagnosis of asthma in the weeks or months preceding their admission.

ACUTE PRESENTATION: PULMONARY EDEMA

The classic presentation of heart failure is with acute pulmonary edema. Such patients present with extreme shortness of breath, often unable to speak due to their rapid respiratory rate. The symptoms may come on very suddenly. Even patients with ischemic heart failure may not report chest pain, either because the ischemia is silent or because the pain is being masked by the profound shortness of breath. Many patients will be unable to give a history due to their shortness of breath, and therefore examination findings and basic investigations are vital to make the diagnosis.

General Examination. Examination may often reveal pallor, sweating, and dyspnea. The patient will have a high respiratory rate and increased work of breathing, using accessory muscles of respiration. Peripheral edema is not always present, particularly in patients presenting with a first episode of heart failure. Equally, the jugular venous pulse may not be elevated.

Respiratory Examination. Percussion is unlikely to be of value, owing to difficulty in examining the patient. A pleural effusion large enough to cause such dyspnea as to simulate severe heart failure will usually be obvious on auscultation. Percussion can be performed afterward if needed to confirm such a diagnosis. Patients with heart failure may well have pleural effusions, but they are usually relatively small and unlikely to benefit from drainage. Auscultation usually reveals extensive fine crepitations, usually equal bilaterally and greatest at the lung bases. However, some patients have predominant wheeze, caused by edema of the bronchial walls, and this may cause diagnostic confusion. In such patients, the preferred option may be to treat both bronchospasm and pulmonary edema. Similarly, in the most severely affected and exhausted patients, the chest may be surprisingly silent, due to reduced tidal volumes. A single dose of an intravenous diuretic agent is unlikely to cause harm to patients with breathlessness of other causes, and in situations of diagnostic difficulty, a rapid response to diuretics may be helpful.

Cardiovascular Examination. Examination of the pulse may reveal atrial fibrillation. Patients in sinus rhythm are usually tachycardic, although patients with a history of ischemic heart disease may well be taking beta-blockers, which mask tachycardia. The blood pressure is preserved in approximately 80% of patients presenting with decompensated heart failure overall, but a significant number are hypotensive at presentation. This is the single most important factor affecting treatment (see later) and is also likely to be altered by treatment, and so must be measured frequently. Palpation may or may not reveal a displaced apex beat, depending on the length of the history. There may be palpable heaves or thrills, but these are likely to be difficult to appreciate in the acutely breathless patient. Auscultation of the heart sounds may well be difficult. There may be a third or fourth heart sound, or there may be murmurs representing chronic stenotic or regurgitant valves, or an acute mitral valve prolapse or ventricular septal defect following myocardial infarction. (These latter two conditions can even occur several days after admission, in a patient with extensive myocardial infarction.) It is important to reexamine the patient regularly; once initial treatment has commenced, the patient may become less breathless, and previously inaudible signs may become clear.

Abdominal Examination. Examination of the abdomen can also be difficult in the acutely breathless patient. Where possible, such examination may reveal ascites, edema of the abdominal wall or genitalia, and enlargement of the liver. Pulsation of the liver can indicate tricuspid regurgitation.

SUBACUTE PRESENTATION: SHORTNESS OF BREATH/PERIPHERAL EDEMA

Many patients with severe heart failure present less acutely, with varying combinations of breathlessness and edema. This is often the case in patients with a previous diagnosis of heart failure and can be precipitated by intercurrent infection or withdrawal of diuretic or other medication (by the patient or a physician). In the early stages, edema may be more prominent unilaterally, and this may result in diagnostic difficulty. Such patients may be referred for exclusion of deep venous thrombosis (and it is important to be aware that the two conditions can coexist). Such patients often report gradually increasing breathlessness, with symptoms of orthopnea (shortness of breath occurring when lying supine) and paroxysmal nocturnal dyspnea (sudden shortness of breath waking the patient from sleep). Patients may resort to sleeping in a chair, leading to additional gravitational edema. Edema of the bowel can lead to reduced appetite, so called "cardiac cachexia," and further edema from hypoproteinemia. Peripheral edema is therefore often multifactorial in patients with heart failure. Differential diagnoses of peripheral edema are listed in Table 99-3.

Examination findings are similar to those for the acute presentation, although the patient is not in extremis and is able to speak sufficiently to give a full history. A full examination is possible more often in this situation, including auscultation of the heart sounds and abdominal examination. Peripheral edema may well be extensive, up to the abdominal wall and sacral areas. The jugular venous pulse may be elevated. Patients with extensive peripheral edema

TABLE 99-3. CAUSES OF PERIPHERAL EDEMA

Heart failure
Hypoproteinemia
Liver cirrhosis
Nephrotic syndrome
Lymphedema
Malnutrition
Gravitational edema

but a low jugular venous pulse may have hypoproteinemia rather then heart failure.

CHEST PAIN

As noted earlier, ischemic heart disease is an extremely common cause of heart failure. Patients presenting with chest pain thought to be ischemic in nature must be examined closely for subtle signs of heart failure. Patients presenting with extensive myocardial infarction may develop symptoms and signs of heart failure hours or days after admission. This may be precipitated by treatment (such as acute use of beta blockers or calcium channel blockers) or by a complication of the myocardial infarction, such as ventricular septal defect or mitral valve prolapse due to chordal rupture.

COLLAPSE/CARDIAC ARREST

Patients with severe heart failure of any cause are at high risk for malignant arrhythmias and thromboembolic disease such as pulmonary embolism. It is therefore not unusual for patients with severe heart failure to present with collapse or cardiac arrest. In such patients, the outlook is extremely poor. Even for patients presenting with ventricular tachycardia or ventricular fibrillation who are successfully cardioverted, the chance of surviving to discharge from hospital is low. Such patients can be considered for implantable cardioverter-defibrillators (see later). Pulmonary embolism and ventricular arrhythmias are covered in Chapters 79 and 96, and so will not be discussed in detail here.

INVESTIGATIONS

ELECTROCARDIOGRAPHY

All patients presenting with severe heart failure require at least one electrocardiogram (ECG). In cases of diagnostic difficulty, an entirely normal ECG virtually excludes systolic heart failure as the cause of symptoms.[10] In heart failure, an ECG is essential to diagnose arrhythmias such as atrial fibrillation, which may complicate management, as well as to look for evidence of myocardial ischemia or infarction, and conduction abnormalities such as left bundle branch block or bradycardia due to high degree atrioventricular block, which may respond to pacing. In patients in whom ischemia is suspected, serial ECGs are recommended, as changes may evolve during the course of the patient's treatment. Patients with acute severe heart failure should have continuous ECG monitoring during the acute phase, as they are at high risk for malignant ventricular arrhythmias.

CARDIAC ENZYMES

All patients presenting with severe heart failure, either as a first presentation or an exacerbation, should raise the question of myocardial infarction. As noted earlier, patients with ischemia often do not report chest pain in the setting of acute heart failure symptoms. Therefore, the use of biomarkers of cardiac muscle necrosis—ideally troponin I or T, assayed at presentation and repeated after 12 hours—is important for most patients presenting with heart failure, in conjunction with ECG findings, as noted earlier.

CHEST RADIOGRAPHY

Acutely, the chest radiograph is useful mainly in cases of diagnostic difficulty. In cases in which the diagnosis is reasonably clear from clinical information, treatment should not be delayed while waiting for a radiograph. However, most patients should have a chest radiograph early in the course of the admission.

The chest radiograph may show cardiomegaly, although this is poorly sensitive or specific for a diagnosis of heart failure (NB: portable films using anteroposterior projection may exaggerate the cardiac outline). A globular heart suggests the presence of pericardial fluid, which can be determined definitively by early echocardiography. Signs of pulmonary edema range from mild blunting of the costophrenic angles, perhaps with evidence of fluid in the horizontal fissure of the right lung, to upper lobe blood diversion (due to hypoxic vasoconstriction in the edematous dependent lung and opposite changes in the relatively edema-free upper lobes), to frank pulmonary edema. The chest radiograph may reveal signs of coexistent consolidation requiring antibiotic therapy.

ECHOCARDIOGRAPHY

Echocardiography should be carried out early in all cases of suspected heart failure. In recent years, bedside echocardiography devices have been developed that can be useful in the emergency department to assess the left ventricle and valves initially. In all cases, a full echocardiogram should be carried out when the patient is sufficiently stabilized.

Echocardiography is useful both to determine the extent of left ventricular dysfunction and to identify the cause. In cases of ischemic cardiomyopathy, regional wall motion abnormalities are commonly seen (although these can occasionally occur in cases of cardiomyopathy of other causes). Valve disease is readily identified by echocardiography. Echocardiography can be used to calculate the left ventricular ejection fraction, but in experienced hands, a qualitative assessment of left ventricular function can be equally useful. Some patients presenting with severe heart failure have preserved systolic function, and echocardiography can also be used to assess diastolic function. In the patient presenting with shortness of breath, in whom the cause is unclear, echocardiography can readily determine the presence or absence of heart failure.

BRAIN NATRIURETIC PEPTIDE

Natriuretic peptides are currently emerging as a novel test in cases of heart failure. The group includes three structurally related peptides, with variable activity at three distinct natriuretic peptide receptor subtypes, of which two are of potential use in patients with heart failure. Atrial natriuretic peptide is released from the atria in response to wall stretch. Brain natriuretic peptide, so called because it was first identified in brain tissue, is mainly released by the cardiac ventricles in response to wall stretch.[11] All the natriuretic peptides are elevated in acute coronary syndromes and myocardial infarction, due to release from myocytes. In addition, decompensated heart failure is associated with elevations of natriuretic peptide levels. Many possible applications for assays of these peptides have been proposed, but at present

the most widely accepted indications for use of brain natriuretic protein (which appears to have the best sensitivity/specificity of all the natriuretic peptides) are as follows:

1. In the acutely dyspneic patient in whom there is diagnostic difficulty, a high brain natriuretic protein level is very suggestive of underlying cardiac failure.
2. In the dyspneic patient with no clinical signs of heart failure, a normal brain natriuretic protein level has a high negative predictive value, that is, it is useful in *excluding* heart failure as a cause.

The use of brain natriuretic protein for monitoring progress in heart failure is controversial: some studies have suggested that brain natriuretic protein may be useful to guide treatment. Indeed, many studies have found that brain natriuretic protein levels may have prognostic implications. It is also important to note that brain natriuretic protein levels must be used in conjunction with clinical assessment of the patient, as unexpected values may occur in some patients, such as a high brain natriuretic protein level in a stable patient. Of particular note is the fact that patients with severe heart failure due to cardiogenic shock may exhibit a paradoxically normal or even low brain natriuretic protein level. It has been suggested that myocytes in such a situation are unable to produce brain natriuretic protein. This theory is supported by studies of serial brain natriuretic protein levels in patients recovering from an episode of cardiogenic shock. An initially low brain natriuretic protein level is followed by a high level as recovery of myocardial function begins, and as recovery continues, the level returns to normal.

INVASIVE INVESTIGATIONS

Central Venous Pressure Catheter

Placement of a central venous catheter may be necessary for certain drugs, such as inotropic agents or amiodarone, which cannot be given into a peripheral vein. The central venous pressure measurement may give some idea as to right-sided filling pressure but does not give reliable information about the status of the left ventricle. In situations in which detailed information regarding filling pressures would affect management of a seriously ill patient, the Swan-Ganz catheter should be considered instead.

Swan-Ganz Catheter

Insertion of a Swan-Ganz catheter may provide additional hemodynamic information. The procedure has been associated with increased mortality and therefore should be used only in severely ill patients in whom the results are likely to influence management. It is important to note that echocardiography can provide much of the information obtainable by Swan-Ganz catheterization when adequate images can be obtained.

TREATMENT

ACUTE TREATMENT

Simple Measures

The patient should be in erect sitting position. High-flow oxygen therapy should be administered to hypoxic patients with pulmonary edema. A single small dose of opiate (such as diamorphine 2.5 mg) may alleviate distress and also temporarily reduce cardiac preload and is also clearly indicated for patients presenting with ischemic chest pain in addition to pulmonary edema.

Urinary catheterization is essential in the severely compromised patient to monitor urine output but may also be therapeutic to reduce the need for exertion, particularly if large doses of diuretics are to be used.

Diuretics

Although not supported by randomized trials, it is clear that intravenous diuretic therapy can cause rapid relief of pulmonary edema and symptoms of acute decompensated heart failure. Care is needed in patients with compromised renal function or hypotension, as diuretic therapy may exacerbate such problems. It is usual to give an initial bolus intravenous dose of diuretic, which should be tailored to the patient's previous use of diuretics. A diuretic naive patient will usually respond to a single 50 mg IV dose of furosemide, whereas patients already taking diuretics long term may need much larger doses. Subsequent therapy is often given as further boluses of intravenous diuretic at intervals, although there is some evidence that a continuous infusion of diuretic may be more efficacious and cause less renal dysfunction.

Some patients with significant fluid overload may require combination diuretic therapy, for example with the addition of a thiazide diuretic such as metolazone. Metolazone is a weak diuretic when used alone, but increased sodium delivery to, and reabsorption in, the distal renal tubule resulting from the use of a loop diuretic is blocked by metolazone, resulting in a profound diuresis. Care is needed to avoid dehydration and hyponatremia with this strategy. An alternative may be to combine furosemide with an aldosterone blocker in the acute phase.

Thromboprophylaxis

Patients with severe heart failure are often poorly mobile, due to breathlessness, peripheral edema, and the presence of monitoring and treatment equipment. They are at high risk for the development of deep venous thrombosis and pulmonary embolism.[12] The MEDENOX (prophylaxis in MEDical patients with ENOXaparin) trial, which included 1102 hospitalized patients, including 376 with NYHA class III/IV heart failure, found that 14.9% of placebo treated patients suffered venous thromboembolism. Importantly, in the group treated with enoxaparin, only 5.5% suffered venous thromboembolism.[13] This trial also included patients with other serious medical illnesses, including cancer, so this may be an overestimate of the risk of thromboembolism in heart failure. In cases of moderate to severe heart failure, particularly in hospitalized patients, some of this increased risk may be related to immobility, which is a well known risk factor for deep venous thrombosis.[14] Indeed, in previous years when bed rest was standard treatment for patients with heart failure, the rate of pulmonary embolism was very high. All patients with severe heart failure who are not anticoagulated and in whom there are no contraindications (such as active bleeding) should receive thromboprophylaxis with unfractionated or low-molecular-weight heparin, with the dose adjusted according to the patient's bodyweight.

Vasodilators: Glyceryl Trinitrate/Sodium Nitroprusside

Infusion of glyceryl trinitrate has been a standard part of therapy for pulmonary edema with preserved blood pressure

for many years. It is a direct acting vasodilator that reduces left ventricular preload and afterload, by release of the potent vasodilator nitric oxide. Glyceryl trinitrate has a very short half-life and is given by continuous intravenous infusion, with dose titrated according to response and the patient's blood pressure. The most frequent adverse effect is hypotension, which is readily reversible on stopping or reducing the rate of infusion. Glyceryl trinitrate is additionally anti-anginal and therefore of particular benefit in the patient with ischemic chest pain and pulmonary edema. Patients receiving glyceryl trinitrate rapidly develop tolerance to the drug, which can limit its effectiveness if given for long periods.

Sodium nitroprusside is an alternative vasodilator that is also effective in patients with heart failure and preserved blood pressure. The drug is given by continuous infusion and must be protected from sunlight. However, its use is limited by concerns over the toxic effects of the metabolites of sodium nitroprusside: cyanide and thiocyanide.

Nesiritide

The natriuretic peptides have a variety of beneficial effects on the heart and circulation, causing diuresis, increasing sodium excretion, and reducing pre- and afterload by causing venous and arterial dilatation. They may also reduce left ventricular remodeling and fibrosis.[15] These attributes have recently led to the therapeutic use of natriuretic peptides in heart failure, and short-term studies have shown that nesiritide infusion is at least as efficacious as standard therapy (dobutamine, milrinone, or glyceryl trinitrate) and is associated with reduced diuretic use in patients with acutely decompensated heart failure.[16] Nesiritide (recombinant human brain natriuretic peptide) has recently been approved by the American Food and Drug Administration for use in patients with acutely decompensated heart failure in whom systolic blood pressure is greater than 90 mm Hg. It is given by intravenous bolus (2 μg/kg) followed by continuous infusion (0.01 μg/kg/min), as an alternative to glyceryl trinitrate. Treatment is usually continued for 24 to 48 hours.

Inotropes

Approximately 80% of patients presenting with acute decompensated congestive heart failure have preserved blood pressure and can therefore receive cardiac load reducing therapy such as glyceryl trinitrate or nesiritide. However, these treatments are contraindicated in hypotensive patients with heart failure. If such patients do not respond to initial diuretic therapy favorably, or show evidence of deterioration, inotropic therapy may be considered. Long-term use of inotropic therapy is likely to be harmful in patients with heart failure,[17] but potentially appropriate uses of inotropes include use as temporary treatment of diuretic-refractory acute heart failure decompensations or as a bridge to definitive treatment such as revascularization or cardiac transplantation.

Intra-aortic Balloon Counterpulsation

Intra-aortic balloon counterpulsation is an invasive strategy to preserve coronary flow in the presence of very poor cardiac output. A percutaneous approach is used to position a balloon in the descending aorta. The balloon is inflated during systole, diverting blood into the coronary arteries. This technique may be used to maintain circulation to the heart and brain at the expense of other tissues as a bridge to transplantation or other surgical intervention. Use of intra-aortic balloon counterpulsation is associated with a significant adverse event rate—up to 60% in one study of patients with cardiogenic shock.[18] There is no definite evidence that use of intra-aortic balloon counterpulsation improves the mortality rate among patients in heart failure; however, a comparison of patients from the Global Utilisation Of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) study showed a significantly lower rate of mortality in those undergoing intra-aortic balloon counterpulsation up to 1 day after admission as compared with all other patients (57% vs 67%).[19]

Assisted Ventilation

Noninvasive Ventilation

Noninvasive ventilation is a form of ventilatory support that does not require paralysis and intubation. Positive pressure is provided via a tight-fitting mask that may lie over the nose only or over the full face. Some patients are unable to tolerate the mask or the sensation of assisted ventilation.

Continuous positive airway pressure has an accepted role in the treatment of sleep apnea syndromes. Recently it has been recognized that sleep apnea is prevalent in patients with heart failure and may play a role in the development and progression of heart failure.[20] In addition, noninvasive ventilation has favorable effects on intrathoracic and left ventricular transmural pressures in patients with congestive heart failure.[21] Noninvasive ventilation has been used to treat acute heart failure. Several randomized trials have suggested that use of continuous positive airway pressure results in more rapid increase in Pa_{O_2}, decrease in P_{CO_2}, and lower rates of intubation compared with standard treatment.[22] Noninvasive ventilation may be considered in patients with rising P_{CO_2} levels despite adequate medical therapy. Noninvasive ventilation results in decreased blood pressure, so may have a deleterious effect in patients who are already hypotensive. To be used successfully, noninvasive ventilation requires careful attention to mask fitting and close patient observation. Noninvasive ventilation should be used only in a high dependency setting, with appropriately trained staff.

Intermittent Positive Pressure Ventilation

Patients with evidence of exhaustion or worsening arterial blood gases despite adequate treatment may require invasive ventilation. The prognosis of patients with such refractory pulmonary edema is poor, but some patients show dramatic improvement after only a short period of intermittent positive pressure ventilation. Intermittent positive pressure ventilation results in decreased venous return due to increased intrathoracic pressure and therefore can have a deleterious effect on blood pressure. Blood pressure must be maintained (with inotropic agents if necessary) before intubation.

Surgery

Valve Replacement

Patients with severe heart failure due to valvular heart disease, or functional mitral regurgitation, may benefit from valve replacement or repair. Ideally, surgery should be delayed until the patient is stable, but selected patients not improving on initial therapy may benefit from emergency valve replacement, although such patients are inherently at high risk for such major surgery. A multidisciplinary team consisting of cardiologist, cardiovascular surgeon, and intensivist/anesthetist is needed to select suitable patients

for intervention. A full discussion of indications for surgery is beyond the scope of this chapter.

Left Ventricular Assist Device

Left ventricular assist devices (LVADs) are surgically implanted devices developed to allow short- or long-term support to the failing left ventricle. Commonly, an inflow cannula receives blood from the left ventricle, which is then pumped out through a cannula in the ascending aorta. Although initially used as a bridge to transplantation, some studies have demonstrated recovery of function allowing explantation of the device after a period of left ventricular support in certain subgroups of patients together with appropriate pharmacologic therapy.[23] LVAD therapy for patients with terminal heart failure but who are not eligible for heart transplantation has been shown in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial[24] to be superior to medical therapy in ameliorating symptoms and to produce a 48% mortality reduction at 2 years' follow-up. However, the frequency of serious adverse events in the LVAD group was more than twice that in the medical-therapy group, mainly due to infection, bleeding, and malfunction of the device.

A number of devices are available. Choice depends on availability and local expertise.

The main complications of LVADs include thromboembolism, right ventricular failure, and device failure (equivalent to severe aortic regurgitation, as the devices do not have valves). Careful patient selection is necessary to gain most benefit from such devices.[25]

Revascularization

It recent years, the phenomena of "stunned" and "hibernating" myocardium have been recognized and widely investigated. Hibernating myocardium is defined as poorly functioning myocardium caused by reduced perfusion, which may recover function if perfusion is restored. Stunned myocardium results from an episode of ischemia. The segment of myocardium regains normal blood flow after the episode, but recovery of function is delayed (although recovery occurs spontaneously). In patients with chronic ischemic cardiomyopathy, revascularization may therefore result in improvement in left ventricular function. Patients with cardiogenic shock due to acute myocardial infarction have a very poor prognosis (see later), and in recent years several studies have addressed the possible benefits of acute revascularization in such patients. Retrospective analysis of the patients from the GUSTO-I study with cardiogenic shock (7.2%) showed that revascularization was associated with decreased mortality rate (overall 30-day mortality, 55%; patients undergoing coronary artery bypass grafting, 29%; patients undergoing percutaneous transluminal coronary angioplasty, 22%).[26]

The treatments were not allocated randomly, however. The two randomized controlled trials of medical therapy versus revascularization (Should We Emergently Revascularise Occluded Coronaries For Cardiogenic Shock [SHOCK] [27] and Swiss Multicentre Angioplasty for SHOCK [SMASH][28]) had difficulties in recruitment, and both reported no significant difference in early mortality, although the SHOCK trial did show decreased mortality rate at 6 months in the intervention group. It is important to note that results from the SHOCK trial registry, which showed that patients selected to undergo angiography had better outcomes whether or not they went on to be revascularized, suggest that bias may be involved in the results of these studies.[29] Current evidence certainly does not support aggressive revascularization of all patients with cardiogenic shock, but revascularization may be appropriate in selected patients.

Stabilization and Chronic Treatment

A full discussion of long-term treatment for patients with heart failure is beyond the scope of this book. However, patients presenting with acute heart failure may need to be established on a variety of medications during their index admission, and so a brief summary of the main drugs used in heart failure maintenance is presented here.

Loop Diuretics

As noted earlier, loop diuretic therapy may provide rapid symptom relief in patients with fluid overload. However, loop diuretics may be associated with a number of adverse effects such as volume depletion, and no mortality benefit has been demonstrated in cases of heart failure. Although some patients with chronic heart failure may be able to have diuretic therapy withdrawn once they are appropriately stabilized, most require at least a small dose of maintenance diuretic, tailored to clinical evidence of fluid overload. Regular weighing is a simple method of monitoring the fluid status of heart failure patients. Care must be taken to monitor renal function in patients on high doses of diuretics. Diuretics may cause hypokalemia, although combining them with angiotensin-converting enzyme (ACE) inhibitors and potassium-sparing diuretics such as spironolactone (see later) may reduce this problem.

Angiotensin-Converting Enzyme Inhibitors/Angiotensin II Receptor Blockers

Multiple large randomized trials have shown that ACE inhibitors (e.g., ramipril, perindopril, lisinopril) are of unequivocal benefit in patients with heart failure and asymptomatic left ventricular dysfunction.[30] All patients should be started on an ACE inhibitor as soon as possible after a diagnosis of heart failure has been made—this is almost always during the index admission. Most patients will require gradual introduction of the drug, with monitoring of blood pressure and renal function. Effort should be made to achieve the highest tolerated dose of the chosen ACE inhibitor.

Some patients are unable to tolerate ACE inhibitors due to cough (caused by elevated levels of bradykinin, which is usually degraded by ACE). An alternative in such patients are angiotensin II receptor blockers, which directly block the angiotensin II receptor and do not cause bradykinin build-up. There is not yet sufficient evidence on angiotensin II receptor blockers to recommend them over ACE inhibitors as first-line therapy in heart failure patients. However, the recent Candesartan in Heart Failure—Assessment of Reduction in Mortality (CHARM) study demonstrated that in patients unable to tolerate ACE inhibitors, the angiotensin II receptor blocker candesartan provided similar mortality benefit.[31] Another arm of the CHARM study (CHARM-ADDED) showed additional benefit (reduction in the primary endpoint of cardiovascular death or hospital admission for congestive heart failure) when candesartan was added to ACE.[32]

Beta-Blockers

For many years, beta-blockers were thought to be harmful in patients with heart failure because of their negative

inotropic effect. More recently, however, several large randomized trials have demonstrated consistent benefit of beta-blockers such as carvedilol,[33] bisoprolol,[34] and metoprolol.[35] Beta-blockers are indicated in patients with stabilized heart failure and are rarely started during the index admission. Their use involves careful dose titration, best supervised in a specialist heart failure clinic.

Aldosterone Inhibitors

The landmark Randomised Aldactone Evaluation Study (RALES) showed that, in patients with severe heart failure, spironolactone reduced mortality by 30%.[36] More recently, a more selective aldosterone inhibitor, eplerenone, has been developed, which (due to its lack of action at sex hormone and glucocorticoid receptor sites) lacks the unpleasant side effects of spironolactone such as painful gynecomastia. The recent EPHESUS study, which recruited 6642 post-myocardial infarction patients with left ventricular ejection fraction less than 40% and clinical heart failure and randomised them to receive eplerenone or placebo (in addition to otherwise optimized medical therapy), demonstrated a 15% reduction in all-cause mortality among the eplerenone group after a mean follow-up period of 16 months.[37] It is likely that aldosterone antagonists will be used increasingly in the management of patients with chronic heart failure.

Aldosterone blockers may cause hyperkalemia, particularly in combination with ACE inhibitors. Patients on this combination should have regular renal function testing.

Antithrombotic Therapy

Patients with heart failure and atrial fibrillation have clear indications for anticoagulation with adjusted-dose warfarin.[38] There is no clear evidence for the use of antithrombotic therapy in patients with heart failure in sinus rhythm, although such patients fulfill Virchow's triad (abnormal flow, abnormal vessel wall, abnormal blood constituents) for a prothrombotic state.[39] It is hoped that ongoing randomized trials comparing antiplatelet agents, warfarin, and placebo will provide more information on the optimal strategy for antithrombotic therapy in heart failure patients.

Direct-acting thrombin inhibitors, such as ximelagatran, may be an alternative to warfarin, and are currently being investigated for a number of indications.[40] Ximelagatran has advantages over warfarin in that dose adjustment and INR monitoring are not required.

Digoxin

Digoxin therapy in patients with heart failure in sinus rhythm (i.e., for inotropic effect) is common practice in North America but is less frequently used in Europe. Evidence of benefit is somewhat limited. Two trials showed withdrawal of digoxin from patients with symptomatic heart failure resulted in increased risk of heart failure decompensation.[41,42] The Digitalis Investigation Group (DIG) trial[43] demonstrated no difference in survival associated with the use of digoxin. A reduction in the risk of death from progressive heart failure in the DIG trial was balanced by an increase in the risk of sudden cardiac death. Digoxin may therefore be considered as additional therapy for patients on ACE inhibitors and beta-blockers but is not an alternative to these drugs.

Cardiac Resynchronization Therapy

Patients with heart failure may exhibit dyssynchronous contraction of the left ventricle, resulting from abnormal electrical conduction pathways. Typically this results in septal contraction occurring some time before contraction of the free wall of the left ventricle. Such dyssynchronous contraction results in significant circulation of blood in the left ventricular cavity, rather than forward flow of blood. The use of biventricular pacing to restore synchronous contraction of the left ventricle (cardiac resynchronization therapy) has increased in popularity in recent years. However, the optimal method for selecting patients for cardiac resynchronization therapy is unclear. Current guidelines use duration of the ECG QRS complex, but recent studies have shown that some patients with narrow QRS complexes may benefit from cardiac resynchronization therapy, and, equally, not all patients with wide QRS complexes benefit. Echocardiographic evidence of dyssynchronous contraction in combination with the ECG may prove to be a better method of selecting candidates for cardiac resynchronization therapy.[44]

Arrhythmia Therapy

Atrial Fibrillation

Atrial fibrillation can result in significant impairment of left ventricular function, due to loss of atrial contraction and abnormal left ventricular filling. Atrial fibrillation in the presence of reduced left ventricular function results in a very high risk of thromboembolic stroke, and so all patients with atrial fibrillation and reduced left ventricular function should be anticoagulated in the absence of contraindications. In the presence of poor left ventricular function or dilated left ventricle or left atrium on echocardiography, DC cardioversion is unlikely to cause sustained conversion to sinus rhythm but could be considered in situations in which palpitations due to atrial fibrillations cause significant distress to the patient. Pharmacologic rate control is likely to be more successful. Digoxin is commonly used for this purpose, although in the presence of renal impairment or diuretic-induced hypokalemia, toxicity is common. If tolerated, beta-blockers may achieve rate control, although the need to introduce such drugs gradually makes them less suitable for initial rate control. It may be possible to control the rate initially with careful digoxin therapy, then consider withdrawing digoxin once the patient is established on a sufficiently high dose of beta-blocker. Amiodarone is an alternative antiarrhythmic safe for use in heart failure patients, which can be used to control atrial fibrillation, although side-effects are problematic.

Ventricular Arrhythmias

Patients with heart failure frequently suffer from sudden death. Although it is now recognized that some episodes of sudden death are caused by thrombosis, such as pulmonary embolism, it is clear that malignant arrhythmias are a common cause of death in heart failure. Surprisingly, therefore, multiple trials of a variety of antiarrhythmic drugs in patients with heart failure have failed to show a mortality benefit (amiodarone),[45] or even shown a worsening of mortality (e.g., flecainide).[46] Routine use of antiarrhythmic drugs in patients with heart failure is therefore not recommended. In contrast, recent studies involving the use of implantable cardioverter-defibrillator devices in patients with reduced ejection fraction following myocardial infarction have shown reduced mortality. The recent COMPANION study,[47] which compared optimal medical treatment alone to optimal medical treatment plus cardiac resynchronization therapy plus or minus implantable cardioverter-defibrillator therapy, found

TABLE 99–4. INDICATIONS FOR IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR THERAPY IN PATIENTS WITH HEART FAILURE

Cardiac arrest due to ventricular fibrillation or ventricular tachycardia
Spontaneous sustained ventricular tachycardia
Syncope of unknown origin with inducible ventricular tachycardia or ventricular fibrillation at electrophysiologic study
Nonsustained ventricular tachycardia with inducible ventricular fibrillation/ventricular tachycardia at electrophysiologic study
Left ventricular ejection fraction <30% at least 1 month after myocardial infarction or 3 months after coronary artery bypass grafting

that combined cardiac resynchronization therapy/implantable cardioverter-defibrillator reduced mortality but not hospitalization as compared with cardiac resynchronization therapy alone. At present, routine use of implantable cardioverter defibrillators (which in any case would be prohibitively expensive in most countries) in all heart failure patients cannot be recommended. Current indications for implantable cardioverter-defibrillator therapy in heart failure are listed in Table 99-4.

FURTHER MANAGEMENT: THE SPECIALIST HEART FAILURE CLINIC

Patients with heart failure are at high risk of further admissions and sudden death. Careful follow-up and adequate secondary prevention using the drugs and devices detailed here is essential to reduce the risk of readmission and other complications of heart failure. Ideally, such patients should be followed in a specialist heart failure clinic, with access to a cardiologist specializing in heart failure, specialist heart failure nursing, and access to investigations such as echocardiography, cardiac catheterization, and brain natriuretic protein. Nurse-led clinics are ideal for dose titration of beta-blockers and ACE inhibitors and also provide opportunities for monitoring of fluid status and symptoms.[48]

PROGNOSIS

Heart failure has a poor prognosis—diagnosis of chronic heart failure is associated with a mortality rate worse than that of many cancers.[49] As noted earlier, patients with severe heart failure often present in extremis but may respond rapidly to prompt effective management. However, their in-patient course is associated with a high risk of complications such as thromboembolism (particularly in the presence of atrial fibrillation) and sudden death, even in patients who show signs of recovery from their initial event. Close follow-up and secondary preventive measures are essential to improve prognosis in this high-risk group.

SUMMARY

Severe heart failure is a common disorder, with high rates of mortality and morbidity. Patients often present in extremis, so good knowledge of initial treatment is essential for all physicians and emergency department staff. Patients often respond rapidly to effective initial treatment, making this a satisfying condition to treat. However, patients may also deteriorate rapidly, and may require involvement of intensivists, cardiologists, and cardiac surgeons. Once stabilized, there are a number of evidence-based treatments that improve prognosis in these patients. Careful follow-up, ideally in a specialist heart failure clinic, is recommended after discharge.

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Echt DS, Liebson PR, Mitchell LB, et al: Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991;324:781-788.

This important randomized placebo-controlled trial identified an increased mortality risk with type I antiarrhythmics in patients with cardiovascular disease.

Halperin JL, for the Executive Steering Committee, SPORTIF III and V Study Investigators: Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: Rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). Am Heart J 2003;146:431-438.

The ongoing SPORTIF III (open label, 23 countries) and V (double blind, 409 US centers) trials are comparing ximelagatran with adjusted-dose warfarin in patients with atrial fibrillation and at least one other risk factor (including heart failure).

MERIT-HF Investigators: Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-2007.

The benefit of beta-blockers in heart failure was proved in these randomized controlled studies (MERIT-HF, CIBIS-II, and US Carvedilol Heart Failure Study), bringing to an end the idea that beta-blockade could be harmful in patients with heart failure.

Rich MW, Beckham V, Wittenberg C, et al: A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. N Engl J Med 1995; 333:1190-1195.

This trial demonstrated that a multidisciplinary intervention involving nutritional advice, counselling, patient education, and exercise training could significantly reduce readmission rates and length of hospital stay in elderly patients with heart failure.

Chapter 100

MYOCARDITIS IN THE INTENSIVE CARE UNIT

Fredric Ginsberg • Joseph E. Parrillo

KEY POINTS

1. Myocarditis is most often caused by a viral infection. Myocardial damage is mediated through activation of cellular immune mechanisms.
2. The clinical course of myocarditis can be benign, with complete resolution, or the illness can be more severe, with the development of dilated cardiomyopathy and congestive heart failure.
3. The pharmacological therapy of heart failure associated with myocarditis is similar to therapy used in other forms of dilated cardiomyopathy. Severe cases may require the use of a ventricular assist device.
4. Fulminant myocarditis is an unusual complication with a rapidly progressive course resulting in cardiogenic shock. These cases should be aggressively managed with pharmacological therapy and ventricular assist devices, because significant improvement in left ventricular function will often occur.
5. Endomyocardial biopsy is frequently used to make the diagnosis of myocarditis and to direct therapy, although there are limitations in the interpretation of biopsy results.
6. Immunosuppressive therapy should not be used routinely in the treatment of myocarditis but should be strongly considered in patients who have severe heart failure early in the course of the illness or whose condition deteriorates despite the use of conventional heart failure treatment.

MYOCARDITIS IN THE INTENSIVE CARE UNIT

Myocarditis is defined as inflammation of heart muscle.[1] The study of myocarditis has been made difficult by a number of factors. The clinical picture of myocarditis varies widely, from asymptomatic patients who suffer no long-term sequelae, to critically ill patients with heart failure and cardiogenic shock. In addition, there are no standardized specific criteria for making the diagnosis of myocarditis or for determining a cause in individual patients.[2] Indeed, many different etiologic agents have been implicated in this disease. Lastly, there has been controversy regarding the most appropriate medical therapy for this condition.

On pathologic examination of myocardial biopsy specimens, or on autopsy series, myocarditis is usually apparent as infiltration of myocardium with lymphocytes and fibroblasts, accompanied by myocyte necrosis (myocytolysis).[2] It is this type of myocarditis, often termed *lymphocytic myocarditis*, that will be referred to in this chapter, unless otherwise specified. Other types of inflammatory reactions can be seen less frequently in cases of myocarditis, involving giant cells, eosinophils, or granulomas, which can be associated with specific clinical conditions.

In most patients with myocarditis, a specific cause is not found.[3] It is presumed, however, that in North America and Europe, the most common etiologic agent is viral.[1] Enteroviruses, specifically coxsackie B, are most commonly implicated. Other viruses have been associated with myocarditis, including adenoviruses, hepatitis C, and influenza virus.[4] Myocarditis is a common finding in patients infected with human immunodeficiency virus (HIV). However, the causative agent responsible in these cases is more likely to be a secondary viral or other infectious agent occurring in these immunocompromised hosts, rather than HIV itself.[1] Infectious illnesses such as Lyme disease, acute rheumatic fever, and diphtheria often have myocarditis as a prominent feature. In Central and South America, the most common cause of myocarditis is the protozoan *Trypanosoma cruzi*, the cause of Chagas' disease. Systemic diseases such as systemic lupus erythematosus, polymyositis, scleroderma, and sarcoidosis can be complicated by myocarditis, and myocarditis can be a feature of the infiltrative cardiomyopathies seen in hemochromatosis or amyloidosis. Lastly, myocarditis can be associated with doxorubicin cardiomyopathy or with peripartum cardiomyopathy, or can be a manifestation of a hypersensitivity reaction to medications (Table 100-1).[5,6]

Unfortunately, it is difficult to make a clinical diagnosis of a specific viral cause of myocarditis. This usually requires the measurement of antiviral antibody titers in acute and convalescent phase sera. Viral cultures of tissue specimens are unreliable.[3] The identification of viral genomes incorporated in myocyte DNA does not specifically indicate the virus as the etiologic agent (Table 100-2).

PATHOGENESIS

Based on observations of human myocarditis, as well as murine models of the disease caused by coxsackie B3, the pathogenesis of viral myocarditis can be described in three stages. The first stage is initiated by viral infection and replication within myocytes. Viral proteases and activation of cytokines may produce myocyte damage and apoptosis.[4] The presence of this viral replication phase is difficult to prove clinically, because patients may be asymptomatic during this phase or may only have nonspecific viremic symptoms.

TABLE 100–1. CAUSES OF MYOCARDITIS*

Infectious	Immune-Mediated	Toxic Myocarditis
Bacterial: brucella, *Corynebacterium diphtheriae*, gonococcus, *Haemophilus influenzae*, meningococcus, mycobacterium, *Mycoplasma pneumoniae*, pneumococcus, salmonella, *Serratia marcescens*, staphylococcus, *Streptococcus pneumoniae*, *S. pyogenes*, *Treponema pallidum*, *Tropheryma whippelii*, and *Vibrio cholerae* Spirochetal: borrelia and leptospira Fungal: actinomyces, aspergillus, blastomyces, candida, coccidioides, cryptococcus, histoplasma, mucormycoses, nocardia, and sporothrix Protozoal: *Toxoplasma gondii* and *Trypanosoma cruzi* Parasitic: ascaris, *Echinococcus granulosus*, *Paragonimus westermani*, schistosoma, *Taenia solium*, *Trichinella spiralis*, visceral larva migrans, and *Wuchereria bancrofti* Rickettsial: *Coxiella burnetii*, *Rickettsia rickettsii*, and *R. tsutsugamushi* Viral: **coxsackievirus,** cytomegalovirus, dengue virus, echovirus, encephalomyocarditis, Epstein-Barr virus, hepatitis A virus, hepatitis C virus, herpes simplex virus, herpes zoster, **human immunodeficiency virus,** influenza A virus, influenza B virus, Junin virus, lymphocytic choriomeningitis, measles virus, mumps virus, parvovirus, poliovirus, rabies virus, respiratory syncytial virus, rubella virus, rubeola, vaccinia virus, varicella-zoster virus, variola virus, and yellow fever virus	Allergens: acetazolamide, amitriptyline, cefaclor, colchicine, furosemide, isoniazid, lidocaine, methyldopa, penicillin, phenylbutazone, phenytoin, reserpine, streptomycin, tetanus toxoid, tetracycline, and thiazides Alloantigens: heart-transplant rejection Autoantigens: **Chagas' disease,** *Chlamydia pneumoniae,* Churg-Strauss syndrome, inflammatory bowel disease, giant-cell myocarditis, insulin-dependent diabetes mellitus, Kawasaki's disease, myasthenia gravis, polymyositis, **sarcoidosis, scleroderma, systemic lupus erythematosus**, thyrotoxicosis, and Wegener's granulomatosis	Drugs: amphetamines, **anthracyclines,** catecholamines, cocaine, cyclophosphamide, **ethanol,** fluorouracil, hemetine, interleukin-2, lithium, and trastuzumab Heavy metals: copper, iron, and lead Physical agents: electric shock, hyperpyrexia, and radiation Miscellaneous: arsenic, azides, bee and wasp stings, carbon monoxide, inhalants, phosphorus, scorpion bites, snake bites, and spider bites

*The most common causes are shown in **boldface** type.
From Feldman A, McNamara D: Myocarditis. N Engl J Med 2000;343:1388–1398.

In addition, there is no rapid screening test to confirm viral infection.

The second stage involves host immune activation. Stimulation of cellular immunity as well as humoral responses attenuates viral proliferation and can result in recovery from the illness. However, unabated immune activation can result in activated T cells targeting myocardial antigens, which cross-react with viral peptides. This leads to release of cytokines such as tumor necrosis factor, interleukin-1, and interleukin-6, resulting in further myocyte damage.[1,4] Activation of CD4 cells and antibody production seem to play a smaller pathogenetic role. It is believed that this secondary immune response to viral infection plays a greater role in disease pathogenesis than the primary infection.[4]

Evidence supporting these mechanisms includes the following: Myocardial biopsy with recombinant DNA techniques can detect viral genomes in 20% to 35% of patients. Tissue specific autoantibodies have been detected in 25% to 73% of patients with evidence of myocarditis on biopsy, and inappropriate expression of the major histocompatibility complex can frequently be demonstrated on biopsy specimens.[1] Enterovirus genome has been identified on biopsy specimens in less than 20% of myocarditis patients and 10% to 34% of idiopathic dilated cardiomyopathy patients. Elevated levels of inflammatory cytokines are detected in patients with active myocarditis.

TABLE 100–2. DISTINCT FORMS OF MYOCARDITIS

Active viral
Postviral (lymphocytic): common form of acute myocarditis
Hypersensitivity
Autoimmune
Infectious
Giant-cell myocarditis

From Haas G: Etiology, evaluation, and management of acute myocarditis. Cardiol Rev 2001; 9:88-95.

Either persistent overactivation of cellular immune activity or incomplete clearing and persistent or recurrent viral replication and host response can lead to the third stage, where significant myocardial damage occurs. This leads to left ventricular dilatation and remodeling, left ventricular systolic dysfunction, and manifestations of heart failure.[4] These processes can then abate, with reduction in left ventricular size and improvement of left ventricular function, or can continue to progress with development of chronic dilated cardiomyopathy and chronic heart failure.

CLINICAL PRESENTATION

The clinical presentation of myocarditis varies widely. Patients can be asymptomatic, as myocarditis is found in 1% to 10% of autopsy specimens of young adults who had no history of cardiac illness. Myocarditis can be found at autopsy in up to 20% of cases of young apparently healthy adults who die suddenly and unexpectedly.[1,3,6]

Patients ill with myocarditis most often present with chest pain, fatigue, dyspnea, and palpitations. Frequently they have recently experienced nonspecific symptoms of a viral infection including fever, malaise, and arthralgias. Physical examination can show fever, tachycardia, S3 and S4 gallop sounds, and a pericardial rub (if myopericarditis is present). Signs of heart failure can be present, including pulmonary rales and wheezes, hepatomegaly, ascites, elevated jugular venous pulse, and peripheral edema. Murmurs of mitral regurgitation and tricuspid regurgitation may be heard. Infrequently, patients can present with a fulminant course, with severe acute heart failure, pulmonary edema, and cardiogenic shock.[3]

The differential diagnosis includes acute myocardial infarction, pericarditis, or chest pain from pulmonary causes, including pulmonary embolism or pneumonia. Generalized sepsis is also a consideration.

Laboratory findings can include leukocytosis, eosinophilia, and an elevated erythrocyte sedimentation rate. Cardiac biomarkers such as CPK, troponin T, and troponin I are

variably elevated depending in part on the chronicity of the process,[1] although recent data suggest that troponin may be useful in diagnosing myocarditis. Rheumatologic serologic markers and HIV status should be evaluated.

The 12-lead electrocardiogram shows sinus tachycardia and nonspecific ST segment and T wave changes most often. Patients may present with chest pain and ST segment elevation with a picture mimicking acute myocardial infarction. More severe cases can be associated with supraventricular or ventricular arrhythmias, conduction disturbances, and heart block.[1]

Echocardiography is essential to diagnose and quantitate regional or global left ventricular wall motion abnormalities, left ventricular and right ventricular size and function, and valvular regurgitation. Findings on myocardial nuclear scintigraphy are frequently abnormal, but this is an insensitive test for the diagnosis of myocarditis. Cardiac magnetic resonance imaging is currently being evaluated to assess the extent of cardiac involvement and to localize inflammation in cases of patchy nonhomogeneous myocarditis. This may aid in determining optimal sites for myocardial biopsy. Cardiac catheterization and coronary angiography are often necessary to exclude acute ischemia as the cause of chest pain or acute heart failure.

DIAGNOSIS

Myocarditis is a difficult diagnosis to make, as there are no specific clinical diagnostic criteria. Even though clinical and laboratory features of this illness, as described earlier, are insensitive and nonspecific,[2] myocarditis remains a diagnosis made on clinical grounds. Percutaneous endomyocardial right ventricular biopsy is currently used to aid in the diagnosis of myocarditis and is considered the most definitive diagnostic technique.

The Dallas criteria have been accepted as the standard for histopathologic diagnosis. These criteria define myocarditis as the presence of an active inflammatory myocardial infiltrate (more than 5 lymphocytes per high-power field) accompanied by myocyte necrosis. "Borderline myocarditis" is defined as active inflammation without myocyte necrosis. However, there is no difference in prognosis in patients with either of these biopsy results.[5] Thus, it appears that lymphocyte infiltration (with or without myocyte necrosis) is the most important diagnostic criterion.

Although endomyocardial biopsy is useful for diagnostic purposes, there are a number of significant limitations. A high frequency of interobserver variation has been noted among pathologists in applying the Dallas criteria. Biopsies are not sensitive in diagnosing myocarditis, as various series have reported positive biopsy results in only 10% to 67% of patients with myocarditis suspected on clinical grounds or recent-onset idiopathic dilated cardiomyopathy. This variability may relate to the timing of biopsies in respect to the stage or chronicity of the patient's illness. In addition, the myocardial inflammation may not be diffuse and may be patchy, or may predominantly involve the left ventricle, so random right ventricular biopsies may miss affected myocardium.[7] Thus, performing a biopsy earlier in a patient's clinical course and taking multiple biopsy specimens, possibly to include left ventricular sites, have been suggested as ways of improving the diagnostic yield. Biopsies should also be done in centers with a high-volume experience, with proven safety, and availability of appropriate pathologic techniques.[8] However, it is important to emphasize that a negative biopsy finding does not preclude the diagnosis of myocarditis.

Although endomyocardial biopsy is an insensitive test with a number of problems, a positive biopsy finding has a high positive predictive value.[5] Some authors question the benefits of performing biopsy with standard staining techniques as a routine in suspected myocarditis cases, but this remains the best diagnostic test currently available. Other analyses such as examining specimens for viral genomes or using immunohistochemistry technology to identify up-regulated HLA proteins may offer improved diagnostic yield in the future.[7] Endomyocardial biopsy should be strongly considered in cases of suspected myocarditis when pathology results will affect management decisions, especially in patients with acute refractory heart failure or continued clinical deterioration despite appropriate aggressive heart failure therapy. Biopsy should also be considered in patients with worsening ventricular arrhythmias, with heart block, or with suspected causes such as sarcoidosis, collagen vascular disease, infiltrative cardiomyopathy, giant cell myocarditis, or eosinophilic myocarditis.[9] Endomyocardial biopsy should always be performed prior to initiating immunosuppressive therapy.

CLINICAL COURSE AND PROGNOSIS

The clinical course and prognosis of acute myocarditis is quite variable. Patients who are asymptomatic, with self-limited disease, or who present with a flu-like illness most often recover without complications. It is felt that some of these patients will progress to chronic dilated cardiomyopathy with manifestations of systolic heart failure,[2] although a precise incidence is not known. The majority of patients who present with manifestations of myocarditis will improve. Patients with heart failure and left ventricular dysfunction will experience spontaneous resolution of their illness in 6 to 12 months in up to 40% of cases, without long-term sequelae. However, a significant percentage of young, apparently healthy adults who die suddenly are found to have myocarditis at autopsy, suggesting that patients even with apparently mild illness can suffer fatal arrhythmias.

Patients with heart failure and myocarditis can recover normal left ventricular function or can progress to chronic dilated cardiomyopathy. Fifteen to 25% of patients who present with new-onset dilated cardiomyopathy have evidence for antecedent myocarditis.[2] There is a reported 1-year mortality rate of 20% in patients with lymphocytic myocarditis.[5] However, it is important to examine the patient population under study and the criteria used for diagnosing myocarditis in any series assessing prognosis and mortality.

A series of 21 patients with active myocarditis on biopsy was analyzed for predictors of disease course. Variables assessed included baseline hemodynamics, use of ventilatory and circulatory support, and serum cardiac biomarkers. Overall, there was a 37% mortality rate (8 of 21) with death occurring at 27.6 ± 6.9 days. Factors predicting a worse prognosis included hypotension (mean 84/49 mm Hg), higher pulmonary capillary wedge pressure (mean of 24 mm Hg), and use of mechanical ventilation. Factors that were not predictive of mortality included sex, age, heart rate, cardiac index, peak CPK or tumor necrosis factor levels, or the use of intra-aortic balloon counterpulsation for circulatory support.[10] However, no clinical markers reliably predict

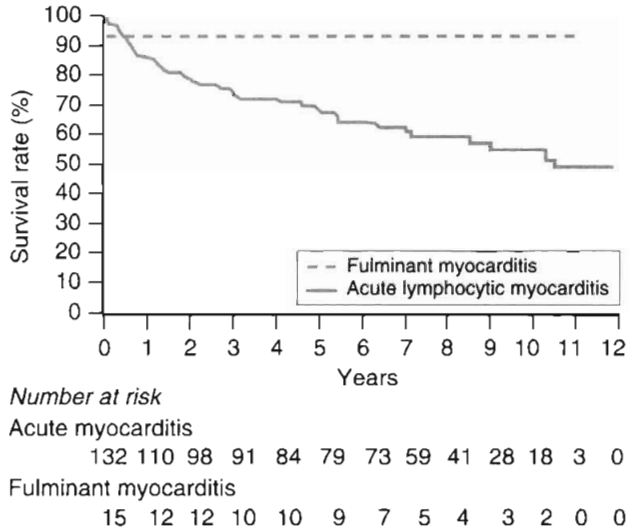

FIGURE 100–1. Unadjusted transplantation-free survival according to clinicopathological classification. Patients with fulminant myocarditis were significantly less likely to die or require heart transplantation during follow-up than were patients with acute myocarditis ($P = 0.05$ by the log-rank test). (From McCarthy R, Boehmer J, Hruban R, et al: Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. N Engl J Med 2000;342:690-695.)

which patients with myocarditis are more likely to recover or progress.[5]

FULMINANT MYOCARDITIS

A small percentage of patients with acute myocarditis present critically ill with acute severe heart failure and cardiogenic shock. This presentation is termed *fulminant myocarditis.* Most often these patients give a history of recent fever and symptoms of a viral illness, with a distinct time of onset of heart failure symptoms. This presentation can be contrasted with that of patients with myocarditis who have acute heart failure, but not cardiogenic shock, who demonstrate a less distinct time of onset of heart failure symptoms and less severe hypotension.

In a study of 147 patients presenting with heart failure due to biopsy-positive active myocarditis, with ejection fraction less than 40%, 10% of patients were believed to have fulminant myocarditis and 90% had acute lymphocytic myocarditis.[5] The patients with fulminant myocarditis needed hemodynamic support with high-dose vasopressors or left ventricular assist devices. The acute myocarditis patients had more stable hemodynamics and did not require vasopressors, or received them at low doses. Patients with fulminant myocarditis tended to be younger and have higher heart rates and lower systemic blood pressure. There was no difference between the groups in mean pulmonary capillary wedge pressure or cardiac index.

With aggressive treatment, patients with fulminant myocarditis actually had better survival rates, 93% at 1 year and 93% at 11 years. Patients with acute myocarditis had an 85% 1-year survival rate and a 45% survival rate at 11 years. Patients with lower pulmonary capillary wedge pressure or higher cardiac index at presentation also had better survival.

Thus, it is believed that fulminant myocarditis has a distinct clinical course, with critical illness at presentation but with excellent long-term survival once patients recover from the acute phase of their illness. Healing of myocardial injury and significant improvement of left ventricular systolic function can be expected. Therefore, an aggressive approach to therapy, including the use of ventricular assist devices or other mechanical assist devices, without resorting to early cardiac transplantation, is warranted (Fig. 100-1).[5]

GIANT CELL MYOCARDITIS

Giant cell myocarditis is a distinct form of myocarditis, generally with a rapidly progressive course, without significant likelihood of spontaneous resolution. On endomyocardial biopsy, infiltration with inflammatory giant cells is seen. Although the pathogenesis is not clear, it is believed to be an autoimmune disorder, and CD4 T-lymphocytes are thought to play an important role. A total of 63 patients with biopsy-confirmed giant cell myocarditis were studied retrospectively.[11] Heart failure was the presentation in 75% of cases; 14% presented with ventricular arrhythmias, and 11% presented with chest pain, an abnormal electrocardiogram, or heart block. There was an association with inflammatory bowel disease in 8% of cases. Survival was poor, with a median time of 5.5 months to death or cardiac transplantation (Fig. 100-2).

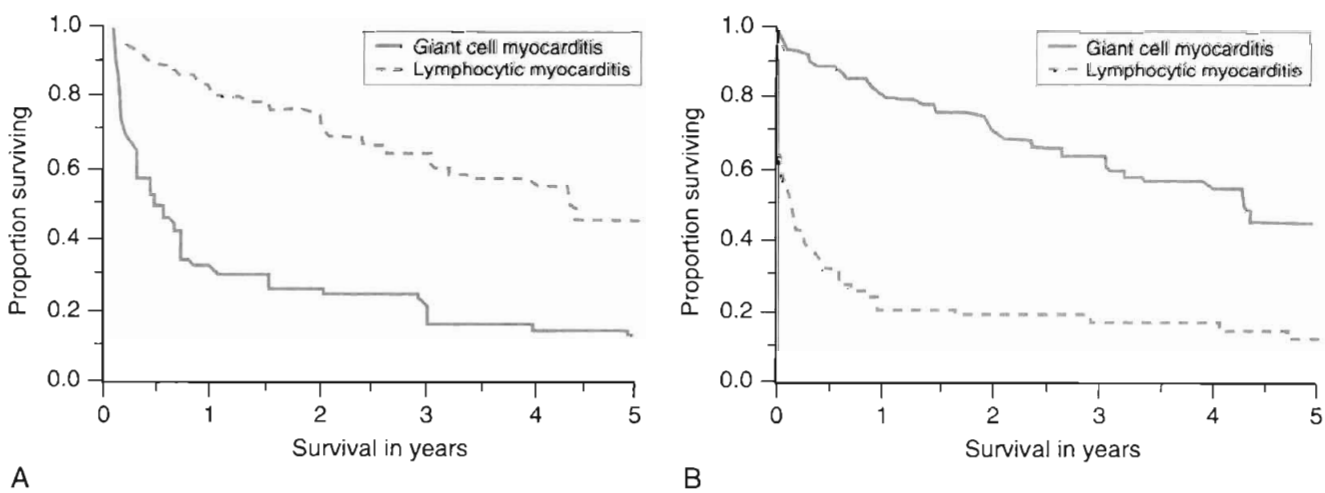

FIGURE 100–2. Line graphs showing the Kaplan-Meier survival curves for patients with giant cell myocarditis and lymphocytic myocarditis from the onset of symptoms (*A*) and from time of presentation to the referring center (*B*). In each case, survival was significantly shorter among those with giant-cell myocarditis. (From Cooper L, Berry G, Shabetai R, for The Multicenter Giant Cell Myocarditis Study Group Investigators: Idiopathic giant cell myocarditis—Natural history and treatment. N Engl J Med 1997;336:1862.)

In this uncontrolled series, immunosuppressive therapy was associated with prolonged survival from 3 months in 30 patients not given immunosuppressive drugs and 3.8 months in patients treated with prednisone, to 11.5 months in patients given prednisone plus azathioprine and 12.6 months in patients who were given cyclosporine as part of their regimen. Prognosis after cardiac transplantation was also worse when compared with other forms of heart disease, with a 30-day mortality rate of 15% and a 26% mortality rate during the 3.7-year post-transplant follow-up period. Twenty-six percent of patients had giant cell infiltrates seen in their transplanted heart at an average time of 3 years after transplant.

EOSINOPHILIC MYOCARDITIS

Eosinophilic myocarditis, sometimes termed *hypersensitivity myocarditis*, is a rare form of myocarditis characterized by eosinophilic infiltration and degranulation seen on endomyocardial biopsy. It is believed that pathogenesis involves a direct role of eosinophil-mediated myocyte damage. There can be associated arteritis. This entity is distinct from eosinophilic endocarditis (Loffler's endocarditis). The clinical manifestations are not specific, aside from a high incidence of eosinophilia in peripheral blood. Patients usually present with heart failure due to left ventricular systolic dysfunction. Fever and rash may be present. Untreated, the disease is often rapidly fatal.

The cause is believed to be a hypersensitivity reaction, usually to medication or, rarely, in association with parasitic infections. Drugs most often implicated are sulfonamides, diuretics, angiotensin-converting enzyme (ACE) inhibitors, cephalosporins, digoxin, or dobutamine. Eosinophilic myocarditis has been reported to occur weeks after smallpox vaccination, with an incidence of 1 in 16,000 vaccinated.[12] The clinical course is unfavorable, often with rapidly worsening heart failure and sudden death due to ventricular arrhythmia. Treatment involves the discontinuation of all potentially offending medication and the use of high-dose corticosteroids. Excellent responses to corticosteroids, as well as some spontaneously resolving illness, have been reported.[13,14]

Eosinophilic myocardial infiltration has been reported in 2% to 7% of myocardial biopsy specimens of patients awaiting cardiac transplantation, or in the explanted heart after transplant. The cause is unclear, but dobutamine therapy, sodium bisulfite used as a preservative in dobutamine solutions, and the use of left ventricular assist devices have been implicated. The presence of eosinophilic myocarditis in this setting did not have an adverse affect on post-transplant survival and did not recur in the transplanted heart.[15,16]

RELATIONSHIP BETWEEN MYOCARDITIS AND IDIOPATHIC DILATED CARDIOMYOPATHY

There are many data from animal models indicating that acute myocarditis often leads to chronic idiopathic dilated cardiomyopathy. An important question in humans is the incidence of unrecognized antecedent myocarditis in patients who present with heart failure and idiopathic dilated cardiomyopathy. The frequency of myocarditis as the cause of dilated cardiomyopathy is unknown, and the importance of immune-mediated mechanisms in the pathogenesis of dilated cardiomyopathy also needs to be defined. Analysis of endomyocardial biopsy specimens from patients with chronic dilated cardiomyopathy shows evidence of viral signals in 50% of cases and the presence of viral genome in 35%, although this does not prove causation.[17] Circulating autoantibodies to myocyte proteins and myocyte surface receptors have also been described in patients with dilated cardiomyopathy,[6,18] although these have also been described in a small number of patients (5%) with ischemic cardiomyopathy. These antibodies thus may be a secondary phenomenon and do not necessarily indicate a primary pathogenic role of immune-mediated injury.

THERAPY

GENERAL MANAGEMENT OF HEART FAILURE

The treatment of myocarditis is based on the clinical presentation. Patients with mild disease can be treated expectantly, with dietary sodium restriction, and avoidance of strenuous exercise for several weeks or months.[2] Animal models indicate that strenuous exercise can worsen myocarditis. Elimination of unnecessary medications is important in patients with eosinophilia.

Nonsteroidal anti-inflammatory drugs should be avoided because they may worsen myocarditis.[3] The routine use of anticoagulants for prophylaxis of systemic emboli is controversial. Patients who present with symptoms of arrhythmia or heart failure should be hospitalized, with continuous cardiac rhythm monitoring performed for evaluation of possible serious or life-threatening arrhythmias or conduction abnormalities. If these are diagnosed, they are treated in a similar matter as in patients with other causes of heart disease, utilizing antiarrhythmic drugs or pacemakers. However, patients should be observed over a period of time to see whether improvement or resolution of the disease takes place prior to implantation of the implantable cardiac defibrillator.

There are no controlled trials in humans that have evaluated standard heart failure medications in patients with myocarditis. However, there are data in murine models of myocarditis supporting the use of captopril,[2] and there are many data in humans supporting the use of ACE inhibitors, beta-blockers, and aldosterone antagonists in patients with dilated cardiomyopathy. Therefore, in patients with myocarditis and heart failure, the use of standard multidrug medical therapy for heart failure and left ventricular systolic dysfunction is indicated.[2,6] These medications have been shown to improve symptoms, prolong life, and regress the adverse left ventricular remodeling that occurs in patients with dilated cardiomyopathy of various causes.[19-21]

Administration of ACE inhibitors should be initiated in all patients with left ventricular systolic dysfunction. Treatment should begin at low doses, with upward titration to maximally tolerated doses. Patients should be closely monitored for potential side effects, including renal insufficiency, hyperkalemia, and angioedema. Relative contraindications to the use of ACE inhibitors include renal failure, hyperkalemia, bilateral renal artery stenosis, and hepatic failure. Patients with hypotension should be treated with parenteral vasopressors or circulatory assist devices prior to initiation of low-dose ACE inhibitor therapy.

Beta-adrenergic blockers have not been studied in humans with myocarditis, and their effects in the murine model have been mixed.[2] Nevertheless, beta-blocker therapy in large series of patients, which included patients with idiopathic dilated cardiomyopathy, have unequivocally shown

benefit in patients with left ventricular systolic dysfunction,[22-26] and these agents should also be used in patients with heart failure due to myocarditis. Beta-blockers should be initiated after patients are on a stable dose of ACE inhibitors and when signs of fluid overload have resolved. Contraindications to beta-blocker therapy include bronchospastic disease or severe chronic obstructive lung disease, heart block, or significant underlying bradycardia. Hypotension should be corrected prior to initiating beta-blocker therapy.

Digoxin has been shown in animal models to decrease levels of cytokines, but digoxin was associated with adverse outcomes in one murine model of myocarditis. Digoxin can be useful in helping to control ventricular rates in patients with atrial fibrillation. The use of digoxin should be considered in patients with significant left ventricular systolic dysfunction, after ACE inhibitors and beta-blockers have been initiated. However, no survival benefit for digoxin has ever been shown in patients with heart failure due to dilated cardiomyopathy.[27] Contraindications to the use of digoxin include renal failure or heart block.

Lastly, the use of the aldosterone antagonist spironolactone has been shown to have symptomatic and survival benefit in patients with class III-IV systolic heart failure.[28] In experimental models, these agents can reverse the progressive myocardial fibrosis that occurs in the remodeling process of dilated cardiomyopathy. These agents have not been studied in patients with myocarditis, but their use should be strongly considered in patients with severe left ventricular dysfunction (ejection fraction less then 35%) and symptomatic heart failure.[2] Contraindications to the use of aldosterone antagonists include renal insufficiency, with serum creatinine levels above 2.0 mg%, or hyperkalemia. Serum potassium levels needs to be carefully monitored during initiation and dose titration.

In critically ill patients with severe heart failure and low cardiac index, parenteral vasodilators should be used. Intravenous nitroprusside is a powerful venous and arterial dilator, which significantly reduces systemic vascular resistance, mean systemic arterial pressure, and pulmonary capillary wedge pressure, raising cardiac index. It must be administered in the ICU with invasive hemodynamic monitoring with a pulmonary artery catheter, to best gauge the appropriate dose of medication and to accurately assess response to therapy. Prolonged use of nitroprusside is associated with accumulation of the toxic metabolites thiocyanate and cyanide, and serum levels of these compounds must be monitored. Intravenous nitroglycerin is also an effective venodilator and coronary vasodilator, with less arterial dilating property than nitroprusside. The use of nitroglycerin in cases of myocarditis has not been studied. Patients often develop tolerance to this drug.[29-31]

Nesiritide (B-natriuretic peptide) is a hormone produced by myocardial ventricular and atrial myocytes in response to stretch from chamber dilatation. It is a counter-regulatory peptide to the renin-angiotensin hormones, causing venous and arterial dilation, natriuresis, and diuresis.

These hemodynamic effects are favorable in patients with severe heart failure, and intravenous infusions of nesiritide are being used more widely in patients with severe heart failure due to left ventricular systolic dysfunction. Reduction in pulmonary capillary wedge pressure occurs more rapidly than with intravenous nitroglycerin. Nesiritide is not proarrhythmic, does not have toxic metabolites, and does not induce tolerance. Nesiritide use can cause significant hypotension in some patients.[32-35]

Patients with severe myocarditis may develop cardiogenic shock, with hypotension, respiratory failure, and signs of end organ hypoperfusion. In these instances, initial treatment with inotropic agents or vasopressors is indicated. Dobutamine is a potent $beta_1$-agonist with less $beta_2$- and alpha-agonist properties. Dobutamine has favorable short-term hemodynamic effects with increased myocardial contractility and reduced systemic vascular resistance and reduced pulmonary capillary wedge pressure. However, dobutamine can be proarrhythmic, and patients can develop tolerance to the drug. In studies utilizing routine use of dobutamine in patients with exacerbations of chronic systolic heart failure, the use of this drug was associated with increased mortality rates when compared with placebo.[36]

Milrinone is another parenteral inotropic agent, which works by inhibiting phosphodiesterase. This drug leads to increased inotropy and decreased systemic vascular resistance and pulmonary capillary wedge pressure, with resultant increased stroke volume and cardiac index. Milrinone may cause hypotension. It is less proarrhythmic than dobutamine and it does not induce tolerance.[37,38]

Arterial vasoconstrictors such as norepinephrine and dopamine can be used in patients with refractory hypotension for short-term urgent blood pressure support. However, these agents cause increased myocardial oxygen consumption and can have deleterious effects on myocardial function.

In patients with fulminant myocarditis or cardiogenic shock, the use of mechanical ventricular assist devices should be strongly considered. These devices offer hemodynamic support and left ventricular afterload reduction and may provide time for spontaneous improvement or recovery of normal left ventricular function. Ventricular assist devices (VADs) are mechanical pumps that take over the function of the failing ventricle, providing normal cardiac output. VADs are usually univentricular but can be biventricular, supporting both right and left ventricular function. They have been inserted via a midline sternotomy, with the inflow conduit to the pump inserted via the left ventricular apex. With improved technology, these devices are being made smaller and are being implanted through smaller incisions. A VAD is now available that can be inserted percutaneously. VADs are connected to an external power pack via a driveline through the skin. The power pack is now small enough so that it can be portable, and thus patients have freedom of movement and can participate in rehabilitation efforts during VAD use. Current devices have textured blood-contacting surfaces so routine anticoagulation therapy is not required. Complications of VADs include local site infection, sepsis, thromboemboli, right ventricular failure, and device failure.[39,40]

In patients with myocarditis, VADs can be used to provide circulatory needs and improve coronary flow during the time necessary for spontaneous resolution of myocarditis to occur. Beneficial reverse remodeling may occur while patients are on VAD support, resulting in improved myocyte structure and function. VADs can provide support for months or even years.

A retrospective study of 22 patients with nonischemic cardiomyopathy who were successfully weaned from left ventricular or biventricular assist devices was analyzed.[41] Patients had either myocarditis or acute onset of idiopathic dilated cardiomyopathy. The average age of patients was 32 years, and the average duration of VAD support was 57 days (range, 12-190 days). Twenty of 22 patients were discharged alive with their native heart, at an average of 22 days

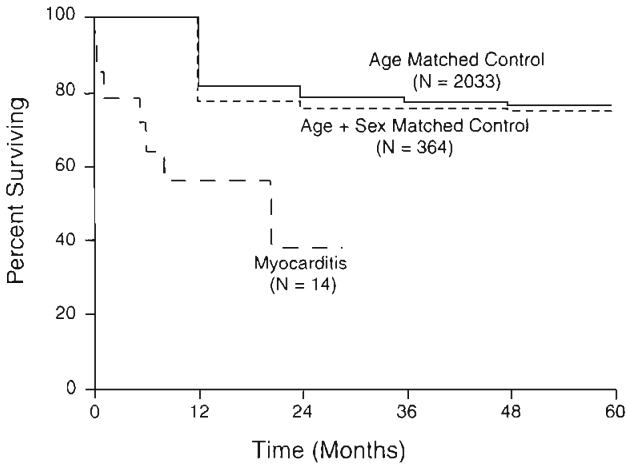

FIGURE 100–3. Graph showing the actuarial survival duration of heart transplant recipients with active lymphocytic myocarditis as compared with that of age-matched (—) and age- and sex-matched (- - -) control patients. (From Haas G: Etiology, evaluation, and management of acute myocarditis. Cardiol Rev 2001;9:88-95.)

after VAD removal. Two patients received cardiac transplants 1 year after VAD removal. Seventeen of the 22 patients remained alive and well with their native hearts at an average of 3.2 years after VAD removal. Sixteen patients were functional class I, and one was functional class II. Thus, the survival of native hearts in this series after being weaned successfully from VAD support was 86% at 1 year and was 77% at 5 years. This survival rate was indistinguishable from the survival rate of patients who received cardiac transplantation after a period of VAD support. These authors thus felt that patients with fulminant myocarditis should be given every opportunity to recover ventricular function, and that cardiac transplantation should be used only as a last resort, when severe heart damage is irreversible.[41]

There are several unresolved issues regarding VAD usage in patients with myocarditis. These include appropriate patient selection, timing of VAD placement, best medical therapy during VAD support, and optimal duration of VAD support. A 50-day course of VAD support in the above study allowed identification of 50% of those patients who ultimately recovered, and a 90-day course identified 80% of patients who recovered. The optimal means of serial assessment of native heart function while on VAD support needs to be delineated, and the best weaning protocol also needs definition.

Cardiac transplantation is the final option for treating critically ill patients with myocarditis. However, these patients have a higher rate of transplant rejection, and a lower survival rate when compared with patients transplanted for ischemic or other causes of cardiomyopathy. Myocarditis has been reported to recur in the transplanted heart (Fig. 100-3).[6]

IMMUNOSUPPRESSIVE THERAPY

Autoimmune mechanisms are believed to be responsible for the clinical manifestations of myocarditis and the development of myocardial necrosis and left ventricular dysfunction. Therefore, therapy with immunosuppressive drugs has been used. However, given the high rate of spontaneous recovery of left ventricular function (up to 40% of patients in some series), placebo-controlled trials are essential to properly evaluate the effects of therapy. In addition, heterogeneous patient populations, consisting of cases of both acute myocarditis and chronic dilated cardiomyopathy, have made it difficult to design effective immunosuppressive regimens.

High-dose daily prednisone therapy was used for a 3-month course in 102 patients with dilated cardiomyopathy, 59% of whom were classified as having "reactive" myocarditis on endomyocardial biopsy.[42] The authors found a significant improvement in left ventricular ejection fraction at 3 months in treated patients with reactive myocarditis (Fig. 100-4), but this improvement was not sustained at 9 months. Improvement did not occur in patients with nonreactive

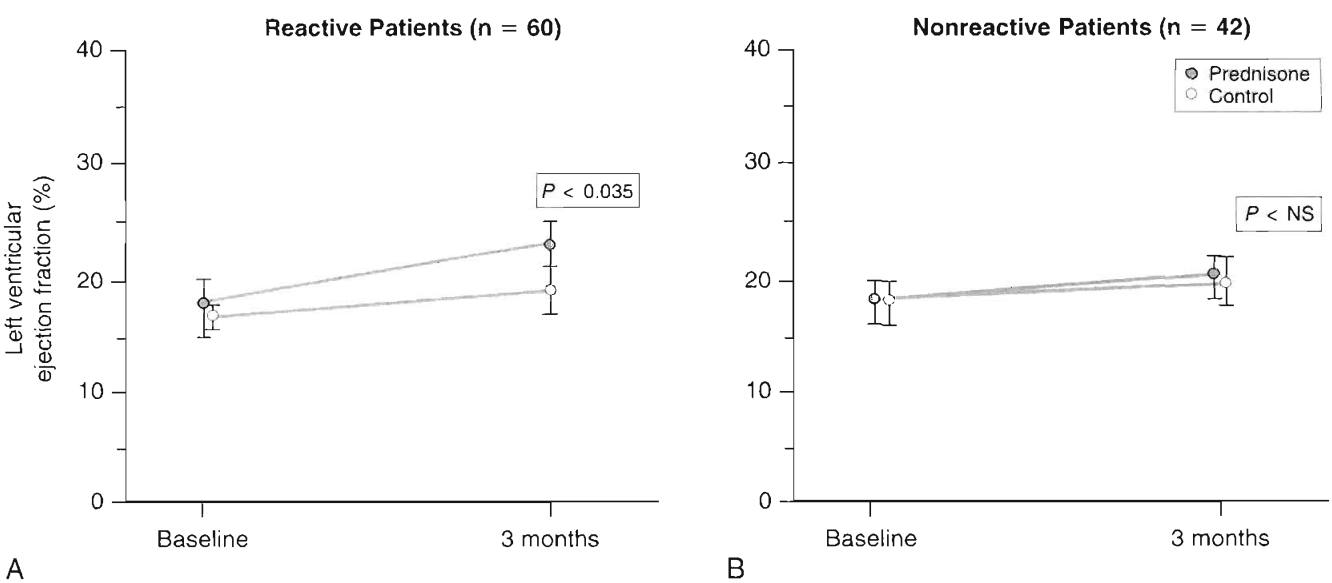

FIGURE 100–4. (*A*) Ejection fraction in reactive dilated cardiomyopathy patients at 3 months. (*B*) Prednisone does not change ejection fraction in nonreactive patients in 3 months. (From Parrillo J, Cunnion R, Epstein S, et al: A prospective, randomized, controlled trial of prednisone for dilated cardiomyopathy. N Engl J Med 1989;321:1061-1068.)

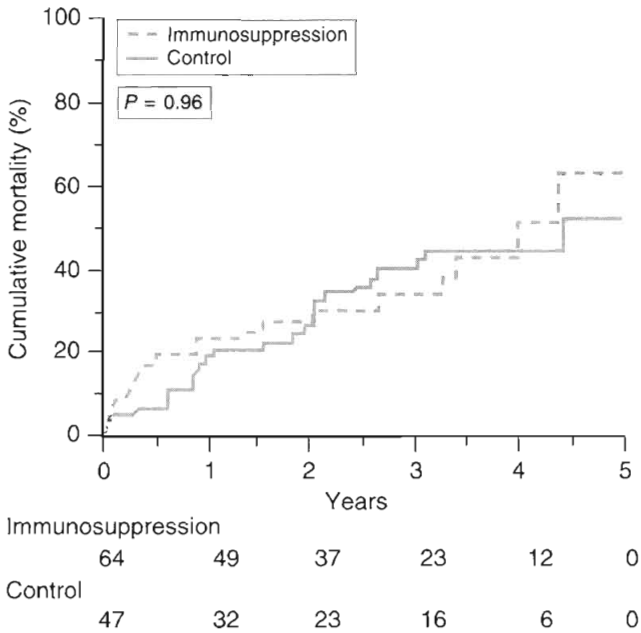

FIGURE 100–5. Actuarial mortality (defined as deaths and cardiac transplantations) in the immunosuppression and control groups. The numbers of patients at risk are shown at the bottom. There was no significant difference in mortality between the two groups. (From Mason J, O'Connell J, Herskowitz A, et al, for The Myocarditis Treatment Trial Investigators: A clinical trial of immunosuppressive therapy for myocarditis. N Engl J Med 1995;333:269-275.)

biopsies treated with prednisone. No significant mortality benefit from immunosuppressive treatment was noted, although this was not a prespecified primary endpoint.

The Myocarditis Treatment Trial enrolled 111 patients with a positive endomyocardial biopsy finding and left ventricular ejection fraction less than 45%, with a duration of illness of less than 2 years.[43] Three treatment groups were compared: daily prednisone plus azathioprine, prednisone plus cyclosporine, and placebo. Overall, these patients had a 20% 1-year mortality rate and 56% 3-year mortality rate. These investigators found no difference in ejection fraction at week 28 or week 52, no change in left ventricular size at week 28, and no difference in 1-year mortality between treated and untreated groups. Their conclusion was that these immunosuppressive strategies were not beneficial. Significant limitations of this study include a 30% dropout rate and significant intraobserver variability among pathologists' diagnoses of biopsy specimens despite utilizing the Dallas criteria (Fig. 100-5).

In view of the limitations of histopathologic diagnosis using the Dallas criteria, another group of investigators utilized immunohistologic markers of inflammation, such as up-regulation of HLA, to diagnose active myocarditis as an indication for immunosuppressive therapy.[44] This criterion has the advantage of indicating that autoimmunity is playing a role in pathogenesis. Also, since HLA is distributed throughout the entire myocardium, biopsy sampling error is eliminated as a confounding variable in assessing response to therapy. In this study, 84 of 202 patients with chronic (>6 months) idiopathic dilated cardiomyopathy (ejection fraction <40%) were found to have strong expression of HLA in biopsy specimens and were randomized to receive placebo or prednisone plus azathioprine for 3 months. At 3 months' follow-up, a significant improvement in the prespecified secondary endpoints of left ventricular ejection fraction, left ventricular volumes, and functional capacity was seen in the treated group, and this improvement was maintained at 2 years (71.8% improvement in the treated group vs. 30.8% in the untreated group). However, there was no improvement in the prespecified composite primary endpoint of death, cardiac transplant, or hospital readmission. This study was limited by a 31% dropout rate.

In another study, patients with positive endomyocardial biopsy specimens and progressive heart failure who responded to 6 months of therapy with prednisone and azathioprine were more likely to have circulating cardiac autoantibodies and no viral genome in their myocardium as compared with nonresponders.[45]

Studies have suggested that in patients with heart failure and low ejection fraction, intravenous immunoglobulin has a pronounced anti-inflammatory effect as measured by circulating levels of inflammatory markers.[46] Uncontrolled studies suggested benefit in patients with myocarditis from treatment with intravenous immunoglobulin.[47,48] However, a placebo-controlled double-blind trial of intravenous immunoglobulin in patients with myocarditis or idiopathic dilated cardiomyopathy of less than 6 months' duration showed no significant improvement with therapy as assessed by ejection fraction or functional capacity at 6 and 12 months.[49] In this study, average left ventricular ejection fraction improved from 25 ± 8% at baseline to 41 ± 17% at 6 months in both treated and untreated groups. One-year event-free survival rate was 91.9% in both groups. Another study suggested benefit with intravenous immunoglobulin as measured by improvement in ejection fraction in patients with chronic cardiomyopathy of greater than 6 months' duration.[46]

In summary, there is no evidence that patients with lymphocytic myocarditis or idiopathic dilated cardiomyopathy benefit from the routine use of immunosuppressive therapy. However, this treatment approach should be considered in patients with myocarditis and positive endomyocardial biopsy findings, those who develop early signs of severe heart failure, and those who are shown to experience progressive worsening of left ventricular function. In patients with idiopathic dilated cardiomyopathy who show worsening left ventricular function on weekly or monthly follow-up, immunosuppressive therapy should be strongly considered.[50] Lastly, immunosuppressive therapy should be used in patients with myocarditis associated with connective tissue diseases, eosinophilic or granulomatous forms of the disease, or giant cell myocarditis (Fig. 100-6).

Current investigations are evaluating antiviral therapies in the acute stage of myocarditis as well as the use of antiviral vaccine in the prevention of disease. Appropriately powered, controlled, prospective studies of homogeneous patient groups utilizing immunosuppressive therapy are still needed. Evaluating the mechanisms of myocardial recovery during VAD support may also help direct research toward other novel approaches to the treatment of myocarditis.

SUMMARY

Among many diverse causes, the most common cause of myocarditis is believed to be viral, with autoimmune mechanisms prominently involved in pathogenesis. Patients with myocarditis can present with acute chest pain, mimicking acute ischemic heart disease or other cardiopulmonary

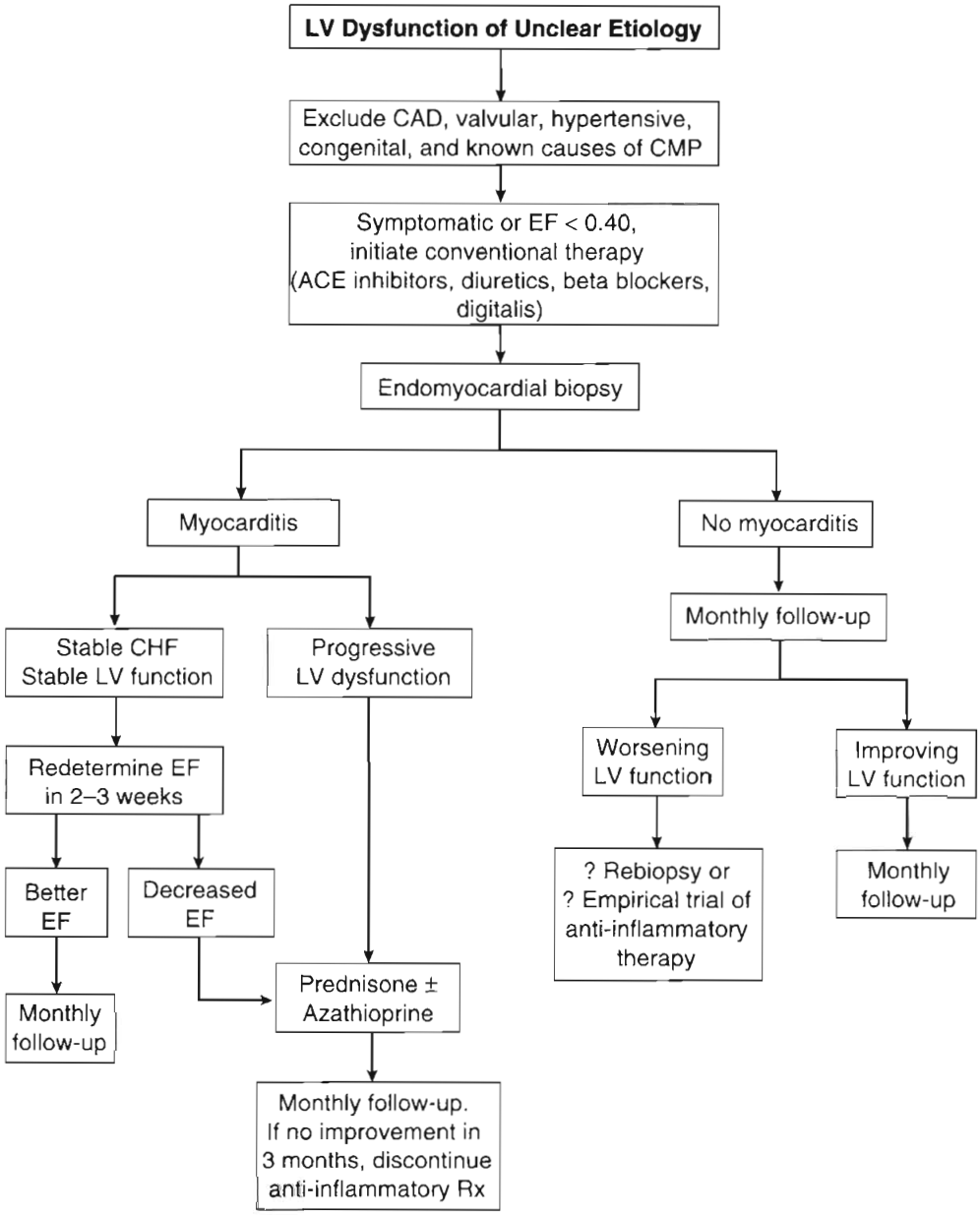

FIGURE 100–6. Algorithm describing a reasonable approach to myocarditis management based on currently available data. ACE, angiotensin-converting enzyme; CAD, coronary artery disease; CHF, congestive heart failure; CMP, cardiomyopathy; EF, ejection fraction; LV, left ventricular. (From Parrillo J: Myocarditis: How should we treat in 1998? J Heart Lung Transplant 1998;17:941-944.)

illnesses, or can present with heart failure due to dilated cardiomyopathy. A smaller percentage of patients present with acute heart failure due to severe left ventricular systolic dysfunction. Oral and parenteral pharmacological therapies that are used in patients with heart failure of the more common causes are also used in these patients. Patients can also present with fulminant myocarditis, characterized by severe heart failure and cardiogenic shock. These patients need intensive, aggressive pharmacological therapy as well as support with VADs, because they very often show significant improvement in left ventricular function so that pharmacological and VAD support can be weaned and discontinued, without having to resort to cardiac transplantation.

Endomyocardial biopsy is used in the diagnosis of myocarditis and for directing therapy, although it is limited by sampling error and by current histopathologic techniques for assessing disease activity. Newer immunohistologic methods may better define those patients who will respond to immunosuppressive therapy. Patients with myocarditis and progressive myocardial failure, despite conventional heart failure therapy, should be considered for immunosuppressive therapy on a case-by-case basis. Such patients should be followed with serial measures of left ventricular performance and endomyocardial biopsies.

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Chapter 101

ACQUIRED AND CONGENITAL HEART DISEASE IN CHILDREN

Duncan J. Macrae

KEY POINTS

1. The immature myocardium has little functional reserve, tolerating both increased preload and afterload poorly.
2. Cardiac output in the neonate is critically dependent on heart rate.
3. A hyperoxic test will usually differentiate cyanosis resulting from intracardiac shunting of deoxygenated blood and that from intrapulmonary ventilation-perfusion mismatch.
4. Manipulation of the pulmonary circulation, especially pulmonary vascular resistance, and the function of the subpulmonary ("right") ventricle are critical to understanding and managing many congenital heart lesions.
5. Mechanical circulatory support is effective in "bridging" many children with severe heart failure to recovery or cardiac transplantation.
6. In the era of mechanical circulatory support, acute fulminant myocarditis in children should be regarded as a condition from which a child can recover.
7. Appropriate intensive care management of the child with congenital heart disease must be based on a sound understanding of the anatomy and pathophysiology of the child's circulation.
8. Issues relating to the management of intracardiac shunts, cyanosis, and the pulmonary circulation and right ventricle are commonly of great importance in the child with congenital heart disease.
9. A specialist's advice should be sought early if children with known or suspected heart disease are admitted to nonspecialist pediatric or adult facilities.

PHYSIOLOGY

CIRCULATORY CHANGES AT BIRTH

During the transition from intrauterine to extrauterine life, major circulatory changes occur that have important implications for the clinical care of the newborn.[1,2] At birth in the normal newborn, the low-resistance placenta is eliminated from the circulation, resulting in an immediate increase in systemic vascular resistance (SVR), and the pulmonary vascular resistance (PVR) falls when the lungs become responsible for gas exchange. The fetal channels, the foramen ovale, and the arterial duct become redundant and close. In addition to the altered hemodynamics in infants born with congenital heart disease, some infants with structurally normal hearts have a persistent right-to-left shunt after birth owing to failure of the transition from fetal to postnatal circulation. Infants with this circulatory pattern, which is characterized by failure of the PVR to fall, have persistent pulmonary hypertension of the newborn (PPHN).[3] PPHN is one of the two principal causes of "nonpulmonary" cyanosis in the neonate, the other being cyanotic congenital heart disease.

The right ventricle (RV) and left ventricle (LV) contribute equally to fetal cardiac output. At birth, the LV becomes responsible for the systemic circulation, characterized by its high vascular resistance. The PVR falls suddenly at birth to approximately 50% of fetal levels to facilitate the required increase in pulmonary blood flow. It continues to fall to adult values during the first 6 to 8 weeks of life as the smooth muscle layer in the media of the pulmonary arterioles progressively thins out. The LV progressively adapts to its "high pressure" role by rapid myocardial growth, in contrast to the RV, which regresses to its "low pressure" subpulmonary role. The presence of congenital heart defects can profoundly alter these adaptive processes.

PHYSIOLOGY OF THE NEONATAL MYOCARDIUM

The neonatal myocardium is functionally immature. Age-dependent changes in intrinsic function and integration with a maturing circulation determine its response to insults such as hypoxia and ischemia.[4,5]

The myocardium matures in the postnatal period by increasing the number and the volume and conformation of its myocytes. The cell membrane (sarcolemma) develops the T tubular system, which facilitates rapid conduction of the action potential to the center of the cell, and the arrangement of myofibrils gradually becomes more uniform, improving its contractile function. In parallel with these structural changes, myocellular metabolism matures. Proper contractile function of the cardiac myocyte depends on an efficient excitation-contraction process, which is activated by the binding of calcium to troponin C. In the adult heart, calcium release from the sarcoplasmic reticulum (SR) is the predominant

TABLE 101–1. CHARACTERISTICS OF THE NEONATAL VENTRICLE

	Comparison to Mature Ventricle
Contractility	Contractility of the neonatal ventricle is reduced compared with the mature ventricle.
Compliance	Neonatal ventricle is inherently noncompliant compared with mature ventricle.
Augmentation Cardiac Output	There is little stoke volume reserve due to low compliance. Therefore, cardiac output is highly heart rate dependent in neonates.
Afterload	Neonatal ventricle tolerates increased afterload poorly.
Energy Substrate	Lactate is primary substrate of neonatal ventricle under aerobic conditions. Glucose is metabolized under anaerobic conditions. By 1 to 2 years there is changeover to primary "adult" substrate, free fatty acids.

source of calcium for troponin C activation whereas, in contrast, in the neonate, activation relies substantially on calcium influx through the "L"-type calcium channels. Optimal function of the neonatal myocardium is therefore exquisitely dependent on maintenance of normal extracellular calcium concentrations. Other elements of myocyte function are age dependent, such as the sarcoplasmic reticulum calcium/adenosine triphosphatase (SERCA), which is present in reduced quantities in the immature heart. This results in relatively inefficient calcium reuptake and therefore slower diastolic relaxation of the neonatal compared with the adult myocyte and is at least in part responsible for the prominence of diastolic dysfunction in the failing neonatal myocardium.

Healthy infants have higher plasma concentrations of catecholamines and higher density cardiac sympathetic innervation than older children and adults. This may partly explain the reduced ability of neonates to increase cardiac output in response to endogenous or exogenous catecholamines. Children in heart failure also have higher plasma catecholamine concentrations[6] but reduced densities of beta-adrenergic receptors compared with age-matched controls.[7] The effects of this are similar to those seen with exogenous agonist-induced desensitization. Children with severe heart failure show evidence of uncoupling of $beta_1$-adrenergic receptors from the enzyme adenyl cyclase[7] and other maladaptive responses, which result in reduced response to receptor agonists. In addition to heart failure, chronic hypoxia such as is seen in cyanotic congenital heart disease induces activation of the sympathetic nervous system with resultant adrenergic receptor desensitization. Developmental aspects of myocardial support have been reviewed.[8] The clinical characteristics of the neonatal ventricle are presented in Table 101-1.

CONGESTIVE HEART FAILURE

Although the basic pathophysiologic mechanisms of heart failure have age-independent common mechanisms, the presentation and management of heart failure changes with age. The overwhelming cause of heart failure in the first year of life is congenital heart disease, usually with an intracardiac left-to-right shunt or a ventricular obstructive lesion (Table 101-2). By contrast, the primary abnormality in adult heart failure is usually LV dysfunction. Heart failure in adults is often gradual in onset; the neonate has little functional reserve, resulting in rapid decompensation and an emergent presentation.

The clinical findings[9] in an infant with heart failure are listed in Table 101-3. A prominent sign of cardiac failure in infancy is difficulty in feeding secondary to increased respiratory rate and effort. This equates to exertional dyspnea in the older child or adult. Failure to thrive results in the classic "wizened" appearance. Although hepatomegaly is a common sign of heart failure in infants (resulting from an increase in total circulating volume and hepatic venous congestion), peripheral edema, ascites, and pericardial or pleural effusions are much less commonly seen than in adults. One relatively common feature of severe heart failure in infancy is the occurrence of compression of the bronchial tree, particularly the left mainstem or lower lobe bronchus as a result of extrinsic compression by an enlarged left atrium or pulmonary artery. This can cause airway obstruction and associated lobar collapse or localized hyperinflation as a result of distal air trapping. Long-standing extrinsic compression may rarely cause tracheobronchomalacia, resulting in long-term respiratory difficulties even after resolution of heart failure.

CYANOSIS

Cyanosis is the visible manifestation of greater than 5 g/dL of reduced deoxygenated hemoglobin in cutaneous blood vessels and is a prominent feature in many types of congenital heart disease. *Peripheral cyanosis* results from high oxygen extraction ratios across the tissue vascular bed reflecting low tissue blood flow or high tissue oxygen demand. *Central cyanosis* results from desaturation of arterial blood, which may be

TABLE 101–2. COMMON CAUSES OF HEART FAILURE IN CHILDHOOD

Neonate < 2 Weeks of Age	Neonate > 2 Weeks of Age, Infant	Older Child
Congenital heart disease	Congenital heart disease	Congenital heart disease
Left-sided obstructive lesions	Left-to-right shunt lesions	Any lesion
Critical aortic stenosis	Ventriculoseptal defect	Following surgery
Aortic coarctation	Atrioventriculoseptal defect	Late deterioration of ventricle in palliated circulations
Hypoplastic left heart syndrome	Truncus arteriosus	Acquired heart disease
Arrhythmias	Total anomalous pulmonary venous drainage	Cardiomyopathies (idiopathic or specific)
Incessant supraventricular tachycardia		Myocarditis
"Congenital" myocarditis		Rheumatic fever
Severe ventricular dysfunction due to birth asphyxia, sepsis, or severe metabolic disorders		Infective endocarditis
		Arrhythmias
		Severe anemia
		Nutritional deficiencies

TABLE 101–3. CLINICAL FEATURES OF HEART FAILURE IN INFANTS

Respiratory signs
Initially tachypnea
Dyspnea manifesting as poor feeding
Later signs: retractions, intercostal recession, nasal flaring
Pulmonary wheeze/rales
Tachycardia—little variability even at rest
Gallop rhythm
Hepatomegaly
Cardiomegaly
Poor peripheral perfusion—in severe failure "ashen" appearance

due to pulmonary disease or to right-to-left shunting of deoxygenated systemic venous blood in association with a congenital heart defect. The "pulmonary" and "cardiac" causes of central cyanosis can usually be differentiated by allowing the child to breathe 100% oxygen (a "hyperoxic test"). During administration of 100% oxygen, a PaO_2 above 160 mm Hg is highly suggestive of a noncardiac diagnosis and a PaO_2 of greater than 250 mm Hg excludes it. Occasionally, *differential cyanosis* is seen in which one or both of the upper limbs are normally saturated and the lower limbs cyanosed. This is caused by deoxygenated blood traversing the arterial duct to enter the aorta distal to the origin of one or both subclavian arteries and supplying the lower limbs while oxygenated blood from the LV predominantly supplies the upper limbs.

Chronic hypoxemia induces the twin physiologic responses of erythropoiesis, resulting in polycythemia and an increase in blood volume in a compensatory attempt to maintain oxygen-carrying capacity. However, as hemoglobin concentrations rise, blood viscosity increases and ultimately leads to sluggish flow in the peripheral circulation, cellular aggregation, and the occurrence of thrombotic lesions. Polycythemic patients are at high risk of thrombotic complications in situations of increased fluid loss (e.g., intercurrent diarrheal illness) or inadequate fluid intake (e.g., preoperative fasting). In addition to polycythemia, most children with chronic cyanosis develop finger clubbing, the result of an increased number of capillaries laid down in the vascular beds of the fingers and toes. Rare but important complications of severe cyanosis include cerebral and pulmonary thrombosis and cerebral abscess.

PULMONARY HYPERTENSION

The pulmonary vascular bed is of central importance to the manifestations of congenital heart disease from the first hours of life.[10] PVR usually falls dramatically in response to aeration of the lungs with first breaths. Thereafter, the smooth muscle of the pulmonary vascular bed thins gradually during the first months of life, with associated fall in PVR to "adult" values by approximately age 2 months. In infants with congenital heart lesions where an intracardiac communication between the systemic and pulmonary circulations is present, such as a ventricular septal defect (VSD), the fall in PVR encourages flow into the low-resistance pulmonary vascular bed and a left-to-right shunt develops. In response to the increased flow and subsequent shear stress this induces, progressive structural changes occur in the pulmonary arteries and arterioles. Initially, these changes consist of accelerated extension of muscle to the distal nonmuscular pulmonary arteries and medial muscular hypertrophy in the proximal muscular arteries. Later changes involve gradual hypertrophy of the arterial intima with deposition of collagen and elastin leading to gradual luminal obstruction and eventual occlusion. Associated with this is the development of plexiform lesions, the histologic hallmark of pulmonary vascular disease. Mild pulmonary vascular changes are of little significance to the cardiac intensivist, but children with more extensive medial muscular hypertrophy of the pulmonary arteries are at risk of labile pulmonary hypertension in the postoperative period. The extent of pulmonary hypertensive changes frequently determines the feasibility of surgical options. Children with established fixed high PVR are not suitable for corrective surgery, because surgical separation of the two circulations in the presence of fixed high PVR will result in immediate RV failure. Smaller elevation in PVR determines operability in the single-ventricle "Fontan" circulation (see later). Calculation of PVR and the response to varying vasodilators can be achieved following a pulmonary reversibility study in the cardiac catheter laboratory.[11]

CIRCULATORY SUPPORT IN CHILDREN

Children presenting with low cardiac output[12] must initially be assessed and managed according to standard resuscitation algorithms. These require that adequate oxygenation and circulating volume be achieved. If cardiac output remains low, cardiovascular drug therapy is usually indicated. The developmental differences noted earlier serve to emphasize the need to adopt age-appropriate pharmacologic strategies when supporting the failing myocardium of the neonate and infant. If cardiac output remains low despite application of such measures, mechanical circulatory support should be considered (Fig. 101-1).

PHARMACOLOGIC SUPPORT

Beta-adrenergic Agonists

Clinical and experimental studies have demonstrated marked age-related differences in the hemodynamic response to inotropic therapy. Although some of the observed differences may be accounted for by differences in drug pharmacokinetics, the variable maturation of the sympathetic nervous system, its receptors, and the cardiac myocytes militate against the recommendation of narrow, specific dose ranges for the use of catecholamines in neonates and children.[8]

In clinical practice, adrenergic agonists are used in a similar manner in children as in adults, that is, titrated to hemodynamic effect (Table 101-4). When systolic ventricular function is impaired, dopamine and dobutamine are commonly used as "first line" inotropes. Additional agents should be administered according to assessment of response judged clinically and from available hemodynamic monitoring. Epinephrine is occasionally useful when more potent inotropic stimulation is required. Norepinephrine or vasopressin can be used if refractory vasodilatation is present, such as occurs rarely after cardiopulmonary bypass (CPB) in children.[13] Isoproterenol is a nonspecific beta-adrenergic agonist whose principal cardiovascular effects are vasodilatation and increasing heart rate effects. The drug is rarely used in intensive care. Caution is needed when higher-dose catecholamine support is used in the neonate, because at high doses the agents induce a rise

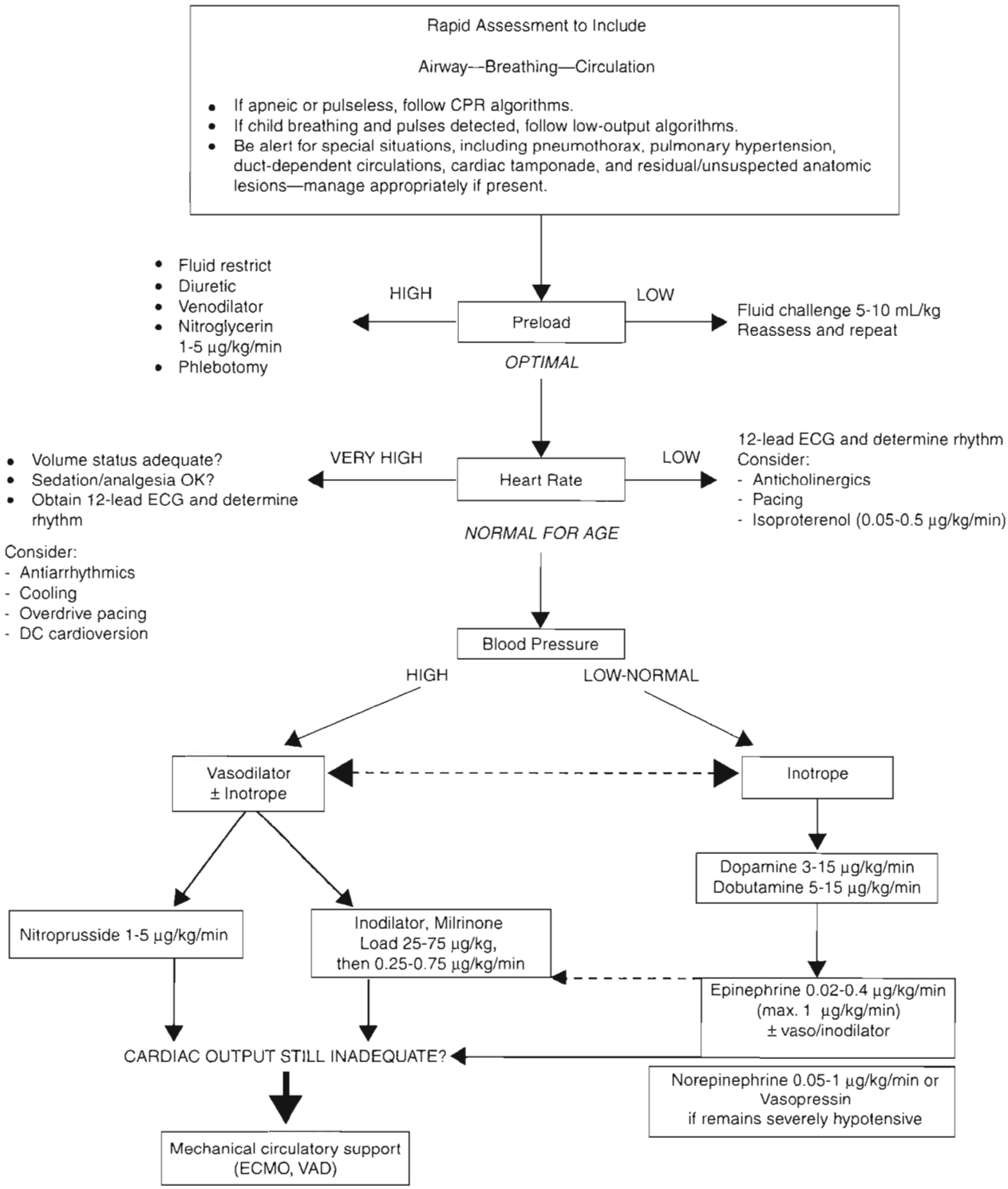

FIGURE 101–1. Guidelines for the management of low cardiac output in children.

in ventricular end-diastolic pressure in a ventricle that is already "developmentally" noncompliant. Catecholamine-induced myocardial necrosis has been identified in neonatal animal models.[14,15]

Phosphodiesterase (PDE) inhibitors have emerged as important agents in the management of neonates and children with cardiac failure. The cardiovascular actions of the clinically available PDE type III inhibitors amrinone,[16] milrinone,[17] and enoximone are similar (Table 101-5). By inhibiting breakdown of cyclic adenosine monophosphate (AMP), intracellular calcium accumulation is promoted and augments the contractile state of the myocyte. In addition, the reuptake of calcium, which is a cyclic AMP–dependent process, is also augmented and these agents may therefore enhance diastolic relaxation, a particularly important aspect of neonatal cardiac function. In one multicenter randomized-controlled study of neonates and young children after cardiac surgery, the prophylactic administration of milrinone

TABLE 101–4. VASOACTIVE AGENTS IN CHILDREN: ADRENERGIC AGONISTS

Agent	Intravenous Dose Range	Alpha 1	Beta 1	Beta 2	Dopa	Comments
Dopamine	1-5 μg/kg/min	0	+/++		++	Beta-mediated inotropic effects
	5-15 μg/kg/min	0/++	++		++	at lower doses; alpha-mediated vasoconstriction at higher doses
Dobutamine	2-15 μg/kg/min	0	+/+++	0/++	0	
Epinephrine	0.02-0.1 μg/kg/min	0 /++	++/+++	++/+++	0	$Beta_2$ effect prominent at lower
	0.2-0.4 μg/kg/min	++/+++	++++	+++	0	doses; alpha constrictor effects at higher doses
Norepinephrine	0.2-0.5 μg/kg/min	++ /++++	+	0	0	Increases systemic vascular resistance. Reserved for treatment of severe hypotension associated with vasodilatation.
Isoproterenol	0.02-0.4 μg/kg/min	0	++++	++++	0	Prominent chronotropic activity. Beta 2 effects cause vasodilatation.

resulted in a lower incidence of low cardiac output.[18] Clinical studies in infants and children have demonstrated a synergistic effect when $beta_1$ agonists and PDE inhibitors such as amrinone, milrinone, or enoximone are co-administered, and this effect may be greater in neonates than in adults. In clinical use, the vasodilating action of the PDE III inhibitors is prominent, a useful property given the usual pattern low cardiac output associated with rising SVR and PVR that has been well documented in young patients after cardiac surgery.[19]

Systemic vasodilators are indicated in situations in which lowering SVR will reduce LV afterload and improve cardiac output. This is especially so in the neonatal setting, where elevation of the SVR is poorly tolerated by the myocardium. Vasodilators are also employed in the management of systemic hypertension as occurs in children after repair of aortic coarctation or other left-sided obstructive lesions. Vasodilators have variable effects on preload through concomitant venodilatation, the manifestations of which are dependent on the position the resultant end-diastolic pressure occupies on the

TABLE 101–5. VASOACTIVE AGENTS IN CHILDREN: CARDIOVASCULAR DRUGS OTHER THAN ADRENERGIC AGONISTS

	Dosage	Effects
PDE Type III Inhibitors		
Amrinone	*Neonates:* 4 mg/kg over 1 hour then 3-5 μg/kg/min i.v.	Cardiac: Mild nonadrenergic inotropic and lusiotropic effects
	> 4 weeks of age: 1-3 mg/kg over 1 hour then 5-15 μg/kg/min i.v.	Vascular: Systemic and pulmonary vasodilator Amrinone may cause thrombocytopenia. Reduce amrinone dose in slow acetylators.
Milrinone	*All ages:* 50-75 μg/kg over 20 minutes *Maintenance:* 0.5-0.75 μg/kg/min i.v.	Reduce milrinone dose in renal failure.
Digoxin	Initial dose 15 μg/kg then 5 μg/kg after 6 hours. Thereafter, 5 μg/kg every 12 hr. Slow i.v. or p.o.	Delays atrioventricular conduction. Used in management of supraventricular tachycardia. Mild inotropic properties. May provide symptomatic relief in congestive heart failure. Bradycardia, supraventricular or ventricular dysrhythmias in overdose. Aim for plasma level 0.8-2.0 ng/mL Dose adjustment required in renal failure.
Esmolol	Short-term management of supraventricular tachycardia and perioperative hypertension 0.5 mg/kg, then 50-200 μg/kg/min i.v.	Bradycardia Hypotension Bronchospasm
Nitroprusside	0.5-5 μg/kg/min i.v. Direct blood pressure monitoring required.	Systemic and pulmonary vasodilatation Systemic hypotension prominent Cyanide toxicity Metabolic acidosis earliest sign Monitor thiocyanate levels when used > 48 hr or in renal failure
Captopril	Oral administration: 0.05 mg/kg as a test dose then incremental increase to 0.4 mg/kg (occasionally up to 1.0 mg/kg), titrated to effect (systemic blood pressure) every 8 hr.	Systemic vasodilatation/hypotension Small increase in plasma potassium levels
Nitroglycerin	0.5-8 μg/kg/min i.v. Direct blood pressure monitoring required.	Systemic and pulmonary vasodilatation
Propranolol	Relief of RV spasmodic RV outflow obstruction in the emergency management of hypercyanosis in tetralogy of Fallot 0.05-0.1 mg/kg i.v. stat Systemic hypertension 2-6 mg/kg in four to six divided doses	Bradycardia Hypotension Bronchospasm Lethargy

ventricular function curve. If preload reduction brings the end-diastolic pressure to the pre-plateau sloping portion of the ventricular function curve, stroke volume can only be maintained or augmented if preload is optimized by appropriate fluid administration. Directly placed left atrial pressure monitoring lines are commonly used to determine LV loading conditions in neonates and others too small for insertion of pulmonary arterial flotation catheters. Systemic vasodilators should be used with extreme caution in patients with systemic hypotension and those with LV outflow obstruction who are at risk of uncompensated severe systemic hypotension and myocardial ischemia.

In children, sodium nitroprusside is frequently the systemic vasodilator of choice because of its powerful arteriolar dilating properties and short half-life, which render it both effective and highly titratable (see Table 101-5). Nitroglycerin is an alternative short-acting drug that acts as an arteriolar dilator at higher doses but is an effective venodilator at lower doses. Phenoxybenzamine, a long-acting alpha-adrenergic blocker, is used in some centers in children undergoing surgery for congenital heart disease.[20]

For longer-term vasodilator therapy in children able to absorb enterally administered drugs, angiotensin-converting enzyme (ACE) inhibitors such as captopril and enalapril are used (see Table 101-5).[21] They have peripheral vascular and neurohormonal effects as well as direct effects on the myocardium through activation of intracellular signaling pathways involved in growth and apoptosis of cardiac myocytes and fibroblasts. Studies in adults have established that ACE inhibitors improve survival and symptoms in heart failure, owing in part to favorable effects on cardiac remodeling. Evidence for the use of ACE inhibitors in children is much less clear. Acute hemodynamic benefits have been demonstrated in children with heart failure caused by left-to-right shunts and systolic dysfunction of the systemic ventricle. Prolonged treatment with ACE inhibitors has been shown to be effective in reducing not only LV volume overload but also LV hypertrophy in the hearts of growing children with chronic LV volume overload.[22,23] The use of ACE inhibitors in the neonatal period has been questioned by the finding that they may influence the balance of apoptosis and cell growth, compromising necessary remodeling.[24]

Digoxin may have weak inotropic actions through its inhibitory effect on Na^+,K^+-ATPase and may also have peripheral effects that attenuate the actions of the neurohormonal system (see Table 101-5) . Several adult studies have shown that digoxin improves symptoms in heart failure, but no studies have shown improvement in survival. Digoxin is widely used to treat heart failure in children, but there are few data to support or refute its use. Recommendations on its rational use in pediatric heart failure can only be implied by extrapolation of the 1997 U.S. Food and Drug Administration recommendations for adults, which state that digoxin can be used in symptomatic patients with heart failure in addition to diuretics, ACE inhibitors, and beta blockers.[21]

Diuretics

It is standard practice to use diuretics in virtually all children with heart failure. There are no pediatric studies showing that diuretic therapy reduces morbidity or mortality, but one adult study has shown that the diuretic spironolactone improves survival in adults with heart failure.[25]

Potent diuretics such as furosemide are widely used in heart failure treatment in childhood[26] and in the perioperative period when controlling fluid balance is crucial and renal function may be impaired. The intravenous route is preferred in these situations. Studies have shown that continuous infusion leads to smoother control of fluid and electrolyte shifts than intermittent intravenous bolus administration.[26]

Beta Blockers

Although there is increasing evidence of survival benefits accruing from beta-adrenergic blocker therapy in adults with moderate and severe heart failure,[27] evidence of similar benefits in children with heart failure is limited.[21,28,29] Although it might be reasonable to extrapolate adult survival advantages to older children with heart failure, extreme caution should be exercised in seeking to apply such therapy in the neonatal period.

Beta blockers have established roles in children in the management of hypertension and in the management of ventricular outflow tract obstruction, such as that which occurs in the tetralogy of Fallot.

Other Inotropic Agents

Triiodothyronine (T_3) has been shown in vitro and in animal studies to play an important role in up-regulating beta adrenoceptors and in increasing cardiac myocyte contractility.[30] Clinical studies have shown that T_3 supplementation can produce elevation in heart rate without concomitant decrease in systemic blood pressure[31] and may enhance cardiac functional reserve after CPB in infants. The calcium sensitizer levosimendan has both inotropic and peripheral vasodilating properties and has produced promising results in early adult studies.[32]

Pulmonary Vasodilators and Other Strategies to Prevent and Treat Pulmonary Hypertension

Oxygen alone is a potent dilator of the pulmonary vascular bed, with both high alveolar oxygen concentration and high systemic oxygen saturation having a favorable influence. PVR is also influenced by lung volume, being raised at both low and very high lung volumes. Most intravenously administered drugs used to treat pulmonary hypertension have nonselective effects, dilating both the pulmonary and systemic vascular beds. Tolazoline, prostaglandin E_1, and prostacyclin are among many agents that have been used as "pulmonary vasodilators." Prostacyclin is a short-acting vasodilator that acts via increasing levels of the intracellular messenger cyclic AMP, which has been widely used in the treatment of primary pulmonary hypertension in children.[33] In contrast, nitrates, nitroprusside, and, indeed, nitric oxide, act via the activation of guanylate cyclase and hence increase cellular levels of cyclic guanosine monophosphate, which is then inactivated by PDE type V. The pulmonary effects of intravenous vasodilators are frequently limited by their nonspecific action, leading to clinically important systemic hypotension.

Elevation of PVR is seen frequently in children after CPB,[19] which will exacerbate any underlying changes in pulmonary hemodynamics.[34] Reactive postoperative pulmonary hypertensive episodes typically occur in children after correction of left-to-right shunt lesions or in those with preoperative pulmonary venous hypertension. These "crises" are particularly associated with long CPB durations. In the current era, early corrective surgery has dramatically reduced the numbers of infants in whom pulmonary hypertension is a major perioperative issue. Postoperative pulmonary hypertension is still seen

TABLE 101–6. STRATEGIES TO PREVENT AND TREAT PULMONARY HYPERTENSION

Strategy	Comment
Perform anatomic investigation.	Rules out residual or undiagnosed anatomic abnormalities.
Permit right-to-left decompression.	Deliberate residual atrial septal defect acts as "pop off" in at-risk situations.
Provide analgesia/sedation.	Facilitates ventilation. Minimizes sympathetic influences.
Avoid acidosis.	Respiratory and metabolic acidosis raises pulmonary vascular resistance.
Maintain oxygenation.	Normal/high alveolar and mixed venous Po_2 lowers pulmonary vascular resistance.
Optimize hematocrit.	Ensures optimal oxygen delivery and higher mixed venous Po_2.
Optimize cardiac output.	Ensures optimal oxygen delivery and higher mixed venous Po_2.
Use pulmonary vasodilators.	Selectively reduces pulmonary vascular resistance.

in neonates and infants in association with lesions such as obstructed total anomalous pulmonary venous drainage, truncus arteriosus, and mitral valve replacement for congenital mitral stenosis. Children with lesser elevations in PVR may also benefit from pulmonary vasodilatation, including children with predominant RV dysfunction, for instance after cardiac transplantation[35] and in Fontan circulations and relatively high PVR.[16] General measures associated with the prevention and treatment of pulmonary hypertension should be considered before deploying specific pulmonary vasodilators (Table 101-6). In patients at high risk of pulmonary hypertension after cardiac surgery, LV filling can be maintained by right-to-left shunting through a small, surgically created atrial septal defect (ASD). Right-to-left shunt acts as a safety valve; and although some systemic desaturation occurs, LV filling and hence cardiac output are maintained.

Nitric oxide is an endogenous endothelial-derived vasodilator and a gas at room temperature. If added to inhaled gas mixtures in children with reactive pulmonary hypertension it induces selective pulmonary vasodilatation.[37] It is distributed to ventilated alveoli, from where it diffuses into the adjacent pulmonary arteriolar smooth muscle. Inhaled nitric oxide has been shown in randomized controlled trials to be effective and safe therapy in neonates with PPHN. Although the evidence for outcome benefit is limited to one randomized controlled study,[38] there is a substantial body of evidence to show that inhaled nitric oxide is effective in pediatric cardiac patients, including those with acute postoperative pulmonary hypertension after congenital heart surgery[39] and after pediatric heart transplantation. Inhaled nitric oxide can be used in the preoperative assessment of patients with pulmonary hypertension.[40]

Other candidate selective pulmonary vasodilators that are undergoing investigation in children include inhaled prostacyclin,[41] the PDE type V inhibitor sildenafil,[42] and bosentan, an endothelin-1 receptor blocker.[43]

MECHANICAL CIRCULATORY SUPPORT

Extracorporeal membrane oxygenation (ECMO) is a technically mature technique that has been used to support over 18,000 neonates with respiratory failure in whom survival rates of 70% to 80% are expected. Its use in this indication is supported by randomized controlled trials that demonstrate good short- and medium-term outcomes.[44] ECMO and ventricular-assist devices (VADs) have also been used to provide temporary circulatory support in children with intractable circulatory failure (see Chapter 70). Reported indications include severe ventricular failure, refractory arrhythmias, and cardiac arrest. The aim of mechanical circulatory support in such circumstances is to provide optimal cardiac output while resting the heart, awaiting its recovery, or to achieve survival by successful support of the child to cardiac transplantation. Single-center series[45] and collaborative registry figures[46] of ECMO or VAD for acute postoperative indications report similar figures for survival to hospital discharge (~40%) in children who it is assumed would not have survived without mechanical support. Rapid deployment ECMO has been reported as an effective intervention for the management of cardiac arrest in the pediatric cardiac ICU.[47] Hospital survival figures for CPR-ECMO seem encouraging,[47] but long-term neurodevelopmental follow-up studies are urgently needed before such strategies can be recommended unequivocally.

CARDIOMYOPATHIES

The two most common causes of heart failure in children are congenital heart disease and cardiomyopathy. Cardiomyopathies are primary myocardial diseases of either known or unknown cause characterized by left or biventricular dilatation and impaired contractility and occur in children and adults of all ages.

Nugent and colleagues reported the incidence of pediatric cardiomyopathy in a 10-year population-based study of Australian children as 1.24 cases per 100,000 children younger than 10 years of age,[48] a remarkably similar finding to a recently reported U.S. study.[49] Of 314 cases of cardiomyopathy reported by Nugent and colleagues, 184 of 314 (59%) were dilated cardiomyopathy, 80 (25%) were hypertrophic cardiomyopathy, 8 (2.5%) were restrictive cardiomyopathy, and 42 (13%) were unclassified, of which 29 (69%) exhibited LV noncompaction. Twenty percent of cardiomyopathy in this study was classified as familial, and in 8.9% specific mitochondrial or metabolic disease etiologically linked to cardiomyopathy was identified. Of the children in Nugent's study who underwent myocardial biopsy, 40.3% had histologic evidence of lymphocytic myocarditis according to the Dallas criteria,[50] which contrasts to an incidence of lymphocytic myocarditis in adult studies of only 10%.[51]

Presentation

Most children present with signs and symptoms of heart failure, including dyspnea, upper abdominal discomfort, nausea, and vomiting. Abdominal symptoms are often misdiagnosed as indicative of gastroenteritis, although the astute clinician will note the absence of diarrhea. It is presumed that these abdominal symptoms result from hepatic congestion and gut edema as a result of right-sided heart failure or ischemia (from splanchnic vasoconstriction). A history of an antecedent flu-like illness is strongly suggestive of a diagnosis of myocarditis. Some children with myocarditis follow a fulminant course typified by rapid onset of cardiogenic shock.[52,53]

The chest radiograph in the patient who presents acutely with a cardiomyopathy typically shows cardiomegaly and pulmonary venous congestion. An echocardiogram will reveal

left atrial and ventricular dilatation and impaired systolic and diastolic function and often mitral or tricuspid regurgitation. ECG features are mostly nonspecific and include ST segment and T wave changes and arrhythmias. The presence of Q waves may indicate anomalous origin of the left coronary artery from pulmonary artery (ALCAPA). If ALCAPA cannot be unequivocally excluded by echocardiography, coronary angiography must be undertaken.

As cardiomyopathies result from a variety of acquired or inherited disorders, the differentiation of secondary (and possibly treatable causes of dilated cardiomyopathy) from the idiopathic form of the disease is of the greatest importance. Endomyocardial biopsies can be obtained to assist in the diagnosis of myocarditis and other specific myocardial diseases.

Prognosis

Recent studies have reported 5-year survival rates in childhood cardiomyopathy of 64% to 84%, although the impact of cardiac transplantation on survival rates is not clear in all studies. In contrast to myocarditis, sudden death is uncommon in children with other forms of dilated cardiomyopathy. Children with cardiomyopathies who fail to respond to conservative treatment and especially those with ongoing requirement for intravenous inotropic support, ventilatory support, or mechanical circulatory support and children with recurrent arrhythmias are candidates for early cardiac transplantation. Late recovery of ventricular function is however possible.[54] The prognosis for cardiomyopathy due to myocarditis in children appears to differ from that in adults, with survival of up to 80% among children who reach hospital alive.[55,56] Many children who survive the acute phase go on to recover normal cardiac function, in marked contrast to adults in whom mortality rates of 20% at 1 year increase to 56% at 5 years.[51]

ICU Management of Dilated Cardiomyopathy and Myocarditis

In children presenting with acute heart failure, hypotension, or cardiogenic shock, beta-adrenergic agonists may improve systolic ventricular function. PDE type III inhibitors such as milrinone are of hemodynamic benefit in acute heart failure, although large trials in adult heart failure have failed to show clear benefit from chronic administration.[57] Although metoprolol and carvedilol may be of benefit in chronic heart failure,[28,28,29] they should be avoided in hemodynamically unstable children. Nasal or mask continuous positive airway pressure (CPAP) has been shown to result in symptomatic improvement both by unloading of respiratory muscles and by lowering of LV afterload as a consequence of raising intrathoracic pressure.[58] Children in severe heart failure have high SVRs and no ventricular reserve. Great care is therefore needed if sedative agents are administered to facilitate tracheal intubation or ICU procedures. Agents with the least effects on the cardiovascular system should be chosen and allowance made for slow circulatory times when titrating sedative doses.

The use of mechanical circulatory support with ECMO or ventricular assist systems can be lifesaving in children with myocarditis or cardiomyopathy who develop cardiogenic shock.[59] A high proportion of children who receive mechanical support for fulminant myocarditis will recover ventricular function. Those who do not may be "bridged" to cardiac transplantation. Clearly, survival with a recovered native ventricle is a better outcome for a child than survival by means of cardiac transplantation. A multicenter series[56] documented a median time to return of ventricular function of 9 days in those who survived without transplantation. The absolute time limits for recovery of native ventricular function have not been established, although pragmatic decisions on whether to proceed to cardiac transplantation should probably be made if cardiac recovery has not occurred after 10 to 14 days of support.

Congenital Heart Disease

Congenital heart disease (CHD) classified as moderate or severe is detected in approximately 6 of 1000 live births, of whom between 2 and 3 will require expert cardiologic care soon after birth. The presence of extracardiac anomalies in children is associated with poorer outcomes.[54] Syndromes associated with cardiovascular involvement are of particular significance to the pediatric intensivist who must coordinate the cardiac and extracardiac aspects of care.[60] Trisomy 21 (Down syndrome) is associated with a high incidence of congenital heart disease, in particular, atrioventriculoseptal defects. Deletion of the q11 region of chromosome 22 is associated with a spectrum of cardiac (conotruncal defects, e.g., truncus arteriosus, hypoplastic left heart syndrome) and extracardiac abnormalities.[61] Of the latter, thymic aplasia places infants at risk for hypocalcemia secondary to hypoparathyroidism and impaired cellular immunity.

Many classifications of congenital heart lesions have been proposed. Although a sequential approach to the description of cardiac anatomy is most frequently employed by pediatric cardiologists, a broader physiologic approach is more useful to the nonspecialist. It is beyond the scope of this chapter to present a detailed overview of all aspects of congenital heart disease. A brief overview is presented, focusing on common lesions and information of particular importance to intensivists. Readers are directed elsewhere for more detailed coverage of pediatric cardiology,[62] pediatric cardiac surgery,[63] and pediatric cardiac intensive care.[64]

LESIONS WITH PREDOMINANT LEFT-TO-RIGHT SHUNT

VSD is the archetypal lesion associated with left-to-right shunting of blood. VSDs may occur in isolation or in association with other cardiac anomalies. Ventricular output will follow the path of least resistance, resulting in blood shunting across the defect and into the lungs as the PVR is lower than the SVR. The magnitude of the shunt, usually expressed as the ratio of pulmonary blood flow to systemic blood flow (Qp:Qs), depends on the size of the VSD and the level of the PVR. Small-diameter defects offer resistance at the level of the ventricular septum, limiting flow from the LV to RV and maintaining a pressure gradient between the two chambers. Larger-diameter defects are unrestrictive, with no pressure gradient between the two ventricles; and in this situation, flow is solely dependent on the ratio of PVR to SVR. Small restrictive VSDs rarely result in symptoms in infancy, typically presenting when a cardiac murmur is detected as an incidental finding. Infants with larger "unrestrictive" VSDs gradually develop congestive cardiac failure owing to the increase in pulmonary blood flow that occurs as the developmental fall in PVR occurs in the first weeks of life.[65] Thus, the

consequences of a moderate or large "unrestrictive" VSD are increased pulmonary blood flow (high Qp:Qs) and extra volume work demanded of the LV. The volume overload of the LV results in LV enlargement and failure. If large left-to-right shunts are left untreated, PVR gradually rises. Although the initial rise is the result of pulmonary arteriolar muscular hypertrophy that is reversible, irreversible pulmonary vascular obstructive disease[66] eventually ensues and may result in the onset of right-to-left shunt (Eisenmenger's syndrome). For this reason, steps must be taken in all children with congenital heart lesions and raised pulmonary blood flow to correct the lesion or protect the lungs by either a corrective procedure or a palliative procedure such as pulmonary artery banding before severe pulmonary vascular changes develop. With the exception of isolated ASDs, most left-to-right shunt lesions that require surgical intervention present in the first year of life as heart failure and are associated with development of pulmonary hypertension. The principal lesions are described next.

VENTRICULAR SEPTAL DEFECT

Anatomy

VSDs occur in any part of the interventricular septum and are classified by location.[67,68]

Pathophysiology

Left-to-right shunting at ventricular level leads to left atrial dilatation, LV volume overload, and increased pulmonary blood flow. The degree of left-to-right shunt is determined by the size of the defect and the PVR. If a defect is "small," shunt flow is determined mainly by the size of the defect. Left-to-right flow across larger "unrestrictive" defects is determined principally by PVR—the lower the PVR, the greater will be the shunt and pulmonary blood flow.

Many small VSDs close spontaneously,[69] but if closure does not occur, infants with unrestrictive defects will fail to thrive and develop congestive heart failure as the PVR falls in early infancy. Untreated VSD leads to pulmonary hypertension and eventual progression to fixed pulmonary vascular obstructive disease. Eventually pulmonary artery pressure and vascular resistance exceeds that of the systemic circulation, leading to shunt reversal and cyanosis (Eisenmenger's syndrome). Patients with a fixed high PVR are not suitable for VSD closure because the RV will not tolerate the excessive afterload of the hypertensive pulmonary vascular bed.

Surgery

Most VSDs are repaired as a primary procedure.[70] Occasionally, pulmonary artery banding is undertaken to reduce pulmonary blood flow and protect the pulmonary vascular bed in neonates in whom primary repair is a high risk. This may be the case with complex conditions such as multiple defects and in very small premature infants. These conservative strategies are questioned by some surgeons.[71,72] VSDs are usually closed surgically on CPB using a sutured patch. Some defects can be closed at cardiac catheterization with an occlusion device.[68]

Postoperative Management

Most children undergoing elective VSD closure progress rapidly to extubation. Patients with severe cardiac failure or high pulmonary artery pressures preoperatively benefit from a more cautious approach in the early postoperative period as do those with complex associated lesions. Low cardiac output or pulmonary edema may be noted in the early postoperative period as a consequence of generalized myocardial hypocontractility or due to the presence of a residual VSD. Pulmonary hypertension is relatively rare in the current era of "early" primary repair of VSD. Cases presenting late may have pulmonary hypertension, and life-threatening pulmonary hypertensive "crises" can occur in the postoperative period. Surgically placed pulmonary artery catheters greatly assist in the early detection and management of such episodes.[73] Junctional ectopic tachycardia (JET)[74,75] and complete heart block are generic risks of surgery in the vicinity of the ventricular septum. Compete heart block may be transient, but if atrioventricular synchrony has not returned by 7 to 10 days, a permanent pacing system is required.[76]

ATRIAL SEPTAL DEFECT

Anatomy

Anatomically, interatrial communications are of four types. Ostium secundum defects are the most common form of ASD and are centrally located in the atrial septum. Ostium primum type defects are part of the atrioventriculoseptal defect spectrum (see later). Sinus venosus defects occur close to the right atrium/superior vena cava or right atrium/inferior vena cava junction and are commonly associated with partial anomalous pulmonary venous drainage. Coronary sinus defects describe a type of ASD associated with absence of the wall between the left atrium and coronary sinus that allows left atrial blood to reach the right atrium via the coronary sinus.[67,77]

Pathophysiology

Left-to-right shunting of blood at atrial level leads to right atrial and ventricular dilatation with increased pulmonary blood flow. Congestive heart failure occurs in up to 5% of children with ASD in the first year of life. Pulmonary hypertension in association with ASD is relatively rare in childhood, with an incidence of 13% in unoperated children younger than age 10 years, although if defects are not closed, patients may progress to irreversible pulmonary hypertension.[78] Occasionally, infants or young children with primary pulmonary hypertension, pulmonary hypoplasia, or similar conditions present with apparently symptomatic ASD with right-to-left shunting. In these situations, the ASD is beneficial, decompressing the right side of the heart, with symptoms being a consequence of pulmonary hypertension rather than simply the presence of an ASD.

ASD CLOSURE

Centrally located secundum ASDs are frequently closed by placement of an ASD closure device at cardiac catheterization.[79] Large defects and non-secundum defects are closed surgically using CPB. Defects are typically closed if a child becomes symptomatic or electively between 3 and 5 years of age. There is essentially no mortality risk associated with closure of an isolated ASD, and good long-term morbidity-free survival is expected.[80]

Postprocedure Management

The vast majority of elective ASD closures progress rapidly to extubation post procedure (hours). Specific

postoperative problems seen after ASD closure include the following:

1. *Sinoatrial node dysfunction* manifests as an inappropriate chronotropic response or as atrial or junctional arrhythmias. The problem is caused either by direct trauma to the sinoatrial node or by interruption to its blood supply during surgery.
2. *Postpericardotomy syndrome* manifests as fever, malaise, lymphocytosis, nausea, vomiting, or abdominal pain in the weeks after surgery. The symptoms are caused by a sterile inflammatory process that can cause pericardial fluid to accumulate to the point at which pericardial tamponade is manifest. A history of recent cardiac surgery with symptoms as just mentioned should raise the suspicion of the syndrome and of potential tamponade, particularly if cardiomegaly is present on a chest radiograph.
3. *Pulmonary hypertension* is relatively rare in children after ASD repair. A previously undiagnosed ASD presenting in adulthood is more likely to be associated with pulmonary hypertension.
4. *Obstruction of pulmonary veins or vena cava* may occur in association with repair of sinus venosus defects.
5. *LV dysfunction* may occur. Transiently elevated left atrial pressure and pulmonary edema are occasionally seen after ASD closure in older patients owing to chronic RV overload and decreased LV compliance.

ATRIOVENTRICULOSEPTAL DEFECT (AVSD)

Anatomy

AVSDs result from failure of the lower part of the atrial septum to fuse with the upper part of the ventricular septum.[77] The hallmark of all AVSDs is the presence of a common atrioventricular (AV) junction and valve with two bridging and three smaller leaflets. The common AV valve has varying degrees of competence. There are three potential components of this defect, an ostium primum ASD, a VSD, and abnormal formation of the AV valves. The condition presents as partial AVSD (sometimes referred to as primum ASD), in which an ASD and cleft AV valve are present, and complete AVSD, which in addition has a VSD. AVSD-spectrum lesions commonly occur in children with Down syndrome.

Pathophysiology

Partial defects behave like a secundum ASD with left-to-right shunt at atrial level causing right atrial and RV volume overload. Associated incompetence of the left AV valve may lead to significant regurgitation and worsening symptoms. In complete defects, left-to-right shunting of blood at the ventricular level leads to congestive heart failure by about 2 months of age. Pulmonary hypertension and pulmonary vascular obliterative disease occur if repair is not undertaken by age 6 to 9 months.

Surgery

Partial or complete AVSDs are repaired under CPB. Partial defects are usually repaired electively at between 1 and 5 years,[81] whereas complete defects are usually repaired at 3 to 6 months to avoid severe pulmonary hypertensive complications.[82,83]

Postoperative Management

Afterload reduction with sodium nitroprusside or milrinone is useful if significant AV valve regurgitation is present post repair. Problems seen after AVSD surgery include pulmonary hypertension,[84] which is however uncommon in the current era of early surgical repair. Residual lesions such as residual left AV valve regurgitation or residual VSD will slow postoperative recovery and require prompt diagnosis and aggressive management, including reoperation if necessary. Elevated left atrial pressure after AVSD repair can occur because of the presence of residual left AV valve regurgitation, left AV valve stenosis, LV outflow tract obstruction, residual VSD, and LV myocardial dysfunction. The precise cause of elevated left atrial pressure must be diagnosed and appropriate management instituted.

PATENT DUCTUS ARTERIOSUS (PDA)

Anatomy

A ductus arteriosus is a vascular communication, necessary in the fetal circulation, between the junction of the main and left pulmonary arteries and the lesser curvature of the aorta, which normally closes within 2 weeks of birth. Persistent patency occurs as an isolated defect, in premature neonates, and in association with other congenital heart lesions.

Pathophysiology

The key pathophysiologic abnormality in PDA, as in VSD, is left-to-right shunting leading to increased pulmonary blood flow, pulmonary hypertension, and LV volume overload. Neonates with this condition usually present with congestive heart failure, apneas, or respiratory problems. In term infants and older children, isolated PDA may present incidentally or with the onset of cardiac failure or problems with recurrent pulmonary infections. Pulmonary hypertension progressing to pulmonary vascular obstructive disease can occur within the first year of life, with the rate of onset of symptoms depending on the size of the duct.

Management

Indomethacin or ibuprofen is used to induce closure of patent ductus in premature neonates, acting through inhibition of the vasodilatory prostaglandin production, with success in approximately 70% of cases.[85] Transcutaneous catheter occlusion can be effective in suitable cases, with a low incidence of associated complications. Surgical ligation or division is required in very small subjects[86] and in older children with large ducts in whom occlusion devices cannot be safely deployed. Surgical closure is carried out via a lateral thoracotomy or as a video-assisted thoracoscopic procedure.[87]

Postprocedural Issues

The principal complications of conservative treatment of PDA with indomethacin or ibuprofen in preterm neonates are failure to induce closure and renal failure.[85] Surgical approaches may be complicated by occlusion failure and complications of thoracotomy, including infection and hemorrhage. Adjacent structures including the thoracic duct, phrenic nerve, and the recurrent laryngeal nerve may be damaged during surgery. Complications after transcatheter closure include residual shunt, embolization of closure device, and hemolysis.

TRUNCUS ARTERIOSUS

Truncus arteriosus is caused by the failure of the common arterial trunk to divide into the aorta and pulmonary artery.

Anatomy

A single arterial vessel originates from both ventricles, overriding the ventricular septum and supplying the coronary, pulmonary, and systemic circulations. Anatomic variations depend on the respective origins of the right and left branch pulmonary arteries from the common arterial trunk, main pulmonary artery, or aorta. A VSD lies immediately below a single ventriculoarterial truncal valve that is commonly dysplastic, leading to stenosis or regurgitation. Coronary artery abnormalities are common and may lead to difficulties when conducting surgical repair. Ten to 15 percent of patients have associated hypoplasia, coarctation, or interruption of the aortic arch, and a small proportion have stenosis or hypoplasia of the pulmonary arteries.

Aortopulmonary window is a rare lesion in which an abnormal vascular communication exists between the ascending aorta and the main pulmonary artery. Like truncus, this lesion is associated with 22q11 chromosomal deletion.[61,88]

Pathophysiology

The RV and LV are pressure and volume overloaded, particularly if truncal valve stenosis or regurgitation is present. Runoff into the pulmonary circulation due to low PVR and into the ventricles due to truncal valve regurgitation leads to a low diastolic pressure, which in the presence of high ventricular end-diastolic pressures may exacerbate myocardial ischemia. Pulmonary blood flow depends on the PVR and the presence or absence of stenoses in the proximal pulmonary arteries. Most commonly, therefore, pulmonary overcirculation and congestive heart failure result as PVR falls in the first weeks of life. The defect is commonly associated with 22q11 chromosomal deletion (DiGeorge syndrome, Shprintzen's syndrome). The important clinical manifestations associated with these include scanty or absent T cells[61,88] and the consequent risk of graft-versus-host reactions if transfused with viable leukocytes. Irradiation of all blood products is recommended unless normal T-cell status is confirmed.

Surgery

The pulmonary arteries are removed from the arterial trunk, leaving a vessel that becomes the neoaorta.[89,90] A valved conduit is then placed from the RV to the pulmonary arteries, and the VSD is closed. Mortality risk is less than 10% if the truncal valve is functionally normal, no other lesions are present, and the child is of an acceptable weight. Long-term results are encouraging, although the valved conduit will require upsizing during childhood.[91]

Postoperative Management

Specific postoperative problems associated with repair of truncus include pulmonary hypertension[84] and low cardiac output.[12] Inotropic support is required routinely, and delayed sternal closure may be employed to prevent tissue tamponade in the early postoperative period. Intensivists must be aware of the possibility of right-to-left shunting because surgeons may leave a smaller interatrial communication to decompress the RV. Failure to appreciate this mechanism may lead to an inappropriate focus on pulmonary causes of cyanosis. Right bundle branch block is common after truncus repair owing to the surgical right ventriculotomy. Heart block and atrial or junctional arrhythmias are also seen.

LEFT-SIDED HEART OBSTRUCTION

Obstruction to the exit of blood from the LV can occur at subvalvular, valvular, or supravalvular levels or more distally in the aortic arch. Infants with severe obstruction of the aortic valve or arch present in the neonatal period with either heart failure or cardiogenic shock. Aortic coarctation, aortic interruption, and critical aortic stenosis are associated with a duct-dependent systemic circulation and typically present in the first few days of life as the arterial duct closes. Less severe obstruction may be detected later as an incidental finding (murmur) or with the gradual onset of signs and symptoms, including those of LV failure. Chronic obstruction to LV outflow causes LV hypertrophy; and whereas systolic function may initially be well preserved, reduced diastolic compliance may occur early in the clinical course. If the obstruction is unrelieved, the subendocardial region becomes ischemic and endocardial fibrosis occurs. Papillary muscle ischemia may also occur and results in acquired mitral valve regurgitation.

VALVULAR AORTIC STENOSIS

Anatomy

Approximately 70% of aortic stenosis occurs only at the valvar level. Valvar aortic stenosis may be associated with other abnormalities, however, including supravalvar aortic stenosis, mitral valve anomalies, aortic insufficiency, and endocardial fibroelastosis. In neonatal aortic stenosis, the LV and other left-sided structures may be hypoplastic.

Pathophysiology

Neonates with clinically apparent valvular aortic stenosis present with acute LV failure or shock. Systemic perfusion may be maintained by right-to-left shunting of blood across a patent ductus with consequent systemic desaturation and the risk of reduced systemic perfusion if the ductus closes spontaneously. The LV exhibits poor performance in both diastole and systole, and as a consequence there are high left atrial pressures. Pulmonary edema is a prominent clinical feature. End organ ischemic damage including renal failure and necrotizing enterocolitis are frequently seen as a consequence of poor systemic perfusion. Less severe aortic stenosis typically presents later in infancy or childhood with exercise-induced syncope, chest pain, or sudden death. In these patients, concentric LV hypertrophy induced by chronic pressure overload is usually seen.

Surgery

A number of treatment options are available, with the choice of procedure dependent on age, clinical status of the child at presentation, associated anomalies, and anatomic complexity. The simplest procedure, percutaneous balloon valvotomy, is appropriate in patients with mild to moderate stenosis and favorable aortic valve anatomy.[92] Open aortic valve surgery is an alternative to balloon valvoplasty and may be favored if additional procedures (e.g., duct ligation) are required. If the native aortic valve cannot be salvaged or reconstructed, surgical choices include replacement of the aortic valve with a homograft or valved conduit or placement of the patient's own pulmonary valve into the aortic position with associated pulmonary homograft autograft (the Ross procedure).[93,94] A variant of the Ross procedure, the Ross-Konno procedure,[95] is indicated for complex LV outflow tract obstruction in

which in addition to the Ross operation, annular enlargement or aortoventriculoplasty is undertaken.[94]

Postoperative Management

Most neonates presenting in heart failure or shock who undergo urgent procedures remain critically ill postoperatively and require ongoing multiorgan support.[96] If low cardiac output persists after repair, residual aortic stenosis or regurgitation must be excluded. Inotropic and vasodilator support of the failing myocardium should be guided by serial hemodynamic and echocardiographic evaluations. Relief of aortic stenosis in older children may be associated with systemic hypertension secondary to the unrestrained force of contraction of the hypertrophied LV. Children undergoing prosthetic valve replacement require long-term anticoagulation therapy.[97]

SUBVALVULAR AORTIC STENOSIS

Subaortic stenosis is seen in various forms including a fibrous diaphragm-like ring with a central orifice, a fibromuscular tunnel (frequently associated with hypoplasia of ascending aorta and LV anomalies), or simply as dynamic obstruction due to hypertrophy of the LV outflow.[98]

Subaortic stenosis presents in neonates in association with other lesions including malalignment-type VSD, double-outlet RV, and aortic or aortic valvular lesions or as an isolated lesion in childhood.

Pathophysiology

Similar to valvular aortic stenosis, pressure overload in LV leads to hypertrophy with resultant raised pressure overload.

Surgery

The choice of surgical procedure depends on the anatomic substrate. Membranous subaortic stenosis requires simple resection. The tunnel form may be suitable for resection or require a more extensive Konno or Ross-Konno[94] type procedure. Finally, the hypertrophic form of subaortic stenosis requires a Ross-Konno operation with resection of LV myocardium.[99]

The perioperative course is usually uneventful after resection of membranous subaortic stenosis with mortality below 5%, although late recurrence is common. After surgery for tunnel and hypertrophic forms of subaortic stenosis the recovery pathway is determined by the age of the child, the nature and complexity of surgery performed, and, most critical of all, the presence of existing LV dysfunction. Specific postoperative problems include residual LV outflow tract stenosis, mitral regurgitation, VSD with left-to-right and left bundle branch block, or complete heart block secondary to resection of LV myocardium.

SUPRAVALVULAR AORTIC STENOSIS

Supravalvular aortic stenosis occurs in isolation and in association with Williams syndrome (supravalvular aortic stenosis, RV outflow tract obstruction (RVOTO), peripheral pulmonary stenoses, renal artery stenoses).[100-102] It may be a localized or diffuse narrowing above the sinotubular junction. The stenosis is occasionally associated with a hypoplastic ascending aorta, and there may be compromise to coronary filling.

Pathophysiology

Similar to valvular aortic stenosis, pressure overload in the LV leads to hypertrophy with resultant raised pressure overload. In addition, coronary arteries fill under high pressure and may become tortuous and dysplastic.

Surgery

Patch angioplasty is performed in most cases.[103]

Postoperative Management

Postoperative course is usually uneventful. Specific postoperative problems include residual aortic or LV outflow tract stenosis leading to cardiac failure and coronary ischemia that occurs if the repair has disturbed the coronary arteries or if LV hypertension and LV subendocardial ischemia persist.

AORTIC COARCTATION

Anatomy

A constriction of the thoracic aorta occurs in the region of the left subclavian artery where the ligamentum arteriosum originates. The complexity of the lesion varies from a discrete narrowing to more extensive aortic arch hypoplasia extending back to proximal aortic arch. Coarctation commonly coexists with VSD and can also be associated with other left-sided lesions, including aortic and mitral valve stenosis.[104]

Pathophysiology

In the neonatal presentation of aortic coarctation, a normal circulation is maintained until ductal tissue contracts, at which point distal aortic flow is severely reduced, leading to a clinical presentation of heart failure or shock and characteristic loss of lower limb pulses.[105] Prostaglandin E_1 or E_2 infusion should be started as soon as the diagnosis of a duct-dependent lesion is suspected, to reopen or maintain patency of the ductus arteriosus. After initial resuscitation, urinary output and resolution of metabolic acidosis are early indicators of successful reperfusion of the distal aorta. Early surgical repair is indicated.

Beyond the early neonatal period, aortic coarctation presents as progressive onset of cardiac failure or as an incidental finding (murmur, upper limb hypertension, absent weak femoral pulses) later in childhood. Thoracic aortic collaterals develop and may be noted as rib notching on a plain chest radiograph.

Surgery

Surgical resection of the narrowed aortic segment and associated ductal tissue and either end-to-end anastomosis or subclavian flap angioplasty are used to repair coarctation in the newborn, without CPB.[63] If aortic arch hypoplasia is more extensive, a homograft or prosthetic tube graft may be incorporated in the repair and CPB may be required.[106] Neonatal coarctation associated with VSD can be palliated by resection of the coarctation and banding of the pulmonary artery to restrict pulmonary blood flow, with delayed VSD repair. Alternatively, both lesions can be corrected in the neonatal period. The mortality rate for repair of neonatal coarctation is low. Kanter and colleagues reported 91% survival in a series that included both isolated and complex coarctation.[107] In older children it is less than 1%, although paraplegia secondary to interruption of spinal cord perfusion remains a concern.

Balloon angioplasty is frequently used to alleviate recurrent aortic coarctation and is increasingly being used with apparent success to address native coarctation particularly in older patients but is not favored in symptomatic neonates.[104,108]

Postoperative Management

Specific postoperative problems include systemic hypertension, which is thought to be due to multiple factors, including altered baroceptor and adrenal catecholamine and renin-angiotensin axes.[109,110] Persistent hypertension is less common after neonatal repair and when present it usually responds to short-term vasodilator therapy.[109,111] Additional beta-adrenergic blockade (esmolol,[112] propranolol, or labetalol) may be required, particularly with late-presenting coarctation. Some children have persistent hypertension after repair[113] and require long-term antihypertensive therapy. Postcoarctectomy syndrome[114] occurs in older patients and is thought to be the result of restoration of higher-pressure pulsatile flow to the mesenteric arterial tree and presents as abdominal distention, abdominal pain, ascites, or, occasionally, enteric infarction. The condition is best managed by avoiding enteral feeding for 24 hours after repair and aggressive treatment of systemic hypertension. The necessity of aortic clamping during surgical repair interrupts distal aortic flow and may result in spinal cord ischemia (rare in neonates, 0.4% incidence in older patients) or renal ischemia. The intensivist must seek positive confirmation of lower limb movement and adequate renal function in the early postoperative period. In neonates,[115] low cardiac output may persist owing to preexisting ventricular dysfunction, although residual coarctation should be excluded. Structures near the aortic arch prone to surgical injury include the thoracic duct, recurrent laryngeal nerve, and the phrenic nerve, leading to postoperative chylothorax, stridor, or hemidiaphragm paralysis.

INTERRUPTED AORTIC ARCH

Anatomy

In this condition the aortic arch is either atretic or interrupted, creating either complete disruption or luminal obstruction (without external interruption). A patent arterial duct is necessary to maintain perfusion of the distal aortic arch, closure of which leads to emergent presentation. A VSD and obstruction of the LV outflow tract commonly coexist. The more common form of interrupted aortic arch (type B) is associated with 22q11 chromosomal deletion (see earlier).[61,88]

Pathophysiology

Interrupted aortic arch should be regarded as a severe form of aortic coarctation, with duct-dependent distal aortic perfusion, and requires similar initial management.[105]

Surgery

Surgical reconstruction of the aortic arch and closure of the associated VSD are usually undertaken under CPB in the neonatal period.

Specific postoperative problems seen after repair of interrupted aortic arch include pulmonary hypertension, residual aortic arch obstruction, and residual VSD. There is a risk of transfusion-associated graft-versus-host disease and hypocalcemia in children with type B interrupted aortic arch with 22q11 deletion and DiGeorge phenotype.[116]

TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION (TAPVC)

Anatomy

All of the pulmonary veins drain anomalously into a systemic venous structure and subsequently to the right atrium rather than directly into the left atrium. In supracardiac TAPVC (45% of cases) the pulmonary veins drain via a vertical vein to the innominate vein or connect directly into the SVC. In intracardiac TAPVC (25% of cases) the venous confluence drains via the coronary sinus into the RA, and in infracardiac TAPVC (25% of cases) the veins drain into the IVC or portal veins. Mixed forms also exist (5% of cases).[117] TAPVC is associated with an obligate ASD to allow mixing of systemic and pulmonary venous return to access the LV and systemic circulation.

Pathophysiology

Two patterns emerge depending on presence of obstruction to the pulmonary venous return. Obstruction of the pulmonary venous pathway is common and causes pulmonary venous hypertension, pulmonary venous edema, reflex pulmonary artery vasoconstriction, and subsequent right-sided heart failure. If obstruction is not present, the main pathophysiologic effects result from complete mixing of systemic and pulmonary venous blood in the right side of the heart with RV volume overload and failure.

Surgery

The pulmonary veins are anastomosed or baffled into the left atrium. In the current era the expected operative mortality is less than 5%,[118] although higher risks are reported in complex cases with associated lesions.[119]

Pulmonary hypertension, which may on occasion be severe or even life threatening, occurs frequently in infants after surgery for obstructed anomalous pulmonary veins.[84] If high pulmonary artery pressure occurs postoperatively it is essential to rule out residual pulmonary venous obstruction. Late re-stenosis is seen in up to 10% of cases and carries a poor prognosis, often related to a progressive fibrotic process occluding the lumen of the pulmonary veins.[120]

CYANOTIC LESIONS

TETRALOGY OF FALLOT

Anatomy

Tetralogy of Fallot (TOF) was initially described in the 19th century as an association of four anatomic findings: VSD, subpulmonary stenosis, aortic override of the ventricular septum, and RV hypertrophy.[63] The four lesions are actually the result of just one central problem, anterior and superior malalignment of the infundibular septum with respect to the muscular septum, which creates an obstruction in the RV outflow tract and leads to the four features seen.

Pathophysiology

Preoperative physiology depends mainly on the degree of RVOTO. Patients with minimal RVOTO have unrestricted pulmonary blood flow with left-to-right shunt through the VSD. Conversely, patients with severe obstruction will be cyanosed with saturations in the 70% to 80% range preoperatively as a result of right-to-left shunting across the VSD. RVOTO is often dynamic and may cause profound cyanosis

(hypercyanotic spells), which requires treatment aimed at alleviating the dynamic RVOTO and maintaining right-sided heart output. Treatment of such episodes requires oxygen, sedation, and volume expansion. The knee-chest and over-shoulder positions compress the liver and increase RV filling. If such maneuvers fail, beta blockade (propranolol, 0.1 mg/kg) or vasoconstriction (e.g., phenylephrine, 5 to 20 μg/kg i.v.) may be required; and, as a last resort, preoperative ECMO support may be required.

Surgery

The timing and type of surgical intervention in TOF is controversial.[121] Complete repair is usually undertaken in the first year of life.[122,123] Some centers adopt a two-stage approach with initial placement of a modified Blalock-Taussig shunt in cyanotic infants. Complete repair is then undertaken when the child is bigger.

Residual VSD is poorly tolerated after TOF repair and requires early surgical closure. Moderate degrees of residual RVOTO may be well tolerated in the early postoperative period, but severe residual obstruction demands early re-investigation and reoperation with placement of a larger RV outflow tract patch or valved RV-PA conduit. All patients with a RV incision develop right bundle branch block. Junctional ectopic tachycardia is poorly tolerated after TOF repair.[74] Low cardiac output due to RV dysfunction is relatively common and should be suspected if the child is hypotensive, is tachycardic, and has a raised central venous pressure and hepatomegaly. The problem is predominantly one of poor RV compliance, often referred to as RV "restriction,"[124,125] and typically resolves in 3 to 5 days. Until recovery occurs, the heart should be supported by optimizing RV filling and ensuring AV synchrony. Negative-pressure ventilation has been shown to improve cardiac output where RV restriction exists.[12,126]

PULMONARY ATRESIA WITH INTACT VENTRICULAR SEPTUM (PA/IVS)

Anatomy

In this condition there is complete obstruction to the outflow of the RV, along with a variable degree of hypoplasia of the RV and tricuspid valve.[127] The tricuspid valve may also be incompetent. Pulmonary blood flow occurs via a PDA. Coronary artery sinusoids or fistulas are often found in "severe" PA/IVS with a small RV. Ten percent of cases will have an RV-dependent coronary circulation, in which coronary sinusoids/fistulas are associated with proximal stenosis and perfusion of areas of myocardium is dependent on flow via the RV. In some patients, the pulmonary arterial supply is abnormal with segments of the lungs being supplied solely or partially (dual supply) from systemic collateral vessels termed major aortopulmonary collateral arteries.[128,129]

Pathophysiology

Preoperatively there is complete mixing of systemic and pulmonary venous return in a duct-dependent circulation. The RV may be very hypertensive because there is no path for egress of blood. Some blood may pass via coronary sinusoids, if present, or back through a regurgitant tricuspid valve.

Surgery

The goal of surgery is to provide a secure source of pulmonary blood flow balanced to systemic flow and to permit the RV to develop to its maximal potential, always aiming for a two-ventricle repair where possible.[130] All infants need procedures in the neonatal period because of duct dependency. Subsequent strategies are chosen according to individual anatomic findings.

In severe forms of the condition (severe RV hypoplasia ± coronary fistulas), a two-ventricle repair will never be possible and a palliative approach is adopted. Initial palliation secures pulmonary blood flow with systemic-pulmonary artery shunts (30% to 40% PA/IVS) with the ultimate aim being a single-ventricle "Fontan" circulation (see later). In contrast, infants with a normal-sized RV may be suitable for RV outflow tract reconstruction in the neonatal period, therefore avoiding shunt and ending up with early anatomic correction (10% of cases). An intermediate group of patients, the majority of cases of PA/IVS, need initial palliation with decompression of the RV by radiofrequency perforation of the atretic pulmonary valve or outflow tract patch and often require a systemic-pulmonary artery shunt. They progress to either a single, one-and-a-half,[131] or biventricular repair, depending on subsequent development of the RV and pulmonary arteries.

Specific postoperative problems include low cardiac output due to excessive runoff through the shunt, myocardial ischemia due to decompressed coronary fistulas, or low systemic diastolic pressure due to excessive shunt runoff.

D-TRANSPOSITION OF THE GREAT ARTERIES (TGA)

Anatomy

In D-transposition, which accounts for 5% to 7% of all congenital heart lesions, the great vessels are transposed so that the aorta arises from the anatomic RV and the pulmonary artery from the LV.[63] The condition occurs with a VSD in approximately 40% of cases. Other commonly associated lesions include coarctation (10%), LV outflow tract obstruction (5%), and coronary abnormalities (33%).

Pathophysiology

The predominant finding in TGA is cyanosis due to parallel rather than serial function of the pulmonary and systemic circulations, with the greatest proportion of the output of a ventricle being recirculated to that ventricle. Survival is therefore dependent on the presence of mixing between the two circulations (Fig. 101-2). The presence of either a PDA or a VSD alone or in combination without an atrial communication does not ensure adequate mixing of the two circulations. If the diagnosis is suspected in a neonate, an infusion of prostaglandin E_1 or E_2 should be established to maintain ductal patency and, following echocardiographic confirmation of the diagnosis, a balloon atrial septostomy is performed to enlarge the foramen ovale and secure mixing at the atrial level. Saturations typically increase from very low levels (<50%) to 65% to 85% after these interventions, and it is then usually possible to discontinue the prostaglandin infusion.

Surgery

The preferred surgical option in the current era is the arterial switch (Jatene) operation,[63,132,133] although long-term results after Senning operations also appear to be acceptable.[134] The switch operation is usually performed within the first 2 weeks of life, beyond which the LV (functioning as a low-pressure subpulmonary or "right" ventricle since birth) is less able to

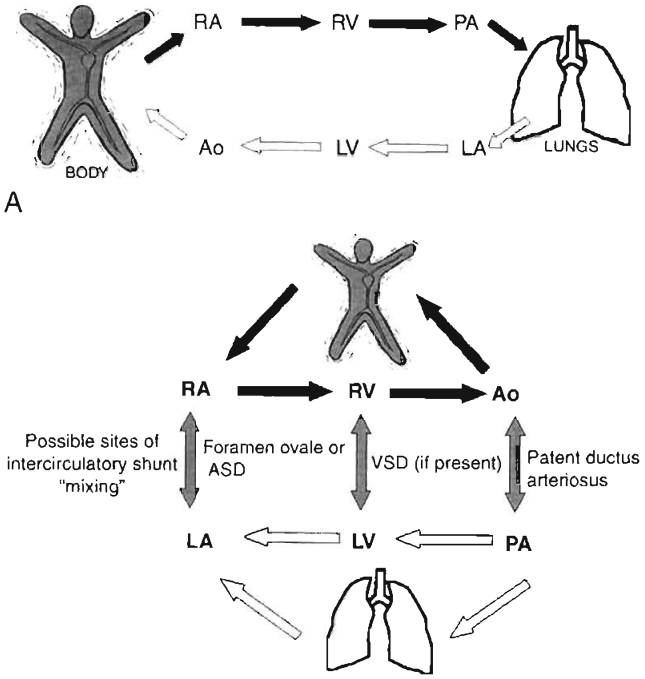

FIGURE 101–2. A, Normal series circulatory arrangement. **B,** Parallel circulation of transposition of the great vessels. RA, right atrium; RV, right ventricle; PA, pulmonary artery; LA, left atrium; LV, left ventricle; Ao, aorta.

cope with systemic pressures.[135] Infants with a large VSD have equal ventricular pressures, and repair can be delayed a little longer, although in practice most surgeons repair TGA with VSD within the first month of life. The operation consists of transection of the aorta and pulmonary artery with reconstruction of the vessels in their anatomic position, which necessitates transfer of the coronary arteries from the pulmonary artery to the neoaorta.

Specific Postoperative Problems after the Arterial Switch Operation

LV dysfunction is seen to some extent in all infants during the first 12 hours after the arterial switch operation.[19] It may be a sign of coronary insufficiency[136] or of acute dysfunction secondary to an "unprepared/involuted" LV or simply nonspecific post-CPB "low cardiac output." In the absence of electrocardiographic or echocardiographic evidence of regional coronary ischemia, low cardiac output is managed conservatively. The postoperative LV of the neonate is poorly compliant. Rapid volume infusion should be avoided because LV distention and ischemia may result. Preload should be augmented gradually, titrating volume infused against measured left atrial pressure.

Alternative Surgical Techniques

Atrial switch operations (the Senning and Mustard procedures) are alternatives to the arterial switch operation and may be chosen in infants presenting beyond the early neonatal period in whom a one-stage arterial switch is not possible owing to deconditioning of the LV. In atrial switch operations, blood is diverted by an atrial baffle to establish a series circulation leaving the RV as the systemic ventricle. It is believed that the burden of late complications such as RV failure is greater after atrial switch procedures. An alternative strategy for late-presenting transposition is a two-stage repair with initial banding of the pulmonary artery to condition the LV with "switch" once the ventricle is conditioned.[137]

Postoperative Care

Atrial switch procedures are usually performed outside the neonatal age group and, compared to "arterial" switch procedures, have a relatively uneventful postoperative course. Atrial volumes and compliance are reduced by the procedure such that postoperatively left and right atrial pressures must be maintained at higher than "normal" levels to maintain ventricular filling. Slow heart rates and arrhythmias are poorly tolerated.

COMPLEX "SINGLE VENTRICLE" CIRCULATIONS

Some defects are such that they can never be corrected to provide two functioning ventricles.[138] These complex arrangements include any heart in which one ventricle is hypoplastic such that it would be incapable of supporting either the pulmonary or systemic circulation independently. Examples of such situations include tricuspid atresia or double-inlet LV. In these examples, the RV has failed to develop adequately and is connected to a dominant LV via a VSD. Flow to the circulation supplied by the rudimentary ventricle originates from the dominant chamber and is dependent on an adequate VSD. Children with this type of anatomy will always have two ventricles, even if one is hypoplastic, but physiologically they behave as if the heart consists of only a "single" ventricle.

Complex "single ventricle" hearts can be palliated with a series of interventions leading to creation of a Fontan circulation when the systemic and pulmonary circulations are completely separated.[139] Initially, adequate intracardiac communications are established to ensure that both systemic and pulmonary venous return have unobstructed access to the dominant ventricle and supply both systemic and pulmonary blood flow. If necessary, pulmonary flow is augmented by the use of a systemic to pulmonary artery shunt (modified Blalock-Taussig shunt). Systemic and pulmonary blood flow is ensured at the expense of mixing of pulmonary and systemic venous returns, with consequent cyanosis and volume loading of the single ventricle.

Subsequently, if hemodynamic conditions are favorable, the Fontan circulation is established usually in a two-stage procedure. Initially, a bidirectional cavopulmonary anastomosis is created in which the superior vena cava is connected to the proximal right pulmonary artery. This has the benefit of reducing the volume load placed on the systemic ventricle by the previously placed systemic-pulmonary shunt. Finally, venous return from the inferior vena cava is also directed to the pulmonary circulation. This is achieved by forming a lateral tunnel[140] or the use of a synthetic extracardiac conduit[141] to channel blood from the inferior vena cava to the inferior aspect of the right pulmonary artery completing the total cavopulmonary connection or "Fontan" circulation.

In the Fontan circulation there is no "subpulmonary" ventricle, all ventricular tissue having been incorporated in the single ventricle, which receives pulmonary venous return and ejects into the systemic circulation. This establishes a form of series circulation and results in normal systemic oxygenation and equality of pulmonary and systemic

blood flow. Pulmonary blood flow in the Fontan circulation is driven by the transpulmonary hydrostatic gradient and is only viable if the pulmonary vascular resistance and systemic ventricular end-diastolic pressures (pulmonary venous pressures) are low. The presence of good systemic ventricular function and low PVR are crucial determinants of operability. Patients with a Fontan circulation tolerate factors that impede systemic venous return such as dehydration, pneumothorax, pericardial effusion, positive-pressure ventilation,[58] raised pulmonary vascular resistance, or compromised ventricular or respiratory[142] function very poorly. Perioperative use of ACE inhibitors has been shown to reduce the severity and duration of pleural drainage,[143] a common problem caused by high postoperative systemic venous pressures.

Long-term follow-up studies have demonstrated that systemic ventricular function remains abnormal after Fontan procedures.[144] Ultimately, the Fontan circulation may fail and cardiac transplantation be considered.

Hypoplastic left heart syndrome (HLHS) encompasses a range of hypoplastic abnormalities of the left-sided cardiac structures and connections, including the ascending aorta. The condition is usually palliated in three stages, first described by Norwood. Some authorities prefer to offer cardiac transplantation without prior palliative surgery.[145] The stage 1 Norwood repair consists of reconstruction of the aortic arch with the establishment of pulmonary blood flow via a central systemic-pulmonary artery shunt. An alternative source of pulmonary blood flow, an RV-PA shunt, has been found to offer advantages (less diastolic runoff) over the central shunt of the classic Norwood 1 operation, which was a major clinical problem after the classic stage 1 operation.[146,147] In stage 2 of the Norwood procedure, undertaken at age 2 to 6 months, a bidirectional cavopulmonary (Glenn) shunt is fashioned with a completion to a Fontan circulation (stage 3) after 18 to 24 months of age. Fetal diagnosis facilitates early and appropriate management and may contribute to improved outcomes in HLHS.[146]

SURGICAL CONTROL OF PULMONARY BLOOD FLOW: PULMONARY ARTERY BANDING

Pulmonary artery banding is a surgical procedure in which a constriction is created in the main pulmonary artery with the aim of limiting pulmonary blood flow. It is performed without CPB through either a left thoracotomy or median sternotomy. The procedure is undertaken to restrict pulmonary blood flow, aiming to maintain a balance between the systemic and pulmonary circulations and to prevent the onset of pulmonary hypertension in some complex anomalies unsuitable for early anatomic repair.[148] Pulmonary artery banding is a palliative procedure and is usually a stepping stone to a more complex repair.

Physiology

A pulmonary artery band reduces pulmonary blood flow and therefore volume loading of the systemic or single ventricle. The intracardiac shunt is predominantly right to left after banding, and systemic arterial saturations are typically 75% to 85% after effective banding. The pressure gradient across an effective pulmonary artery band in a neonate is typically in the range of 40 to 60 mm Hg.

Specific Management Issues

Very low SaO_2 postoperatively (<70%) may indicate that the band is too tight, that is, the pulmonary blood flow is too restricted. Urgent echocardiographic evaluation of the band gradient and exclusion of other causes of hypoxemia should be undertaken. If hypoxemia persists, and particularly if significant metabolic acidosis develops, urgent removal of the band may be indicated. Pulmonary artery bands may occasionally be too loose to adequately reduce pulmonary blood flow, resulting in SaO_2 in excess of 90%. Signs of congestive cardiac failure may be noted and require medical treatment (diuretics) or further surgical intervention (rebanding or correction of lesion).

OTHER LESIONS

VASCULAR RINGS AND SLINGS

Vascular rings and slings[149] result from abnormal branching or positioning of the great vessels that results in encirclement or compression of the trachea and/or esophagus. They are seen in isolation or in association with intracardiac defects.

Anatomy

Three common types occur either in isolation or in association with other cardiac lesions, including right aortic arch, TOF, and AVSD.

Double Aortic Arch

This results from failure of the embryonic regression of one of the arches. The right arch, which is commonly dominant and usually larger, passes posterior to the esophagus and trachea to connect to the left-sided descending thoracic aorta forming a vascular ring. The left arch is commonly smaller and may exhibit varying degrees of hypoplasia, coarctation, or true atresia. The carotid and subclavian arteries originate from both arches. Sometimes a persistent ductus or ligamentum arteriosum forms a true ring around the trachea.

Right Aortic Arch with Aberrant Left Subclavian Artery

In this condition the left subclavian has its origin from the ascending aorta and courses to the left behind the esophagus with the vascular ring completed by the ligamentum arteriosum.

Pulmonary Artery Sling

The left pulmonary artery arises from the right pulmonary artery and crosses to the left by passing behind the trachea. The trachea is squeezed between the aorta and left pulmonary artery, and a true ring may be formed by a persistent ductus or ligamentum arteriosum.

Pathophysiology

Vascular rings have the potential to compress both trachea and esophagus. Pulmonary artery slings usually cause chronic tracheal compression, which eventually results in destruction of the tracheal skeleton with resultant tracheal stenosis in 50% of cases.

Surgery

Vascular rings are usually approached via a lateral thoracotomy (usually left). The left arch or ligamentum is divided to

release the ring, and the descending aorta is dissected away from the esophagus. To correct pulmonary artery sling, the anomalous left pulmonary artery is transected and rerouted anteriorly and reanastomosed to the central pulmonary artery.[150,151]

Postoperative Care

This is usually uneventful. Extubation at the end of anesthesia or early in the ICU course is expected. Tracheomalacia may persist or present postoperatively, especially after pulmonary artery sling surgery, and may require long periods of respiratory support postoperatively via a tracheostomy.

ANOMALOUS LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY (ALCAPA)

Anatomy

This usually occurs as an isolated lesion in which the left coronary artery arises from the pulmonary artery rather than the aorta.

Pathophysiology

Symptoms develop gradually as the PVR falls during early infancy. There is progressive onset of myocardial ischemia as left coronary flow falls in parallel with the fall in pulmonary artery pressure. The myocardium is initially well perfused by desaturated pulmonary artery blood, but as coronary flow falls, severe LV ischemia and dysfunction occur.

Surgery

Surgical intervention is necessary to reconnect the left coronary with the aorta, and this can be achieved either by creating a tunnel from the left coronary orifice to the aorta[152] (the Takeuchi operation) or by directly reimplanting the coronary artery.[153]

Postoperative Care

The principal perioperative problem in infants with symptomatic ALCAPA is management of low cardiac output. Beta-adrenergic agonists, PDE III inhibitors such as milrinone,[18] and occasionally mechanical circulatory support may be required.

SPECIFIC ISSUES FOR THE INTENSIVIST

DELAYED STERNAL CLOSURE

Complex cardiac surgery involving CPB results in edema of the myocardium and other mediastinal tissues. Under these circumstances, sternal closure may cause cardiac compression ("tissue tamponade"), which decreases ventricular compliance and leads to reduced cardiac output and elevated pulmonary venous pressures.[154,155]

INFECTIVE ENDOCARDITIS

Infective endocarditis is a condition characterized by microbial infection of the heart valves or other structures and is associated with substantial morbidity and mortality in both children and adults. The subject has been extensively reviewed.[156] Infective endocarditis can occur sporadically, but most patients have predisposing intracardiac structural abnormalities such as congenital heart disease, prosthetic heart valves, or acquired valvular regurgitation (e.g., post-rheumatic heart disease or mitral valve prolapse). Infection commonly occurs after a surgical procedure, including dental procedures, in which microorganisms are seeded into the bloodstream. In the pediatric cardiac ICU, infective endocarditis is often associated with the presence (and presumed colonization or infection) of indwelling central venous catheters. Intensivists should aim to minimize line-related infective complications by employing "best-practice" guidelines in the care and surveillance of central venous lines.[157] Consensus guidelines have been established that recommend the circumstances and type of antibiotic prophylaxis required to minimize the chances of at-risk patients acquiring infective endocarditis.[158]

ANNOTATED REFERENCES

Cullen S, Shore D, Redington A: Characterization of right ventricular diastolic performance after complete repair of tetralogy of Fallot: Restrictive physiology predicts slow postoperative recovery. Circulation 1995;91:1782-1789.

This paper characterized isolated diastolic dysfunction of the RV ("restrictive physiology") as a major cause of this low cardiac output state in children after surgical repair of tetralogy of Fallot. Knowledge of the presence of restrictive physiology allows the intensivist to adopt physiologically appropriate management strategies.

Duncan BW, et al: Mechanical circulatory support for treatment of children with acute fulminant myocarditis. J Thorac Cardiovasc Surg 2001;122: 440-448.

Viral myocarditis may follow a rapidly progressive and fatal course in children. This report demonstrates that mechanical circulatory support may be a lifesaving measure with a high proportion of survival attributed to recovery of native ventricular function.

Hoffman TM, et al: Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation 2003;107:996-1002.

Low cardiac output syndrome (LCOS), affecting up to 25% of neonates and young children after cardiac surgery, contributes to postoperative morbidity and mortality. This study evaluated the efficacy and safety of prophylactic milrinone in pediatric patients at high risk for developing LCOS. It is the largest randomized controlled trial in a pediatric cardiac surgical population, and one of the few double-blind randomized-controlled trials performed in this population.

McElhinney DB, et al: Management and outcomes of delayed sternal closure after cardiac surgery in neonates and infants (comment). Crit Care Med 2000;28:1180-1184.

This study demonstrates that delayed sternal closure is an effective approach to the management of neonates and infants at risk for hemodynamic, respiratory, or hemostatic instability early after cardiac surgery.

Nugent AW, et al: The epidemiology of childhood cardiomyopathy in Australia (comment). N Engl J Med 2003;348:1639-1646.

The incidence and age distribution of primary cardiomyopathy in children were previously not well defined. The centralization of pediatric cardiology services in Australia enabled these authors to undertake this retrospective, population-based cohort study of all Australian children who presented with cardiomyopathy over a 10-year period. The study succeeds in adding to our understanding of the distribution of cardiomyopathy types and the timing and severity of their presentation in children.

Chapter 102

PERICARDIAL DISEASES

Bernhard Maisch • Arsen D. Ristic

KEY POINTS

1. **Diagnosis of acute pericarditis** is based on clinical presentation (chest pain, pericardial friction rub) and typical four-stage ECG changes. For etiologic diagnosis, pericardiocentesis, pericardioscopy, and pericardial/epicardial biopsy may be necessary.
2. **Echocardiography is essential** in all patients with pericarditis to detect pericardial effusion and determine its physiologic significance, as well as to check for signs of constriction, concomitant heart disease, or paracardial pathology.
3. A large proportion of patients usually classified as having **"idiopathic" pericarditis** actually have **viral and autoreactive pericarditis.** The diagnosis of viral pericarditis is not possible without the evaluation of pericardial effusion and/or pericardial/epicardial tissue, preferably by polymerase chain reaction (PCR) or in-situ hybridization.
4. PCR identification of *Mycobacterium tuberculosis*, high adenosine deaminase activity, and interferon gamma concentration in pericardial effusion are diagnostic with a high sensitivity and specificity for **tuberculous pericarditis.**
5. **Pericardiocentesis is indicated for** cardiac tamponade, for a high suspicion of purulent, tuberculous, or neoplastic pericarditis, or in patients with very large effusions without signs of tamponade (>20 mm in echocardiography in diastole). Electrical alternans and pulsus paradoxus are clinically important signs of advanced stage of cardiac tamponade and indicate the need for prompt pericardial drainage.
6. **Aortic dissection is a major contraindication** to pericardiocentesis. Relative contraindications include uncorrected coagulopathy, anticoagulant therapy, thrombocytopenia less than 50,000/mm^3, and small, posterior, and loculated effusions.
7. In cardiac wounds, postinfarction myocardial rupture, or dissecting aortic hematoma emergency **cardiac surgery** is lifesaving. Loculated effusions may require open surgery or thoracoscopic drainage.
8. **Postinfarction pericardial effusions** larger than 10 mm in diastole are frequently associated with cardiac rupture. Urgent surgical treatment is indicated.
9. **Intrapericardial instillation** of antineoplastic and/or sclerosing agents (e.g., cisplatin, thiotepa) can prevent recurrences of neoplastic pericardial effusions. Intrapericardial instillation of triamcinolone is highly efficient in preventing recurrences in patients with autoreactive pericardial effusion, mainly avoiding adverse effects of systemic corticosteroid therapy.
10. Pericardiectomy is the only treatment for permanent **constrictive pericarditis**. However, surgery should not be indicated too early (to avoid operating on patients with transient constriction). Even more important is not to perform surgery too late or in patients with myocardial fibrosis and/or atrophy. If the indication for surgery is established early, long-term survival after pericardiectomy corresponds to that of the general population.

ETIOLOGY AND CLASSIFICATION OF PERICARDIAL DISEASE

The spectrum of pericardial diseases consists of congenital defects, pericarditis (dry, effusive, effusive-constrictive, constrictive), neoplasm, and cysts. The etiologic classification comprises infectious pericarditis, pericarditis in systemic autoimmune diseases, type 2 (auto)immune process, post–myocardial infarction syndrome, and autoreactive (chronic) pericarditis.[1-3]

PERICARDIAL SYNDROMES

CONGENITAL DEFECTS OF THE PERICARDIUM

Congenital defects of the pericardium occur in 1 in 10,000 autopsies. Pericardial absence can be partial left (70%), right (17%), or total bilateral (rare). Additional congenital abnormalities occur in approximately 30% of patients.[4] Most patients with a total pericardial absence are asymptomatic. Homolateral cardiac displacement and augmented heart mobility impose an increased risk for traumatic aortic dissection.[5] Partial left-side defects can be complicated by herniation and strangulation of the heart through the defect (chest pain, shortness of breath, syncope, or sudden death).

TABLE 102–1. DIAGNOSTIC PATHWAY AND SEQUENCE OF PERFORMANCE IN ACUTE PERICARDITIS

Diagnostic Measure	Characteristic Findings
Obligatory	
Auscultation	Pericardial rub (monophasic, biphasic, or triphasic)
ECG*	*Stage I:* anterior and inferior concave ST segment elevation. PR segment deviations opposite to P wave polarity
	Early stage II: all ST junctions return to the baseline. PR segments deviated.
	Late stage II: T waves progressively flatten and invert
	Stage III: generalized T wave inversions in most or all leads
	Stage IV: ECG returns to prepericarditis state
Echocardiography	Effusion types B to D (Horowitz)
	Signs of tamponade
Blood analyses	Erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase, leukocytes (inflammation markers)
	Troponin I†, CK-MB (markers of myocardial involvement)
Chest radiograph	Ranging from normal to "water bottle" shape of the heart shadow
	Performed primarily to reveal pulmonary or mediastinal pathology
Mandatory in Tamponade, Optional in Large/Recurrent Effusions or if Previous Tests Inconclusive in Small Effusions	
Pericardiocentesis/drainage	Polymerase chain reaction and histochemistry for etiopathogenetic classification of infection or neoplasia
Optional or if Previous Tests Inconclusive	
CT	Effusions, pericardium, and epicardium
MRI	Effusions, pericardium, and epicardium
Pericardioscopy, pericardial/epicardial biopsy	Establishing the specific etiology

*Typical lead involvement: I, II, aVL, aVF, and V3-V6. The ST segment is always depressed in aVR, frequently in V1, and occasionally in V2. Stage IV may not occur, and there are permanent T wave inversions and flattenings. If ECG is first recorded in stage III, pericarditis cannot be differentiated by ECG from diffuse myocardial injury, "biventricular strain," or myocarditis. ECG in early repolarization is very similar to stage I. Unlike stage I, this ECG does not acutely evolve and J-point elevations are usually accompanied by a slur, oscillation, or notch at the end of the QRS just before and including the J point (best seen with tall R and T waves—large in early repolarization pattern). Pericarditis is likely if in lead V6 the J point is greater than 25% of the height of the T wave apex (using the PR segment as a baseline).
†A cTnI rise was detectable in 38/118 patients (32.2%), more frequently in younger, male patients, with ST-segment elevation and pericardial effusion at presentation. An increase beyond 1.5 ng/mL was rare (7.6%), and associated with CK-MB elevation. cTnI increase was not a negative prognostic marker regarding the incidence of recurrences, constrictive pericarditis, cardiac tamponade, or residual left ventricular dysfunction (Imazio).
Data from references 2, 3, and 7 to 19.

Surgical pericardioplasty (Dacron, Gore-Tex, or bovine pericardium) is indicated for imminent strangulation.[6]

ACUTE PERICARDITIS

Acute pericarditis is dry, fibrinous, or effusive, independent of its etiology. Major symptoms are retrosternal or left precordial chest pain (which radiates to the trapezius ridge, can be pleuritic or simulate ischemia, and varies with posture) and shortness of breath. A prodrome of fever, malaise, and myalgia is common, but elderly patients may not be febrile. The pericardial friction rub can be transient and monophasic, biphasic, or triphasic. Pleural effusion may be present. Heart rate is usually rapid and regular. Echocardiography is essential to detect effusion and concomitant heart or paracardial disease (Table 102-1).[7-19]

Hospitalization and symptomatic treatment is warranted. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay. Indomethacin should be avoided in elderly patients, owing to its effect on reducing flow in the coronaries. Ibuprofen (300 to 800 mg tid) is preferred for its rare side effects, favorable impact on coronary flow, and large dose range.[7] Colchicine (0.5 mg twice daily) added to an NSAID or as monotherapy also appears to be effective for the initial attack and for prevention of recurrences.[20] It is well tolerated with fewer side effects than NSAIDs. Systemic corticosteroids should be restricted to connective tissue diseases and autoreactive or uremic pericarditis. Intrapericardial application is effective and avoids systemic side effects.[2]

CHRONIC PERICARDITIS

Chronic (>3 months) pericarditis includes effusive (inflammatory or hydropericardium in heart failure), adhesive, and constrictive forms.[7] Symptoms are usually mild (chest pain, palpitations, fatigue), related to the degree of cardiac compression and pericardial inflammation. The detection of the curable causes (e.g., tuberculosis, toxoplasmosis, myxedema, autoimmune, and systemic diseases) allows successful specific therapy. Symptomatic treatment and pericardiocentesis should be applied if indicated. For recurrences, balloon pericardiotomy or pericardiectomy may be considered.[21,22]

RECURRENT PERICARDITIS

The term *recurrent pericarditis* encompasses (1) the intermittent type (symptom-free intervals without therapy) and (2) the incessant type (discontinuation of anti-inflammatory therapy ensures a relapse). Massive pericardial effusion, overt tamponade, or constriction is rare. Symptomatic management relies on exercise restriction and the regimen used in acute pericarditis. Colchicine may be effective when NSAIDs and corticosteroids fail to prevent relapses.[20,23,24] Corticosteroids should be used only in patients with poor general condition or in frequent crises.[7] A common mistake is to use a dose too low to be effective or to taper the dose too rapidly. The recommended regimen is prednisone, 1 to 1.5 mg/kg, for at least 1 month. If patients do not respond adequately, azathioprine (75 to 100 mg/day) or cyclophosphamide can be added.[25]

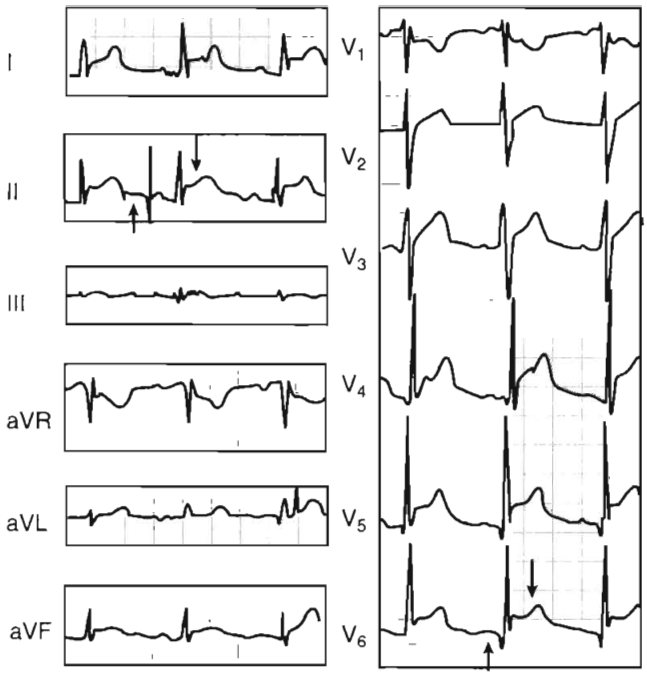

FIGURE 102–1. Typical electrocardiographic changes in acute pericarditis: PR depression *(small arrow)* and concave ST segment elevation *(large arrow)*.

Corticosteroids should be tapered over a 3-month period. Toward the end of the taper, introduce anti-inflammatory treatment with colchicine (0.5 mg bid or tid) or an NSAID. Renewed treatment should continue for 3 to 6 months. Pericardiectomy is indicated only in frequent and highly symptomatic recurrences resistant to medical treatment.[37] Before pericardiectomy, a corticosteroid-free regimen should be applied for several weeks.

PERICARDIAL EFFUSION AND CARDIAC TAMPONADE

Pericardial effusion may appear as transudate (hydropericardium), exudate, pyopericardium, or hemopericardium. Large effusions are common with neoplastic, tuberculous, cholesterol, uremic, myxedema, and parasitoses pericarditis.[27] Loculated effusions are more common when scarring has supervened (e.g., postsurgical, post trauma, purulent pericarditis). Effusions that develop slowly can be remarkably asymptomatic, whereas rapidly accumulating smaller effusions can present as tamponade. Cardiac tamponade is the decompensated phase of cardiac compression caused by effusion accumulation and the increased intrapericardial pressure. Heart sounds are distant. Orthopnea, cough, and dysphagia, occasionally with episodes of unconsciousness, can be observed. Insidiously developing tamponade may present as the signs of its complications (renal failure, abdominal plethora, shock liver, worsening of glaucoma,[28] and mesenteric ischemia). Tamponade without two or more inflammatory signs (typical pain, pericardial friction rub, fever, diffuse ST-segment elevation) is usually associated with a malignant effusion (likelihood ratio 2.9).[29]

Electrocardiography demonstrates low QRS and T-wave voltages, PR-segment depression (Fig. 102-1), ST-segment/T-wave changes, bundle branch block, and electrical alternans (rarely seen in the absence of tamponade).[7] Microvoltage and electrical alternans are reversible after effusion drainage.[19] In chest radiography large effusions are depicted as globular cardiomegaly with sharp margins ("water bottle" silhouette) (Fig. 102-2).[12] The size of effusions can be graded in echocardiography as (1) small (echo-free space in diastole < 10 mm), (2) moderate (10 to 20 mm) (Fig. 102-3), (3) large (≥20 mm), or (4) very large (≥20 mm and compression of the heart). In large pericardial effusions, the heart may move freely within the pericardial cavity ("swinging heart") inducing pseudoprolapse and pseudosystolic anterior motion of the mitral valve, paradoxical motion of the interventricular septum, and midsystolic aortic valve closure (Table 102-2).[30-40] Up to one third of patients with an asymptomatic large pericardial chronic effusion develop unexpected cardiac tamponade.[21] Triggers for tamponade include hypovolemia, paroxysmal tachyarrhythmia, and intercurrent acute pericarditis. Further details on cardiac tamponade and pericardiocentesis are available in Chapter 213.

CONSTRICTIVE PERICARDITIS

Constrictive pericarditis is a rare but severely disabling consequence of the chronic inflammation of the pericardium, leading to an impaired filling of the ventricles and reduced ventricular function. Until recently, increased pericardial thickness has been considered an essential diagnostic feature of constrictive pericarditis. However, in the large surgical series from the Mayo Clinic constriction was present in 18% of the patients with normal pericardial thickness.[41] Tuberculosis, mediastinal irradiation, and previous surgical

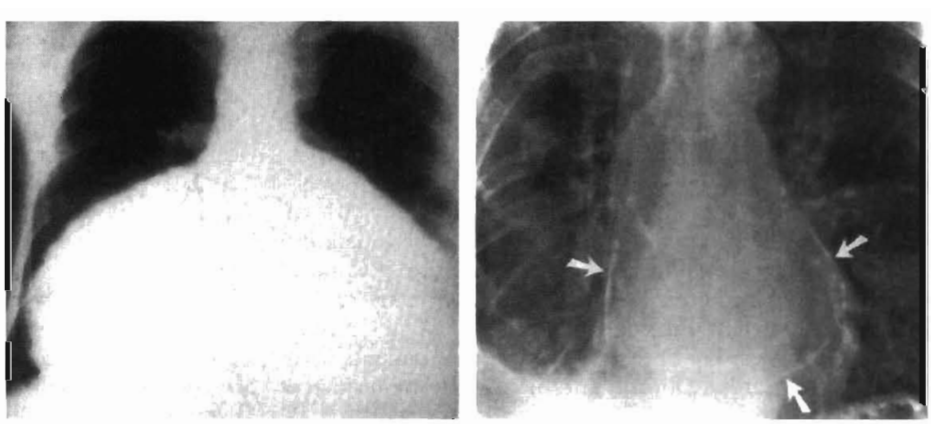

FIGURE 102–2. Chest radiographs in a patient with very large pericardial effusion—"water bottle" sign *(left)* and in a patient with constrictive pericarditis and pericardial calcifications *(white arrows)* *(right)*.

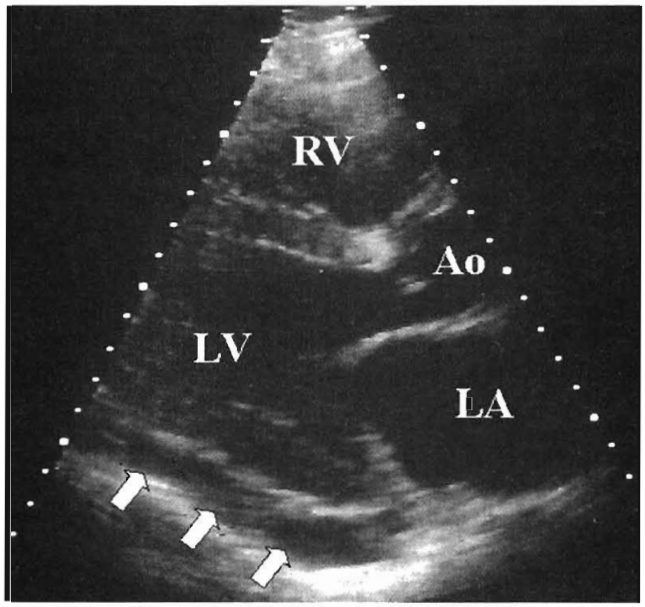

FIGURE 102–3. Echocardiographic findings in a small-moderate pericardial effusion *(white arrows)*. Long-axis parasternal view. LV, left ventricle; LA, left atrium; RV, right ventricle; Ao, aortic root.

procedures are frequent.[42] Constrictive pericarditis may rarely develop only in the epicardial layer in patients with previously removed parietal pericardium.[43] Transient constrictive pericarditis is an uncommon but important entity, because pericardiectomy is not indicated in these patients.[44]

Patients complain about fatigue, peripheral edema, breathlessness, and abdominal swelling, which may be aggravated by a protein-losing enteropathy. In decompensated patients venous congestion, hepatomegaly, pleural effusions, and ascites may occur. Hemodynamic impairment can be additionally aggravated by a systolic dysfunction due to myocardial fibrosis or atrophy. Differential diagnosis has to include acute dilatation of the heart, pulmonary embolism, right ventricular infarction, pleural effusion, chronic obstructive lung diseases,[45] and restrictive cardiomyopathy. The best way to distinguish constrictive pericarditis from restrictive cardiomyopathy is the analysis of respiratory changes with or without changes of preload by Doppler and/or tissue Doppler echocardiography,[46] but physical findings, electrocardiogram (ECG), chest radiography (see Fig. 102-2, right), computed tomography (CT) (Fig. 102-4, left), magnetic resonance imaging (MRI) (see Fig. 102-4, right), hemodynamics, and endomyocardial biopsy may be helpful as well.[7]

Pericardiectomy is the only treatment for permanent constriction. The indications are based on clinical symptoms, echocardiography findings, CT/MRI, and heart catheterization. A primary installation of cardiopulmonary bypass (CPB) is not recommended (diffuse bleeding following systemic heparinization). Pericardiectomy for constrictive pericarditis has a mortality rate of 6% to 12%.[47–50] The complete normalization of cardiac hemodynamics is reported in only 60% of patients.[47,49] Major complications include acute perioperative cardiac insufficiency and ventricular wall rupture.[51] Cardiac mortality and morbidity at pericardiectomy are mainly caused by the presurgically unrecognized presence of myocardial atrophy or myocardial fibrosis.[42] Exclusion of patients with extensive myocardial fibrosis and/or atrophy reduced the mortality rate for pericardiectomy to 5%. Postoperative low cardiac output[51] should be treated by fluid substitution and catecholamines, high doses of digitalis, and intra-aortic balloon pump in most severe cases. If the indication for surgery is established early, long-term survival after pericardiectomy corresponds to that of the general population.[48,49] However, if severe clinical symptoms were present for a longer period before surgery, even a complete pericardiectomy may not achieve a total restitution.

PERICARDIAL CYSTS

Congenital pericardial cysts are uncommon; they may be unilocular or multilocular, with the diameter ranging from 1 to 5 cm.[52] Inflammatory cysts comprise pseudocysts as well as encapsulated and loculated pericardial effusions, caused by rheumatic pericarditis, bacterial infection, particularly tuberculosis, trauma, and cardiac surgery. Echinococcal *cysts* usually originate from ruptured hydatid cysts in the liver and lungs. Most patients are asymptomatic and cysts are detected incidentally on chest radiographs as an oval, homogeneous radiodense lesion, usually at the right cardiophrenic angle.[53] However, the patients can also present as chest discomfort, dyspnea, cough, or palpitations, owing to the compression of the heart. Echocardiography is useful, but additional imaging by CT (density readings) or MRI is often needed.[54] The treatment of congenital and inflammatory cysts is percutaneous aspiration and ethanol sclerosis.[55,56] If this is not feasible, video-assisted thoracotomy or surgical resection may be necessary. The surgical excision of echinococcal cysts is not recommended. Percutaneous aspiration and instillation of ethanol or silver nitrate after pretreatment with albendazole (800 mg/day 4 weeks) is safe and effective.[56]

SPECIFIC FORMS OF PERICARDITIS

VIRAL PERICARDITIS

Viral pericarditis is the most common infection of the pericardium. Inflammatory abnormalities are due to direct viral attack, the immune response (antiviral or anticardiac), or both.[3,57] Early viral replication in pericardial and epimyocardial tissue elicits cellular and humoral immune responses against the virus and/or cardiac tissue. Viral genomic fragments in pericardial tissue may not necessarily replicate, yet they serve as a source of antigen to stimulate immune responses. Deposits of IgM, IgG, and occasionally IgA can be found in the pericardium and myocardium for years.[57] Various viruses cause pericarditis (e.g., enteroviruses, echoviruses, adenoviruses, cytomegaloviruses, Ebstein-Barr virus, herpes simplex, influenzaviruses, parvovirus B19, hepatitis C, human immunodeficiency virus [HIV]). Attacks of enteroviral pericarditis follow the seasonal epidemics of coxsackievirus A+B and echovirus infections.[58] Cytomegalovirus (CMV) pericarditis has an increased incidence in immunocompromised and HIV-infected hosts.[59] Infectious mononucleosis may also present as pericarditis.

The diagnosis of viral pericarditis is not possible without the evaluation of pericardial effusion and/or pericardial/epicardial tissue, preferably by polymerase chain reaction (PCR) or in-situ hybridization. A fourfold rise in serum antibody levels is suggestive but not diagnostic for viral pericarditis.

Treatment of viral pericarditis is directed to resolve symptoms (see acute pericarditis), prevent complications,

TABLE 102–2. DIAGNOSIS OF CARDIAC TAMPONADE

Clinical Presentation	Elevated systemic venous pressure,* hypotension,† pulsus paradoxus,‡ tachycardia,§ dyspnea or tachypnea with clear lungs
Precipitating Factors	Drugs (cyclosporine, anticoagulants, thrombolytics), recent cardiac surgery, indwelling instrumentation, blunt chest trauma, malignancies, connective tissue disease, renal failure, septicemia‖
ECG	Can be normal or nonspecifically changed (ST-T wave), electrical alternans (QRS, rarely T), bradycardia (end stage), electromechanical dissociation (agonal phase)
Chest Radiograph	Enlarged cardiac silhouette with clear lungs
M mode/Two-Dimensional Echocardiogram	Diastolic collapse of the anterior RV free wall,¶ RA collapse, LA and rarely LV collapse, increased LV diastolic wall thickness "pseudohypertrophy," IVC dilatation (no collapse in inspiration), "swinging heart"
Doppler	Tricuspid flow increases and mitral flow decreases during inspiration (reverse in expiration) Systolic and diastolic flows are reduced in systemic veins in expiration and reverse flow with atrial contraction is increased.
M-mode Color Doppler	Large respiratory fluctuations in mitral/tricuspid flows
Cardiac Catheterization	Confirmation of the diagnosis and quantification of the hemodynamic compromise RA pressure is elevated (preserved systolic x descent and absent or diminished diastolic y descent). Intrapericardial pressure is also elevated and virtually identical to RA pressure (both pressures fall in inspiration). RV mid-diastolic pressure is elevated and equal to the RA and pericardial pressures (no dip-and-plateau configuration). Pulmonary artery diastolic pressure is slightly elevated and may correspond to the RV pressure. Pulmonary capillary wedge pressure is also elevated and nearly equal to intrapericardial and right atrial pressure. LV systolic and aortic pressures may be normal or reduced. Documenting that pericardial aspiration is followed by hemodynamic improvement** Detection of coexisting hemodynamic abnormalities (LV failure, constriction, pulmonary hypertension) Detection of associated cardiovascular diseases (cardiomyopathy, coronary artery disease)
RV/LV Angiography	Atrial collapse and small hyperactive ventricular chambers
Coronary Angiography	Coronary compression in diastole

LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; IVC, inferior vena cava.
*Jugular venous distention is less notable in hypovolemic patients or in "surgical tamponade." An inspiratory increase or lack of fall of the pressure in the neck veins (Kussmaul sign), when verified with tamponade or after pericardial drainage, indicates effusive-constrictive disease.
†Heart rate is usually greater than 100 beats/min but may be lower in hypothyroidism and in uremic patients.
‡Pulsus paradoxus is defined as a drop in systolic blood pressure greater than 10 mm Hg during inspiration, whereas diastolic blood pressure remains unchanged. It is easily detected by simply feeling the pulse, which diminishes significantly during inspiration. Clinically significant pulsus paradoxus is apparent when the patient is breathing normally. When this sign is present only in deep inspiration it should be interpreted with caution. The magnitude of pulsus paradoxus is evaluated by sphygmomanometry. If the pulsus paradoxus is present, the first Korotkoff sound is not heard equally well throughout the respiratory cycle, but only during expiration at a given blood pressure. The blood pressure cuff is therefore inflated above the patient's systolic pressure. Then it is slowly deflated while the clinician observes the phase of respiration. During deflation, the first Korotkoff sound is intermittent. Correlation with the patient's respiratory cycle identifies a point at which the sound is audible during expiration but disappears when the patient breathes in. As the cuff pressure drops farther, another point is reached when the first blood pressure sound is audible throughout the respiratory cycle. The difference in systolic pressure between these two points is the clinical measure of pulsus paradoxus. Pulsus paradoxus is absent in tamponade, complicating atrial septal defect, and in patients with significant aortic regurgitation.
§Occasional patients are hypertensive, especially if they have preexisting hypertension.
‖Febrile tamponade may be misdiagnosed as septic shock.
¶Right ventricular collapse can be absent in elevated right ventricular pressure and right ventricular hypertrophy or in right ventricular infarction.
**If after drainage of pericardial effusion intrapericardial pressure does not fall below atrial pressure, the effusive-constrictive disease should be considered.
Data from references 30 to 40.

and eradicate the virus. In patients with chronic or recurrent symptomatic pericardial effusion and confirmed viral infection the following specific treatment is under investigation[60]:

1. CMV pericarditis: hyperimmune globulin—once per day 4 mL/kg on days 0, 4, and 8; 2 mL/kg on days 12 and 16
2. Coxsackievirus B pericarditis: interferon alfa or beta 2.5×10^6 IU/m^2 subcutaneously three times per week
3. Adenovirus and parvovirus B19 perimyocarditis: immunoglobulin treatment: 10 g intravenously on days 1 and 3 for 6 to 8 hours

Pericardial manifestation of HIV infection can be due to infective, noninfective, and neoplastic diseases (Kaposi's

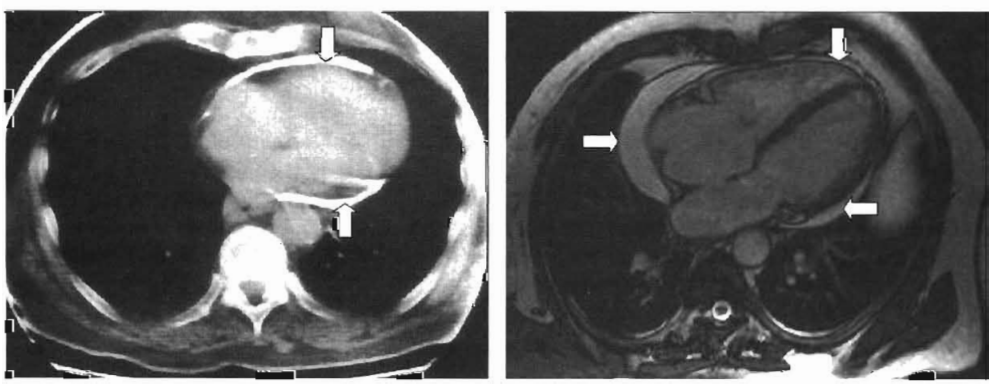

FIGURE 102–4. CT findings in constrictive pericarditis *(left). White vertical arrows* are depicting thickened pericardium and pericardial calcification. MR image of a patient with effusive-constrictive pericarditis is shown on the right-sided image. *Horizontal arrows* show loculated pericardial effusion, and the *vertical arrow* shows thickened pericardium.

sarcoma and/or lymphoma). Infective (myo)pericarditis results from the local HIV infection and/or from other viral (CMV, herpes simplex), bacterial *(Staphylococcus aureus, Klebsiella pneumoniae, Mycobacterium avium,* and *M. tuberculosis),* and fungal co-infections *(Cryptococcus neoformans).*[61] In progressive disease the incidence of echocardiographically detected pericardial effusion is up to 40%.[62] Cardiac tamponade is rare.[63] During treatment with retroviral compounds, lipodystrophy can develop (best demonstrated by MRI) with intense paracardial fat deposition leading to heart failure. Treatment is symptomatic, whereas in large effusions and cardiac tamponade pericardiocentesis is necessary. The use of corticosteroid therapy is contraindicated except in patients with secondary tuberculous pericarditis, as an adjunct to tuberculostatic treatment.[64]

BACTERIAL PERICARDITIS

Purulent pericarditis in adults is rare but always fatal if not treated.[65-68] The mortality rate in treated patients is 40%, mostly due to cardiac tamponade, toxicity, and constriction. It is usually a complication of an infection originating elsewhere in the body, arising by contiguous spread or hematogenous dissemination.[69] Predisposing conditions are pericardial effusion, immunosuppression, chronic diseases (e.g., alcohol abuse, rheumatoid arthritis), cardiac surgery, and chest trauma. The disease appears as an acute, fulminant infectious illness with short duration. Percutaneous pericardiocentesis must be promptly performed, and obtained pericardial fluid should undergo Gram, acid-fast, and fungal staining, followed by cultures of the pericardial and body fluids. Rinsing of the pericardial cavity, combined with effective systemic antibiotic therapy is mandatory (antistaphylococcal antibiotic plus aminoglycoside, followed by tailored antibiotic therapy according to pericardial fluid and blood cultures).[66] Intrapericardial instillation of antibiotics (e.g., gentamicin) is useful but not sufficient. Frequent irrigation of the pericardial cavity with urokinase or streptokinase, using large catheters, may liquefy the purulent exudate,[67,68] but open surgical drainage through subxiphoid pericardiotomy is preferable.[65] Pericardiectomy is required in patients with dense adhesions, loculated and thick purulent effusion, recurrence of tamponade, persistent infection, and progression to constriction.[66] Surgical mortality is up to 8%.

Tuberculous Pericarditis

In the past decade, tuberculous pericarditis in developed countries has been primarily seen in immunocompromised patients (acquired immunodeficiency syndrome [AIDS]).[70] The mortality rate in untreated effusive tuberculous pericarditis approaches 85%. Pericardial constriction occurs in 30% to 50%.[71,72]

The clinical presentation is variable: acute pericarditis with or without effusion; cardiac tamponade; silent, often large pericardial effusion with a relapsing course; toxic symptoms with persistent fever; acute constrictive pericarditis; subacute constriction; effusive-constrictive or chronic constrictive pericarditis; and pericardial calcifications.[3,73] The diagnosis is made by the identification of *M. tuberculosis* in the pericardial fluid or tissue and/or the presence of caseous granulomas in the pericardium.[70] Importantly, PCR can identify DNA of *M. tuberculosis* rapidly from only 1 μL of pericardial fluid.[74,75] Increased adenosine deaminase activity and interferon gamma concentration in pericardial effusion are also diagnostic, with a high sensitivity and specificity. Both pericardioscopy and pericardial biopsy have also improved the diagnostic accuracy for tuberculous pericarditis (Fig. 102-5).[15] Pericardial biopsy enables rapid diagnosis with better sensitivity than pericardiocentesis (100% vs. 33%).

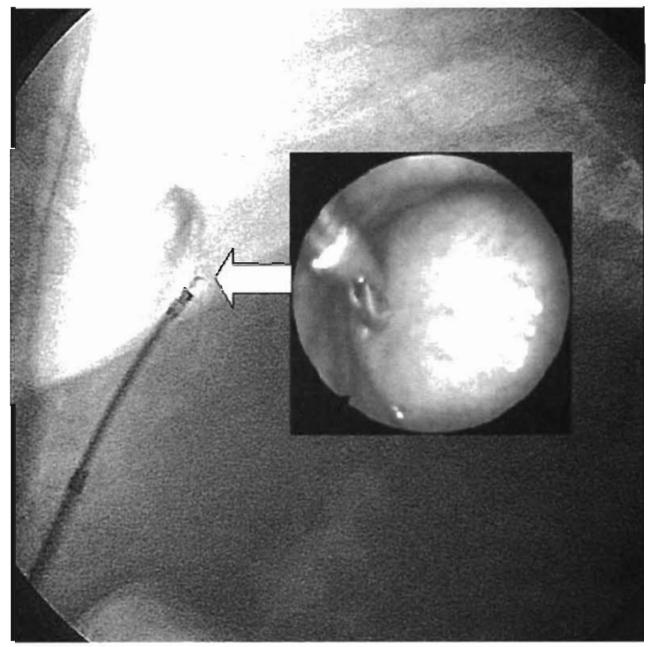

FIGURE 102–5. Flexible percutaneous pericardioscopy and epicardial biopsy *(arrow).*

Pericarditis in a patient with proven extracardiac tuberculosis is strongly suggestive of tuberculous etiology (several sputum cultures should be taken).[76] The tuberculin skin test may be false negative in 25% to 33% of tests[71] and false positive in 30% to 40% of patients.[70] The more accurate enzyme-linked immunospot (ELISPOT) test detects T cells specific for *M. tuberculosis* antigen.[77] Perimyocardial tuberculous involvement is also associated with high serum titers of antimyolemmal and antimyosin antibodies.[78] The diagnostic yield of pericardiocentesis in tuberculous pericarditis ranges from 30% to 76% according to the methods applied for the analyses of pericardial effusion.[71,74] Pericardial fluid demonstrates high specific gravity, high protein levels, and high white blood cell count (from 0.7 to 54 × 10^9/L).[70]

Various antituberculous drug combinations of different durations (6, 9, 12 months) have been applied.[70,71,76,79-82] However, only patients with proven or very likely tuberculous pericarditis should be treated. Prevention of constriction in chronic pericardial effusion of undetermined etiology by "ex iuvantibus" antitubercular treatment was not successful.[79] The use of corticosteroids remains controversial.[76,80-83] A meta-analysis of patients with effusive and constrictive tuberculous pericarditis[81,82] suggested that tuberculostatic treatment combined with corticosteroids might be associated with fewer deaths and less frequent need for pericardiocentesis or pericardiectomy.[76,84] If given, prednisone should be administered in relatively high doses (1 to 2 mg/kg/day) because rifampicin induces its liver metabolism.[7] This dose is maintained for 5 to 7 days and progressively reduced in 6 to 8 weeks. If, in spite of combination therapy, constriction develops, pericardiectomy is indicated.

PERICARDITIS IN RENAL FAILURE

Renal failure is a common cause of pericardial disease, producing large pericardial effusions in up to 20% of patients.[85] Two forms have been described:

1. Uremic pericarditis—in 6% to 10% of patients with advanced renal failure (acute or chronic) before dialysis has been instituted or shortly thereafter.[86] It results from inflammation of the visceral and parietal pericardium and correlates with the degree of azotemia (blood urea nitrogen > 60 mg/dL).
2. Dialysis-associated pericarditis—in up to 13% of patients on maintenance hemodialysis[87] and occasionally with chronic peritoneal dialysis due to inadequate dialysis and/or fluid overload.[88] Pathologic examination of the pericardium shows adhesions between the thickened pericardial membranes ("bread and butter" appearance). The clinical features may include fever and pleuritic chest pain, but many patients are asymptomatic. Pericardial rubs may persist even in large effusions or may be transient. Because of autonomic impairment in uremic patients, heart rate may remain slow (60 to 80 beats/min) during tamponade, despite fever and hypotension. Anemia, due to induced resistance to erythropoietin, may worsen the clinical picture.[89] The ECG does not show the typical diffuse ST-segment/T-wave elevations observed with other causes of acute pericarditis, owing to the lack of the myocardial inflammation.[90] If the ECG is typical of acute pericarditis, intercurrent infection must be suspected.

Most patients with uremic pericarditis respond rapidly to hemodialysis or peritoneal dialysis with resolution of chest pain and pericardial effusion. To avoid hemopericardium heparin-free hemodialysis should be used. Hypokalemia and hypophosphatemia should be prevented by supplementing the dialysis solution when appropriate.[91] Intensified dialysis usually leads to resolution of the pericarditis within 1 to 2 weeks.[92] Peritoneal dialysis, which does not require heparinization, may be therapeutic in pericarditis resistant to hemodialysis or if heparin-free hemodialysis cannot be performed. NSAIDs and systemic corticosteroids have limited success when intensive dialysis is ineffective.[93] Cardiac tamponade and large chronic effusions resistant to dialysis must be treated with pericardiocentesis. Large, nonresolving symptomatic effusions should be treated with intrapericardial instillation of corticosteroids after pericardiocentesis or subxiphoid pericardiotomy (triamcinolone hexacetonide, 50 mg every 6 hours for 2 to 3 days).[87,93] Pericardiectomy is indicated only in refractory, severely symptomatic patients owing to its potential morbidity and mortality. After renal transplantation, pericarditis has also been reported in 2.4% of patients within 2 months.[94] Uremia or infection (CMV) may be the causes.

AUTOREACTIVE PERICARDITIS AND PERICARDITIS IN SYSTEMIC AUTOIMMUNE DISEASES

The diagnosis of autoreactive pericarditis is established using the following criteria[2]:

1. Increased number of lymphocytes and mononuclear cells greater than 5000/mm^3 (autoreactive lymphocytic) or the presence of antibodies against heart muscle tissue (antisarcolemmal) in the pericardial fluid (autoreactive antibody-mediated)
2. Inflammation in epicardial/endomyocardial biopsies by more than 14 cells/mm^2
3. Exclusion of active viral infection both in pericardial effusion and endomyocardial/epimyocardial biopsies (no virus isolation, no IgM-titer against cardiotropic viruses in pericardial effusion, and negative PCR for major cardiotropic viruses)
4. Tuberculosis, *Borrelia burgdorferi*, *Chlamydia pneumoniae*, and other bacterial infection excluded by PCR and/or cultures
5. Neoplastic infiltration absent in pericardial effusion and biopsy samples
6. Exclusion of systemic metabolic disorders and uremia. Intrapericardial treatment with triamcinolone is efficient with rare side effects.

Pericarditis occurs in systemic autoimmune diseases: rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, polymyositis/dermatomyositis, mixed connective tissue disease, seronegative spondyloarthropathies, systemic and hypersensitivity vasculitides, Behçet's syndrome, Wegener's granulomatosis, and sarcoidosis.[7] Intensified treatment of the underlying disease and symptomatic management is indicated.

THE POST–CARDIAC INJURY SYNDROME: POSTPERICARDIOTOMY SYNDROME

Post–cardiac injury syndrome develops within days to months after cardiac or pericardial injury or both.[7,95,96] It resembles the post–myocardial infarction syndrome, both appearing to be variants of a common immunopathologic process. Pericardial effusion also occurs after orthotopic heart transplantation (21%). It is more frequent in patients receiving aminocaproic acid during the operation.[97] Cardiac tamponade after open heart surgery is more common after valve surgery than coronary artery bypass grafting and may be related to the preoperative use of anticoagulants.[98]

Warfarin administration in patients with early postoperative pericardial effusion imposes the greatest risk, particularly in those who did not undergo pericardiocentesis and drainage of the effusion.[99] Symptomatic treatment is as in acute pericarditis (NSAIDs or colchicine for several weeks or months, even after disappearance of effusion).[100] Long-term (3 to 6 months) oral corticosteroids or preferably pericardiocentesis and intrapericardial instillation of triamcinolone (300 mg/m^2) are therapeutic options in refractory forms. Redo surgery is rarely needed. Primary prevention of postpericardiotomy syndrome using short-term perioperative corticosteroid treatment or colchicine is under investigation.[101]

POSTINFARCTION PERICARDITIS

Two forms of postinfarction pericarditis can be distinguished: an "early" form (pericarditis epistenocardica) and a "delayed" form (Dressler's syndrome).[102] Epistenocardiac pericarditis, caused by direct exudation, occurs in 5% to 20% of transmural myocardial infarctions but is clinically discovered rarely. Dressler's syndrome occurs from 1 week to several months

after clinical onset of myocardial infarction with symptoms and manifestations similar to the post–cardiac injury syndrome. It does not require transmural infarction[103] and can also appear as an extension of epistenocardiac pericarditis. Its incidence is 0.5% to 5%[104] and is lower still in patients treated with thrombolytics (<0.5%)[105] but more frequent in cases of pericardial bleeding after antithrombotic treatment.[102,106] Of note, ECG changes are often overshadowed by myocardial infarction changes. Stage one ECG changes are uncommon and suggest "early" post–myocardial infarction syndrome, whereas failure to evolve or "resurrection" of previously inverted T waves strongly suggests myocardial infarction pericarditis.[107,108] Postinfarction pericardial effusion greater than 10 mm is most frequently associated with hemopericardium, and two thirds of these patients may develop tamponade/free wall rupture.[109] Urgent surgical treatment is lifesaving. If the immediate surgery is not available or contraindicated, pericardiocentesis and intrapericardial fibrin-glue instillation could be an alternative in subacute tamponade.[109,110] Ibuprofen, which increases coronary flow, is the agent of choice.[111] Aspirin, up to 650 mg every 4 hours for 2 to 5 days, has also been successfully applied. Corticosteroids can be used for refractory symptoms but may delay the healing after infarction.[7]

TRAUMATIC PERICARDIAL EFFUSION AND HEMOPERICARDIUM IN AORTIC DISSECTION

Direct pericardial injury can be induced by accidents or iatrogenic wounds.[112-115] Iatrogenic tamponade occurs most frequently in percutaneous mitral valvuloplasty, during or after transseptal puncture, particularly if no biplane catheterization laboratory is available and a small left atrium is present. Whereas the puncture of the interatrial septum is asymptomatic, the passage of the free wall induces chest pain immediately. If high-pressure–containing structures are punctured, rapid deterioration occurs. However, if only the atrial wall is passed, the tamponade may be delayed for 4 to 6 hours. Rescue pericardiocentesis is successful in 95% to 100%, with a less than 1% mortality.[116]

Transection of the coronary artery and acute or subacute cardiac tamponade occur very rarely during percutaneous coronary interventions.[117,118] A breakthrough in the treatment of coronary perforation has been the development of membrane-covered graft stents.[119,120]

During right ventricular endomyocardial biopsy the catheter may pass the myocardium, particularly when the bioptome has not been opened before reaching the endocardial border or it is directed to the right ventricular free wall instead of to the septum. Frank cardiac perforations are accompanied by sudden bradycardia and hypotension.[121] A perforation rate of 0.3% to 5% was reported, leading to tamponade and circulatory collapse in less than half of the cases.[121-123] The incidence of pericardial hemorrhage in left ventricular endomyocardial biopsy is lower (0.1% to 3.3%). Severe complications, leading to procedure-related mortality, were reported in only 0.05% in a worldwide survey of more than 6000 cases[122] and in none of the 2537 patients in our center.[123]

Pacemaker leads penetrating the right ventricle or epicardial electrodes may cause pericarditis with tamponade, adhesions, or constriction.[124-127] A right bundle branch block instead of a usually induced left bundle branch block is a clue.

Blunt chest trauma is the major risk of car accidents. The deceleration force can lead to myocardial contusion with intrapericardial hemorrhage, cardiac rupture, pericardial rupture, or herniation. Transesophageal echocardiography or immediate CT should be performed.[128] Pericardial laceration and partial extrusion of the heart into the mediastinum and pleural space may also occur after injury.[113]

In dissection of the ascending aorta, pericardial effusion can be found in 17% to 45% of the patients and in 48% of the autopsy cases.[128] In a clinical series of aortic dissection, pericardial tamponade was found by CT,[130] MRI,[131] or echocardiography[132] in 17% to 33% of patients with type I dissection, 18% to 45% in type II dissection, and 6% in type III dissection.[130] Pericardiocentesis is contraindicated, owing to the risk of intensified bleeding and extension of the dissection.[133,134] Surgery should be performed immediately.

NEOPLASTIC PERICARDITIS

Primary tumors of the pericardium are 40 times less common than metastatic ones.[7] Mesothelioma, the most common of the primary tumors, is almost always incurable. The most common secondary malignant tumors are lung cancer, breast cancer, malignant melanoma, lymphomas, and leukemia. Effusions may be small or large with an imminent tamponade (frequent recurrences) or constriction. Tamponade may even be the initial sign of malignant disease.[135] With small effusions most patients are asymptomatic. The onset of dyspnea, cough, chest pain, tachycardia, and jugular venous distention is observed when the volume of fluid exceeds 500 mL. Pulsus paradoxus, hypotension, cardiogenic shock, and paradoxical movement of the jugular venous pulse are important signs of cardiac tamponade. The diagnosis is based on the confirmation of the malignant infiltration within the pericardium by cytology or biopsy. Of note, in almost two thirds of the patients with documented malignancy pericardial effusion is caused by nonmalignant diseases (e.g., radiation pericarditis or opportunistic infections).[136,137] The chest radiograph, CT, and MRI may reveal mediastinal widening, hilar masses, and pleural effusion.[7] The analysis of pericardial fluid and pericardial or epicardial biopsy are essential for the confirmation of malignant pericardial disease.

Cardiac tamponade is an absolute indication for pericardiocentesis. In suspected neoplastic pericardial effusion without tamponade, systemic antineoplastic treatment as baseline therapy can prevent recurrences in up to 67% of cases.[135] However, pericardial drainage is recommended in all patients with large effusions because of the high recurrence rate (40% to 70%).[138-144] Prevention of recurrences may be achieved by intrapericardial instillation of sclerosing, cytotoxic agents, or immunomodulators. Intrapericardial treatment tailored to the type of the tumor indicates that administration of cisplatin is effective in secondary lung cancer, and intrapericardial instillation of thiotepa appears to be highly effective in breast cancer pericardial metastases.[145-150] No patient showed signs of constrictive pericarditis. Tetracyclines as sclerosing agents also control the malignant pericardial effusion in around 85% of cases, but side effects and complications are quite frequent: fever (19%), chest pain (20%), and

atrial arrhythmias (10%).[135,143,144] Although intrapericardial administration of radionuclides has yielded very good results, it is not widely accepted because of the logistic problems connected with their radioactivity.[151] Radiation therapy is very effective (93%) in controlling malignant pericardial effusion in patients with radiosensitive tumors such as lymphoma and leukemia. However, radiotherapy of the heart can cause myocarditis and pericarditis by itself.[135]

RARE FORMS OF PERICARDIAL DISEASE

Fungal pericarditis occurs mainly in immunocompromised patients or in the course of endemic, acquired fungal infections.[152] It is mainly due to endemic *(Histoplasma, Coccidioides)* or opportunistic fungi *(Candida, Aspergillus, Blastomyces)* and semifungi *(Nocardia, Actinomyces).*[153-155] Diagnosis is obtained by staining and culturing pericardial fluid or tissue. Antifungal antibodies in serum are also helpful in establishing the diagnosis.[3] Treatment with fluconazole, ketoconazole, itraconazole, amphotericin B, liposomal amphotericin B, or amphotericin B lipid complex is indicated. NSAIDs can support the treatment with antifungal drugs. Patients with histoplasmosis pericarditis do not need antifungal therapy but respond to NSAIDs given for 2 to 12 weeks. Sulfonamides are the drugs of choice for nocardiosis. Combination of three antibiotics including penicillin should be given for actinomycosis. Pericardiocentesis or surgical treatment is indicated for hemodynamic impairment. Pericardiectomy is indicated in fungal constrictive pericarditis.

Radiation pericarditis may begin already during exposure (very rare) or months and years later—with latency of up to 15 to 20 years. Its occurrence is influenced by the applied source, dose, fractionation, duration, radiation exposed volume, form of mantel field therapy, and the age of the patient.[156] The effusion may be serous or hemorrhagic, later on with fibrinous adhesions or constriction, typically without tissue calcification. The symptoms may be masked by the underlying disease or the applied chemotherapy. Imaging should start with echocardiography, followed by cardiac CT or MRI if necessary. Pericarditis without tamponade may be treated conservatively. Pericardial constriction occurs in up to 20% of patients, requiring pericardiectomy. The operative mortality is high (21%) and the postoperative 5-year survival is poor (1%), mostly owing to myocardial fibrosis.[157]

Chylopericardium refers to a communication between the pericardium and the thoracic duct, as a result of trauma or congenital anomalies, or as a complication of open-heart surgery,[158] mediastinal lymphangiomas, lymphangiomatous hamartomas, lymphangiectasis, and obstruction or anomalies of the thoracic duct.[159] Infection, tamponade, or constriction may aggravate the prognosis.[160] The pericardial fluid is sterile, odorless, and opalescent with a milky white appearance and the microscopic finding of fat droplets. The chylous nature of the fluid is confirmed by its alkaline reaction, specific gravity between 1010 and 1021, Sudan III stain for fat, and the high concentrations of triglycerides (5 to 50 g/L) and protein (22 to 60 g/L).[161,162] Enhanced CT, alone or combined with lymphography, can identify not only the location of the thoracic duct but also its lymphatic connection to the pericardium.[163,164]

Treatment depends on the etiology and the amount of chylous accumulation.[165] Chylopericardium after thoracic or cardiac operation is preferably treated by pericardiocentesis and diet (medium-chain triglycerides).[166,167] If further production of chylous effusion continues, surgical treatment is mandatory. When conservative treatment and pericardiocentesis fail, a pericardioperitoneal window is a reasonable option.[168,169] Alternatively, when the course of the thoracic duct is precisely identified, its ligation and resection just above the diaphragm is the most effective treatment.[170]

Drug- and toxin-related pericarditis, tamponade, adhesions, fibrosis, or constriction may be induced by several drugs.[7,171] Mechanisms include drug-induced lupus reactions, idiosyncrasy, "serum sickness," foreign substance reactions, and immunopathy. Management is based on the discontinuation of the causative agent and symptomatic treatment.

Pericardial effusion in hypothyroidism occurs in 5% to 30% of patients.[7] Fluid accumulates slowly and tamponade occurs rarely. In some cases, cholesterol pericarditis may be observed. The diagnosis is based on serum levels of thyroxine and thyroid-stimulating hormone. Bradycardia, low voltage of the QRS and T wave inversion or flattening in the ECG, cardiomegaly on the radiograph, and pericardial effusion on echocardiography, as well as a history of radiation-induced thyroid dysfunction, myopathy, ascites, pleural effusion, and uveal edema may be observed.[172-176] Therapy with thyroid hormone decreases pericardial effusion.

Pericardial effusion and constriction in pregnancy may manifest as a minimal to moderate clinically silent hydropericardium by the third trimester. Cardiac compression is rare.[177] ECG changes of acute pericarditis in pregnancy should be distinguished from the slight ST-segment depressions and T-wave changes seen in normal pregnancy.[177,178] Occult constriction becomes manifest in pregnancy owing to the increased blood volume.[178] Most pericardial disorders are managed as in nonpregnant women.[179,180] Caution is necessary because high-dose aspirin may prematurely close the ductus arteriosus, and colchicine is contraindicated in pregnancy. Pericardiotomy and pericardiectomy can be safely performed if necessary and do not impose a risk for subsequent pregnancies.[180,181]

Fetal pericardial fluid can be detected by echocardiography after 20 weeks' gestation and is normally 2 mm or less in depth. More fluid should raise questions of hydrops fetalis, Rh disease, neoplasia, hypoalbuminemia, immunopathy, or maternally transmitted mycoplasmal or other infections.[182]

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Chapter 103
EMERGENT VALVULAR DISORDERS

Catherine M. Otto

KEY POINTS

ACUTE MITRAL REGURGITATION

1. Causes include endocarditis, mitral prolapse, and acute myocardial infarction.
2. It presents as pulmonary edema.
3. Murmur may be soft or absent.
4. Prompt echocardiography is essential.
5. Pulmonary wedge v wave is not always seen.
6. Intra-aortic balloon pump improves hemodynamics.
7. Definitive treatment is mitral valve surgery.

ACUTE AORTIC REGURGITATION

1. Causes include endocarditis and aortic dissection.
2. Diastolic murmur may be soft.
3. Prompt echocardiography is essential.
4. Treatment is emergency surgery.

MITRAL STENOSIS

1. Rheumatic mitral stenosis typically occurs in young women.
2. It may present during pregnancy.
3. Echocardiography is diagnostic.
4. Acute decompensation can be treated conservatively.
5. Percutaneous balloon mitral valvuloplasty is the optimal intervention.

AORTIC STENOSIS

1. Aortic stenosis is common in the elderly.
2. Decompensation occurs with increased hemodynamic demand.
3. Physical examination shows a systolic murmur.
4. Echocardiography is diagnostic.
5. Conservative management for decompensation is appropriate.
6. Severe symptomatic disease requires aortic valve replacement.

PROSTHETIC VALVES

1. Mechanical valves are at risk of valve thrombosis.
2. Management of prosthetic valve thrombosis is controversial.
3. Tissue valves undergo degeneration 10 to 15 years after implantation.
4. Acute regurgitation is similar to native valve disease.

In the critical care setting there are two distinct presentations of valvular heart disease: (1) acute valve dysfunction resulting in acute heart failure and (2) chronic valve disease with decompensation due to increased metabolic demands (Table 103-1).[1] Valve regurgitation is the most common type of acute valve dysfunction. Valve stenosis, with rare exceptions, is a chronic, slowly progressive disease. However, in patients with asymptomatic chronic valve stenosis, acute deterioration can occur if there is a superimposed hemodynamic burden. For example, the patient with previously asymptomatic mitral stenosis may present with pulmonary edema in the setting of a systemic infection. Another example is the elderly adult with asymptomatic aortic stenosis who presents with cardiogenic shock in the setting of an acute gastrointestinal hemorrhage.

The key concepts in the management of the critically ill patient with valvular heart disease are the use of echocardiography to provide an accurate diagnosis of disease severity and the appropriate use of invasive hemodynamic monitoring to optimize loading conditions.

MITRAL REGURGITATION

ETIOLOGY

Mitral regurgitation may be caused by disease or distortion of any component of the mitral valve apparatus, including the mitral annulus, leaflets, chordae, and papillary muscles as well as by alterations in left ventricular (LV) geometry or systolic function (Fig. 103-1).[2] Primary causes of chronic mitral regurgitation include myxomatous valve leaflets (mitral valve prolapse) and rheumatic disease. Chronic secondary mitral regurgitation may be due to dilated cardiomyopathy or to coronary artery disease with regional or global left ventricular dysfunction.

Acute mitral regurgitation also may be due to involvement of the valve leaflets or the left ventricle. Patients with

TABLE 103–1. CAUSES OF ACUTE VALVE DYSFUNCTION

Mitral Regurgitation
Myxomatous disease with flail leaflet
Spontaneous chordal rupture
Endocarditis
Acute myocardial infarction
Papillary muscle rupture
Regional wall motion abnormality
Left ventricular dilation and systolic dysfunction
Aortic Regurgitation
Endocarditis
Spontaneous rupture of a congenital fenestration
Aortic dissection
Tricuspid Regurgitation
Endocarditis
Penetrating chest trauma
Blunt chest wall trauma
Prosthetic Valves
Endocarditis
Valve thrombosis
Paravalvular dehiscence
Leaflet tear

myxomatous mitral valve disease may develop acute regurgitation due to spontaneous chordal rupture.[3,4] Bacterial endocarditis results in acute mitral regurgitation due to destruction of valve tissue, often with leaflet perforation. Mitral regurgitation complicates 3% to 16% of acute myocardial infarctions (AMIs) due to papillary muscle dysfunction or rupture as a result of impaired function of the myocardial wall underlying the posterolateral papillary muscle.[5-7]

CLINICAL PRESENTATION

Although patients with chronic mitral regurgitation may be asymptomatic for many years, the regurgitant lesion imposes a volume load on the left ventricle because an increased total stroke volume is needed to maintain a normal forward cardiac output. LV volume overload results in progressive LV dilation and may lead to an irreversible decline in ventricular contractility, even in the absence of clinical symptoms. Evaluation of ventricular contractility is problematic in patients with mitral regurgitation given that measures of ventricular performance are affected by preload and afterload.[8] However, based on outcomes after mitral valve surgery, the empirical parameters of ventricular end-systolic dimension and ejection fraction can be used to optimize the timing of surgical intervention. Thus, patients with moderate to severe chronic regurgitation undergo periodic echocardiography with valve repair or replacement recommended when the end-systolic dimension is 45 mm or more and the ejection fraction is 60% or less.[9]

Chronic mitral regurgitation usually is well tolerated even when there is a superimposed hemodynamic load such as systemic infection, pregnancy, or trauma. However, mitral regurgitant severity may acutely worsen by at least two mechanisms. First, an increase in afterload, for example with a hypertensive crisis, may increase regurgitant severity due to an increased driving pressure from the left ventricle to the left atrium. Second, alteration in LV geometry, for example with ventricular dilation due to decompensated heart failure, may change the orientation of the papillary muscles such that leaflet closure is impaired, resulting in a larger regurgitant orifice area.[10] In this situation, a vicious cycle may ensue in

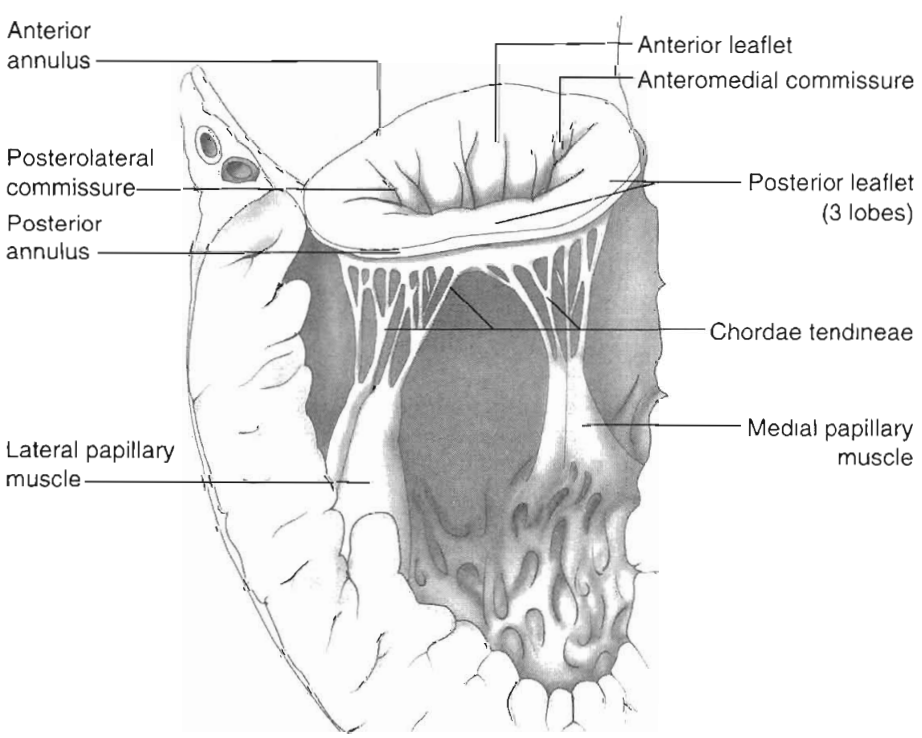
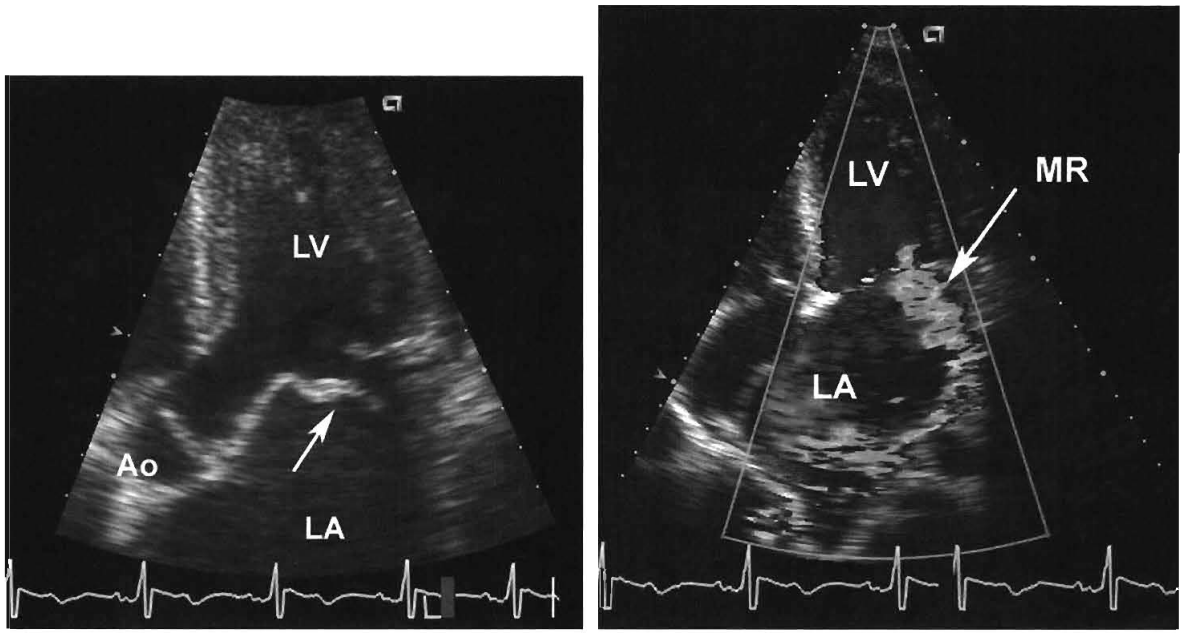


FIGURE 103–1. The mitral valve consists of the mitral annulus, anterior and posterior leaflets, chordae tendineae, and papillary muscles. Mitral regurgitation may be due to a disease that primarily affects the valve leaflets, such as mitral valve prolapse or rheumatic mitral valve disease, or may result from alterations in the function or structure of the left ventricle, such as those induced by ischemic disease or dilated cardiomyopathy. (From Otto CM: Clinical practice: Evaluation and management of chronic mitral regurgitation. N Engl J Med 2001;345:740-746.)



A B

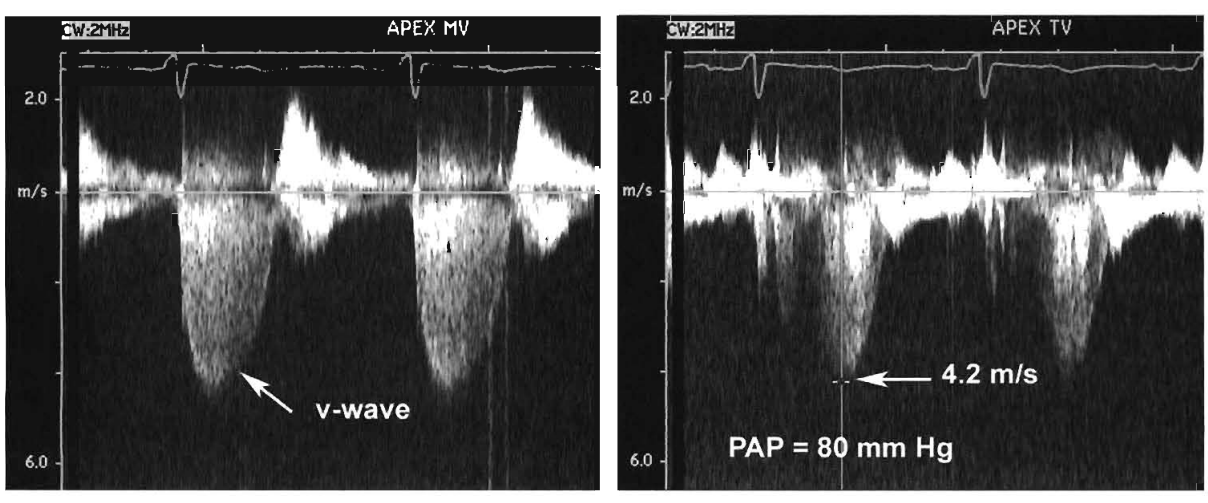
FIGURE 103–2. In this 24-year-old man with chronic mitral prolapse, chordal rupture resulted in a flail anterior leaflet seen in an apical four-chamber view (**A,** *arrow*). Severe mitral regurgitation (MR) was seen with a posterior and laterally directed jet on Doppler color flow imaging (**B,** *arrow*). Ao, aorta; LA, left atrium; LV, left ventricle. (See Color Section in this text.)

which LV dilation worsens mitral regurgitant severity, which increases LV dilation, and so forth.

Acute mitral regurgitation presents as acute pulmonary edema and is a surgical emergency (Figs. 103-2 and 103-3). Mitral chordal rupture results in the acute presentation of heart failure, often in patients who were unaware of a diagnosis of mitral valve prolapse. Patients with mitral valve perforation due to endocarditis present with pulmonary edema superimposed on signs and symptoms of endocarditis. Papillary muscle rupture or dysfunction after myocardial infarction usually presents several days after AMI; in some cases, the initial presentation is acute pulmonary edema, with the myocardial infarction being clinically silent.[11]

DIAGNOSIS

A high level of clinical suspicion is needed to make the diagnosis of acute mitral regurgitation (Table 103-2). Acute pulmonary edema often obscures the signs and symptoms of the underlying disease process. The classical finding is a



A B

FIGURE 103–3. In the same patient as Figure 103-2 severe mitral regurgitation was recorded with continuous wave Doppler ultrasound (**A**). The rapid rise in left atrial pressure due to the regurgitant jet entering the left atrium results in a rapid decline in the Doppler velocity in late systole—the Doppler equivalent of the v wave seen on a pulmonary wedge pressure tracing. The continuous wave Doppler recording of the maximum tricuspid regurgitant jet velocity (**B**) of 4.2 m/s indicates a right ventricular to right atrial pressure difference of 70 mm Hg. The patient's right atrial pressure was estimated to be 10 mm Hg, based on the size and respiratory variation in the inferior vena cava, so that the estimated pulmonary systolic pressure is 80 mm Hg.

TABLE 103–2. DIAGNOSTIC APPROACH TO ACUTE VALVE DYSFUNCTION

Physical Examination	Unreliable Consider valve dysfunction in all patients with pulmonary edema
Echocardiography (transthoracic)	Accurate diagnosis of etiology of disease Quantitation of severity of stenosis or regurgitation Measurement of ventricular ejection fraction Estimation of pulmonary pressures
Transesophageal Echocardiography	Sensitive for detection of valvular vegetations Detection of paravalvular abscess Essential for prosthetic mitral valve dysfunction Useful for prosthetic aortic valve dysfunction
Right-Sided Heart Catheterization	Not reliable for diagnosis of valve disease May be helpful for optimizing loading conditions
Chest CT	Sensitive and specific for diagnosis of aortic dissection
Angiography	Used when coronary angiography is needed

holosystolic murmur at the apex radiating to the axilla.[12] However, although there is some correlation between the loudness of the murmur and regurgitant severity with chronic regurgitation, the murmur may be soft with acute severe mitral regurgitation. In patients with severe mitral regurgitation after myocardial infarction a murmur cannot be appreciated at all in up to 50% of patients.[13]

Thus, in patients presenting with acute pulmonary edema or cardiogenic shock, prompt echocardiography is essential. Transthoracic images often are diagnostic, allowing identification of the etiology of valve dysfunction, quantitation of regurgitant severity, estimation of pulmonary pressures, and measurement of ventricular size and systolic function. If transthoracic images are nondiagnostic, transesophageal echocardiography (TEE) can be performed at the bedside in the ICU. TEE provides excellent images of valve anatomy and Doppler evaluation of valve function.

Other diagnostic tests are based on the clinical presentation. Multiple blood cultures should be obtained in febrile patients with pulmonary edema to exclude the possibility of endocarditis. In patients with an abnormal electrocardiogram (ECG), chest pain, or a history of coronary artery disease, coronary angiography may be needed.

In the patient with acute pulmonary edema or cardiogenic shock after myocardial infarction, the differential diagnosis includes acute mitral regurgitation, a ventricular septal defect (VSD), or a contained rupture of the ventricular free wall. All these possibilities can be diagnosed by echocardiography, in an experienced center.

Invasive hemodynamic monitoring with a Swan-Ganz catheter for measurement of pulmonary pressures and cardiac output is needed in the patient with suspected acute mitral regurgitation. At the time of placement, oxygen saturations in the right atrium, right ventricle, and pulmonary artery should be measured; a VSD results in a "step-up" in oxygen saturation between the right atrium and ventricle due to oxygenated blood from the left ventricle entering the right ventricle. The pulmonary wedge pressure tracing should be examined for the presence of a v wave. The presence of a prominent v wave supports the diagnosis of acute mitral regurgitation, although some patients have severe regurgitation with no v wave and a v wave can be seen in the absence of severe mitral regurgitation in patients with a prosthetic mitral valve.[14,15]

MANAGEMENT

In patients with chronic mitral regurgitation and heart failure, management is directed at treating the process leading to decompensation and optimizing loading conditions (Table 103-3). For example, in a patient with a systemic infection, treatment of the infection, control of fever and tachycardia, and invasive monitoring to optimize preload and afterload are utilized. Medical therapy typically includes afterload reduction with nitroprusside or other vasodilators and preload reduction with diuretics.[16,17] The goal is to support the patient through the period of decompensation. Typically, hemodynamics return to the baseline compensated state after the acute illness.

In contrast, acute severe mitral regurgitation is a surgical emergency.[18] Medical stabilization should occur concurrently with consultation by a cardiac surgeon. Acutely, placement of an intra-aortic balloon pump (IABP) provides optimal afterload reduction while improving diastolic coronary blood flow.

The timing and risk of surgical intervention depend on the etiology of acute mitral regurgitation. Spontaneous chordal rupture usually can be treated early with mitral valve repair.[19] Compared with valve replacement, mitral valve repair is associated with a lower operative mortality, improved preservation of LV function, and better long-term survival. In addition, the risks of a prosthetic valve and anticoagulation are avoided.

The timing of surgery for endocarditis depends on the disease course in that individual, but most centers now advocate early surgical intervention in the patient with heart failure to prevent progressive valve damage and paravalvular abscess formation. Recent studies suggest that delaying surgery does not decrease the risk of recurrent infection. Valve repair is preferred but may not be possible depending on the extent of tissue destruction.

In patients with acute ischemic mitral regurgitation, treatment depends on the exact etiology of valve dysfunction.[20] In patients with acute mitral regurgitation due to a regional wall motion abnormality, myocardial function may improve after percutaneous revascularization.[6,21] In these patients, an

TABLE 103–3. THERAPEUTIC APPROACH TO ACUTE VALVE DYSFUNCTION

1. Accurate diagnosis with echocardiography—differentiate acute valve dysfunction from acute decompensation with chronic valve disease.
2. Treat the underlying disease process associated with decompensation (e.g., endocarditis, acute myocardial infarction, anemia).
3. Optimize loading conditions using diuretics, vasodilators, and other agents with invasive hemodynamic monitoring.
4. Consult the cardiac surgery team as soon as the diagnosis is made.
5. Use intra-aortic balloon pump for acute mitral regurgitation.
6. Consider surgical or percutaneous intervention for acute valve dysfunction.

IABP and medical therapy may be used during the acute episode with weaning of therapy as myocardial function improves.

Mitral regurgitation due to partial or complete papillary muscle rupture requires surgical intervention. Although the risk of surgery is high with an operative mortality rate of about 50%, outcome is even worse with medical therapy, with a mortality of 75% at 24 hours and 95% within 2 weeks after complete papillary muscle rupture.[5,22,23] With the use of echocardiography, partial papillary muscle rupture can be recognized; prognosis in these patients depends on the extent of myocardial damage and severity of mitral regurgitation.[24] With partial papillary muscle rupture, some surgeons prefer to stabilize the patient and delay surgery for 6 to 8 weeks after myocardial infarction to avoid operating on the necrotic myocardial tissue. However, many patients cannot be stabilized so acute intervention must be considered. Again, valve repair is preferred but myocardial necrosis may necessitate valve replacement. Risk factors for surgery include older age, female gender, and poor LV systolic function.[25] In some patients, the risk of surgical intervention may be so high as to be futile.

AORTIC REGURGITATION

ETIOLOGY

Chronic aortic regurgitation most often is due to a congenital bicuspid valve, rheumatic valve disease, or aortic root dilation. There are numerous causes of aortic root dilation, including hypertension, cystic medial necrosis, Marfan syndrome, and a bicuspid aortic valve.[26] The most common causes of acute aortic regurgitation are endocarditis, rupture of a congenital fenestration, and acute aortic dissection.[27] Endocarditis results in aortic regurgitation by destruction of the valve leaflet tissue, with a high percentage of cases also having paravalvular abscess formation. Aortic dissection results in acute aortic regurgitation either due to enlargement of the aortic annulus or to extension of the dissection into the valve region resulting in a flail aortic valve leaflet.

CLINICAL PRESENTATION

The acute backflow of blood from the aorta into the left ventricle in diastole results in an acute elevation in LV end-diastolic pressure with consequent pulmonary edema.[28] Because there has been no time for compensatory LV dilation, forward cardiac output falls abruptly due to the regurgitant flow across the valve in diastole so that patients with acute aortic regurgitation also may be in cardiogenic shock.[29] Decreased coronary perfusion pressure results in diffuse subendocardial ischemia, further impairing ventricular function.[30]

DIAGNOSIS

The clinical diagnosis of acute aortic regurgitation differs markedly from chronic aortic regurgitation (Fig. 103-4).[31] In contrast to the high-pitched diastolic decrescendo murmur of chronic aortic regurgitation, there is a "to-and-fro" murmur across the aortic valve that many clinicians fail to recognize as indicating aortic regurgitation. The pulse

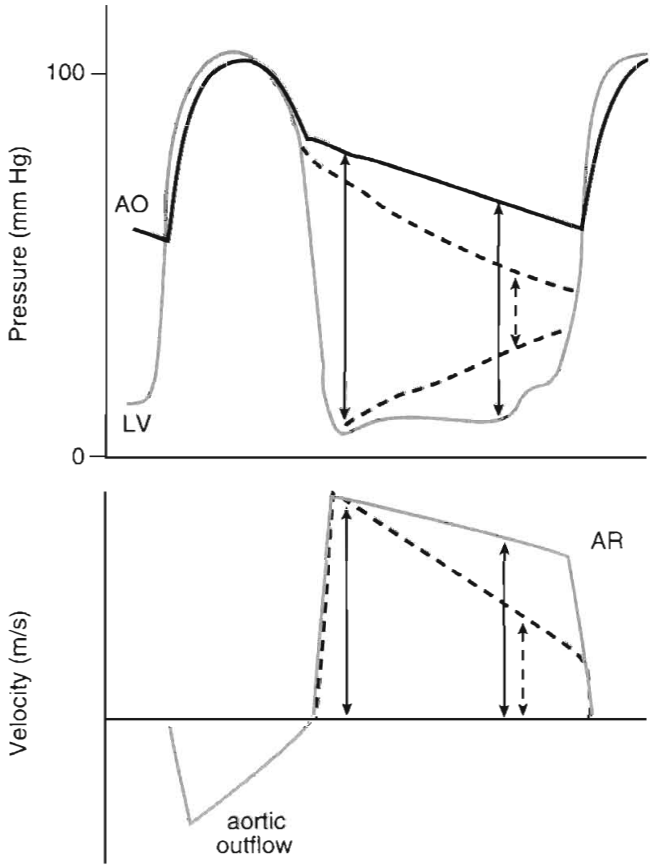


FIGURE 103–4. Left ventricular (LV) and central aortic (Ao) pressures and the corresponding Doppler velocity curves are shown for chronic *(solid lines)* and acute *(dashed lines)* aortic regurgitation. The shape of the velocity curve is related to the instantaneous pressure differences across the valve, as stated in the Bernoulli equation. With acute aortic regurgitation, aortic pressures fall more rapidly and ventricular diastolic pressure rises more rapidly, resulting in a steeper deceleration slope on the Doppler curve. (From Otto CM: The Textbook of Clinical Echocardiography, 3rd ed. Philadelphia, WB Saunders, 2004, p 326.)

pressure is narrow, owing to the low forward stroke volume, and peripheral signs of aortic regurgitation are not seen. As with acute mitral regurgitation, the physical examination findings often are subtle so a high index of suspicion and prompt echocardiography are needed to make this diagnosis.

Acute aortic regurgitation should be considered in the patient with signs or symptoms of endocarditis, in patients with a personal or family history of aortic root disease, and in those with a presentation consistent with acute aortic dissection.

Echocardiography allows imaging of the aortic valve and root and determination of the severity of aortic regurgitation based on a combination of two-dimensional imaging and pulsed, continuous wave, and color Doppler modalities (Figs. 103-5 to 103-7).[32] The continuous wave Doppler curve shows a steep diastolic slope corresponding to the rapid equalization of diastolic pressure in the aorta and left ventricle. With severe acute regurgitation, there is no pressure gradient at end diastole so that cuff diastolic blood pressure is equal to LV end-diastolic pressure. Echocardiography also allows accurate assessment of LV size and systolic function. When the differential diagnosis includes aortic dissection, transthoracic echocardiography is inadequate to exclude this

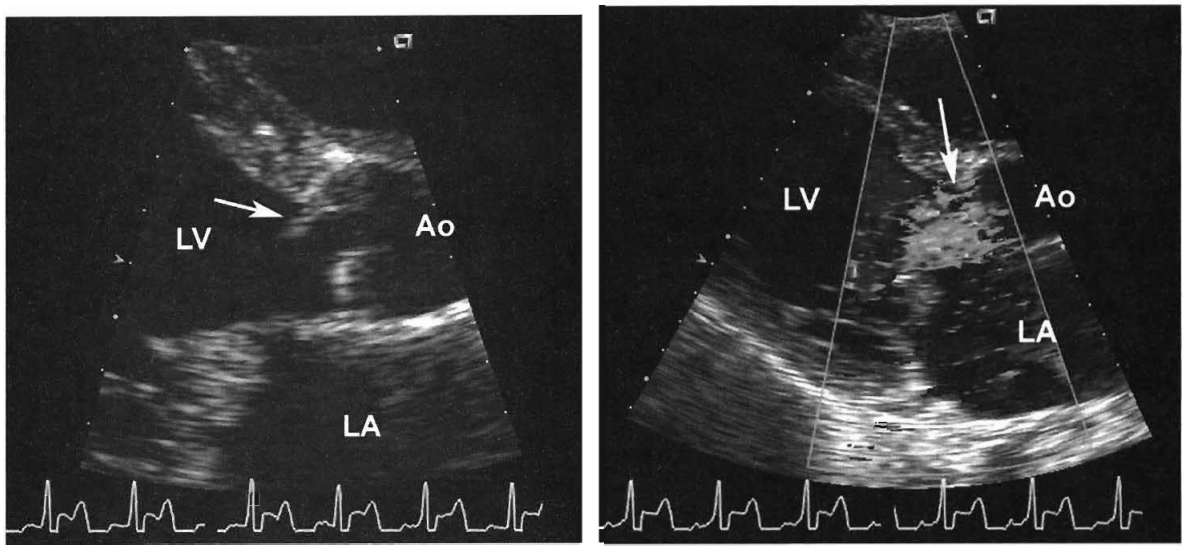


FIGURE 103–5. Endocarditis resulting in acute severe aortic regurgitation. In a long-axis view of the aortic valve (**A**) a flail aortic valve leaflet is seen *(arrow)* with the leaflet prolapsing into the left ventricular (LV) outflow tract in diastole. Color flow imaging (**B**) in the same view shows a broad jet of diastolic flow filling the outflow tract consistent with severe regurgitation. Ao, aorta; LA, left atrium; LV, left ventricle. (See Color Section in this text.)

possibility. Instead, TEE or computed tomography (CT) images should be obtained.

MANAGEMENT

Acute aortic regurgitation is a surgical emergency.[33] Preoperative management is supportive with ventilatory support and invasive hemodynamic monitoring. While the diagnosis is being made, therapy may include the use of diuretics, inotropic agents, and nitroprusside or other vasodilators in an attempt to stabilize hemodynamics.[17,34-36] However, an IABP is contraindicated because inflation of the balloon in the descending thoracic aorta in diastole will increase the amount of backflow across the aortic valve.

If acute aortic regurgitation is due to aortic dissection, acute surgical intervention is needed. The surgical approach may be replacement of the ascending aorta and valve with a Dacron or Gore-Tex valved conduit. When the valve leaflets are normal, some centers will preserve the native valve by re-suspension of the leaflets in a prosthetic conduit (called the David procedure).

When acute aortic regurgitation is due to endocarditis, surgical options include a mechanical valve, a heterograft tissue valve such as a porcine aortic valve or bovine pericardial valve, or a cryopreserved homograft aorta valve. Rarely, the patient may undergo valve repair if there is a simple perforation with adjacent normal leaflet tissue. Many surgeons prefer an aortic homograft in patients with endocarditis

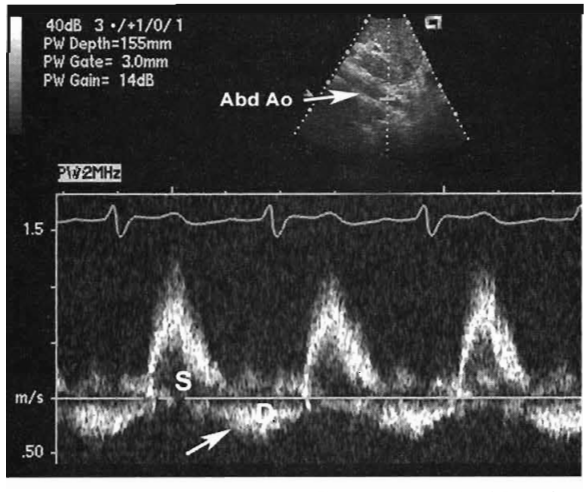


FIGURE 103–6. In the same patient as Figure 103-5, pulsed Doppler flow in the proximal abdominal aorta (Ao) shows normal forward flow in systole (S), with abnormal flow in diastole (D) that extends throughout diastole. This finding is highly specific for severe aortic regurgitation and can be helpful in the acute setting.

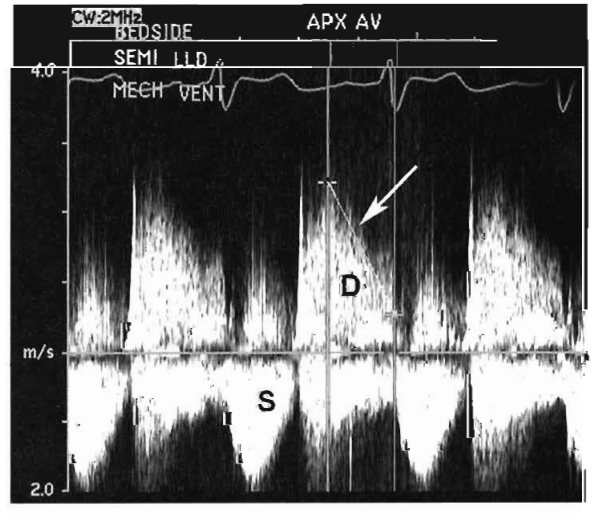


FIGURE 103–7. In the same patient as Figure 103-5, continuous wave Doppler flow of the flow across the aortic valve shows an increased antegrade velocity in systole (S) consistent with a high transaortic stroke volume. In diastole (D), a dense signal of retrograde flow is seen with a steep deceleration slope *(arrow)* consistent with equalization of pressures between the aorta and left ventricle in diastole.

because of relative resistance to reinfection and the frequent occurrence of paravalvular extension of the infection. A cryopreserved aortic homograft typically includes the valve, the ascending aorta, and the anterior mitral leaflet. The surgeon trims the homograft, retaining tissue to repair the aortic annulus, base of the ventricular septum, and anterior mitral leaflet as needed.

MITRAL STENOSIS

ETIOLOGY AND CLINICAL PRESENTATION

Mitral stenosis is nearly always due to rheumatic disease, with only rare cases of calcific mitral stenosis seen in the elderly. Rheumatic mitral stenosis is a slowly progressive disease with an insidious decline in exercise tolerance and symptom onset over many years.[37] However, in the asymptomatic patient with compensated moderate or severe mitral stenosis, acute decompensation can occur in the setting of increased systemic hemodynamic demands. Because mitral stenosis is more common in women (80% of cases) and occurs during the reproductive years, the most common emergency presentation of mitral stenosis is a pregnant woman with heart failure.[38,39] Many of these patients are unaware of underlying valve disease and are initially diagnosed during pregnancy. The clinical presentation may also be due to, or exacerbated by, the onset of atrial fibrillation.

A large atrial myxoma may mimic the clinical presentation of mitral stenosis, presenting as acute hemodynamic compromise due to obstruction of the mitral valve orifice by the tumor mass.

DIAGNOSIS

The apical diastolic rumble and opening snap of mitral stenosis is challenging to appreciate even in a quiet room with optimal patient positioning and frequently is inaudible in the ICU setting.[31] However, the diagnosis is easily made by transthoracic echocardiography with the mitral leaflet showing the characteristic findings of rheumatic disease: commissural fusion, chordal shortening and fusion, and restriction of the diastolic opening of the leaflets (Fig. 103-8).[40] Mitral stenosis severity can be quantitated by calculation of valve area by two-dimensional planimetry or by the Doppler pressure half-time method with moderate to severe stenosis defined as a valve area less than 1.5 cm^2 (Fig. 103-9). Transthoracic echocardiography also provides information on LV size and systolic function, left atrial size, pulmonary pressures, and any associated valve lesions. If evaluation for left atrial thrombus is needed, TEE has a sensitivity of only 60% compared with a sensitivity of nearly 100% from the transthoracic approach.

MANAGEMENT

Most patients with mitral stenosis and acute decompensation can be managed conservatively with treatment of the superimposed illness.[17] Efforts should be directed toward decreasing overall metabolic demand and increasing oxygen delivery by controlling fever, maintaining a normal hemoglobin level, and providing supplemental oxygen. If atrial fibrillation is present, rate control is essential, preferably with conversion back to sinus rhythm. Even when sinus rhythm is present, beta blockers may improve ventricular diastolic filling by prolonging the duration of diastole as heart rate is decreased.[41-44] Invasive hemodynamic monitoring and ventilatory support may be needed when severe heart failure is present.

In patients who do not respond to conservative therapy, emergency intervention should be considered. The optimal intervention is percutaneous balloon mitral valvotomy (PBMV), which typically results in an increase in mitral

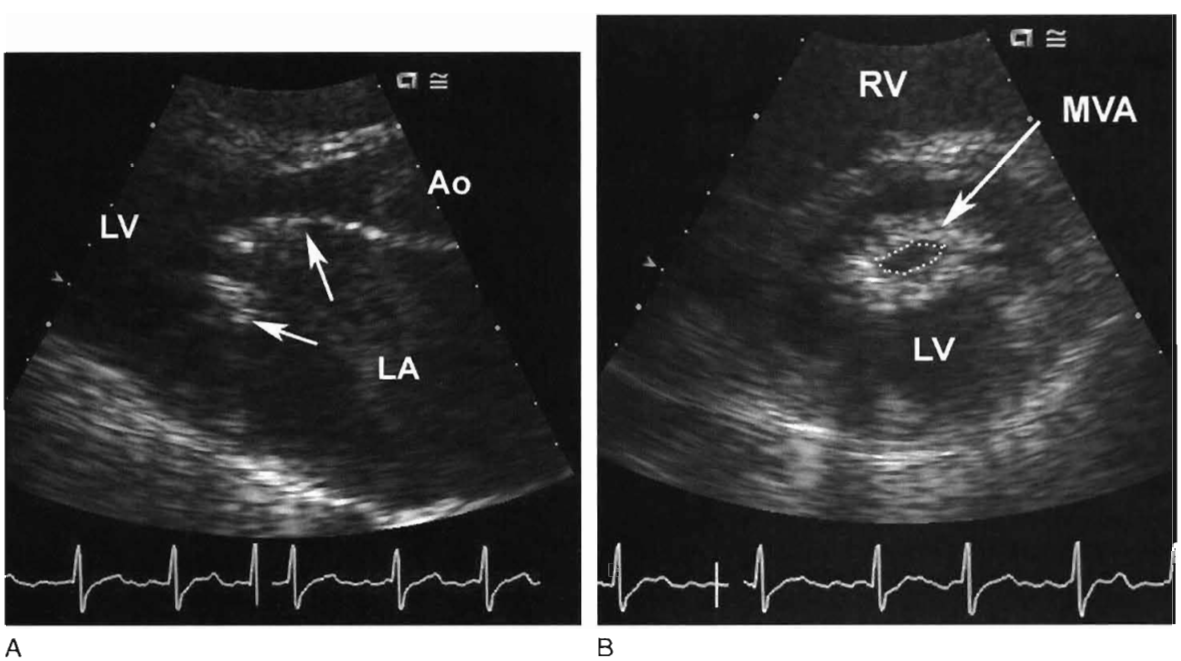


FIGURE 103–8. In this patient with mitral stenosis, the long-axis view demonstrates the classic findings of diastolic doming of the leaflets *(arrows)* due to commissural fusion with thickening predominantly at the leaflet tips (**A**). In the short-axis view (**B**), the restricted mitral orifice with fusion of the commissures can be visualized, providing an accurate measurement of valve area (MVA) by direct planimetry. In this case, the valve area of 0.7 cm^2 indicates severe valve obstruction. Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

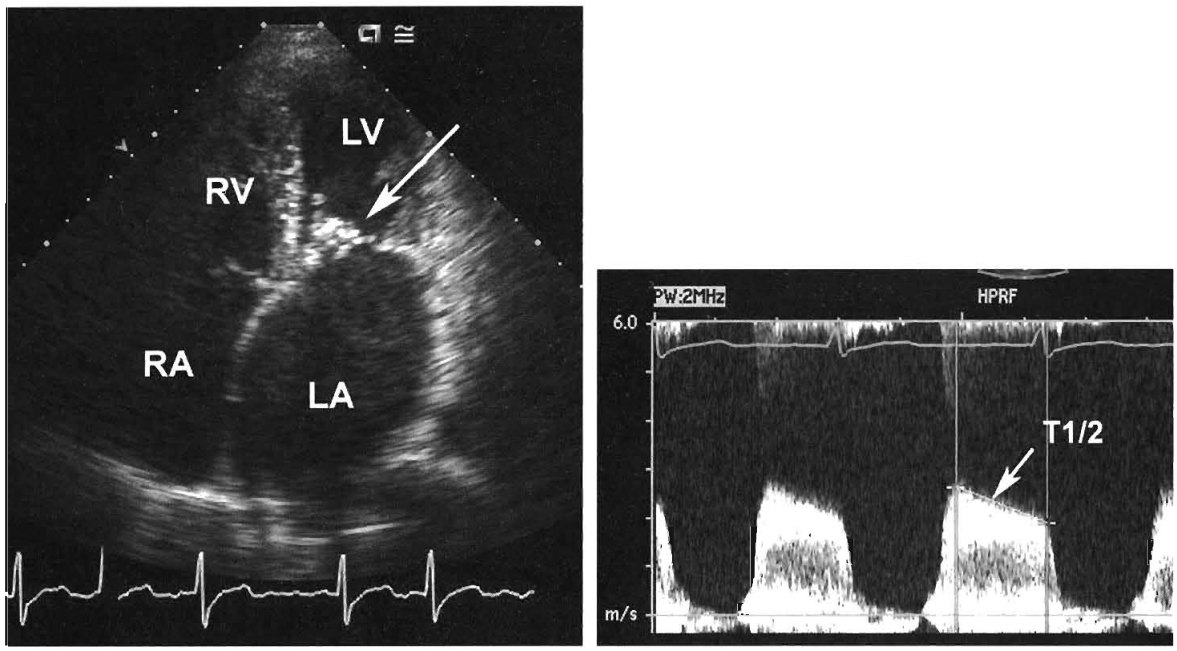


FIGURE 103–9. In the same patient as Figure 103-8, the apical four-chamber view (**A**) shows severe left atrial enlargement due to mitral obstruction with thickened valve leaflets *(arrow)*. The haziness in the left atrium is due to stasis of blood flow with spontaneous contrast medium enhancement on echocardiography. Continuous wave Doppler recording of flow across the mitral valve (**B**) shows an increased velocity corresponding to the transvalvular pressure gradient. The pressure half-time (T1/2) can be used to accurately calculate mitral valve area (0.7 cm^2).

valve area to greater than 1.5 cm^2. PBMV can be safely performed even during pregnancy.[45-47] Patients with a left atrial thrombus, coexisting moderate to severe mitral regurgitation, or heavily calcified and deformed mitral valves are not candidates for PBMV; in these patients, surgical mitral valve replacement may be needed.

AORTIC STENOSIS

ETIOLOGY AND CLINICAL PRESENTATION

Valvular aortic stenosis in adults is most often due to calcification of a normal trileaflet or congenital bicuspid valve (Fig. 103-10). Rheumatic aortic stenosis is less common and is invariably accompanied by mitral valve involvement. In younger adults, congenital aortic stenosis may be encountered; some of these patients have restenosis after prior commissurotomy in childhood.

Like mitral stenosis, aortic valve stenosis is a chronic, slowly progressive disease that presents acutely only in patients who have not been receiving regular medical care.[48-50] As in mitral stenosis, acute decompensation may occur with a superimposed systemic condition. Young women with congenital aortic stenosis may present with angina or heart failure during pregnancy. In older adults, asymptomatic patients with moderate to severe valve obstruction may present with heart failure in the setting of pneumonia, anemia, or other conditions with increased metabolic demands.

DIAGNOSIS

The classic physical examination findings for aortic stenosis include a delayed and decreased carotid upstroke, a narrow pulse pressure, a single second heart sound (S_2), and a systolic ejection murmur at the aortic region that radiates to the carotid. However, while a grade 4 murmur (palpable thrill) with a single S_2 and diminished carotids is specific for severe stenosis, these findings are very insensitive for the diagnosis.[51] Particularly when the patient is decompensated, the murmur may be soft and carotid upstrokes may be altered by coexisting vascular disease or loading conditions.

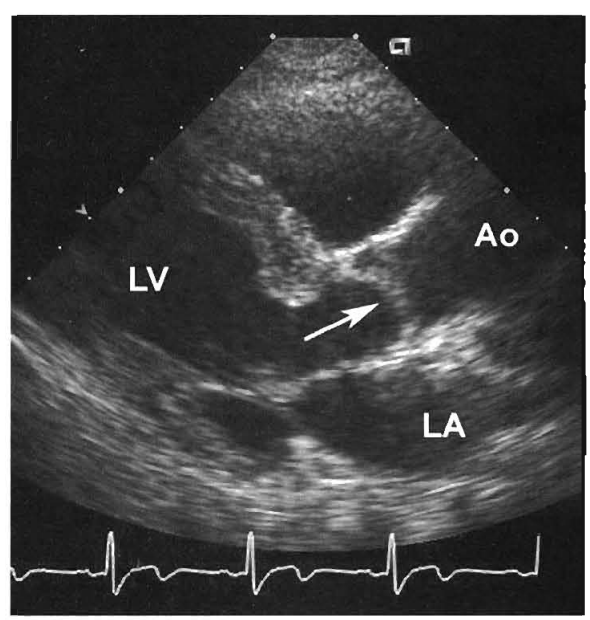


FIGURE 103–10. In this 26-year-old pregnant woman with a loud systolic murmur, the long-axis view shows doming of the aortic valve in systole *(arrow)*. Short-axis images confirmed a unicuspid aortic valve. Ao, aorta; LA, left atrium; LV, left ventricle.

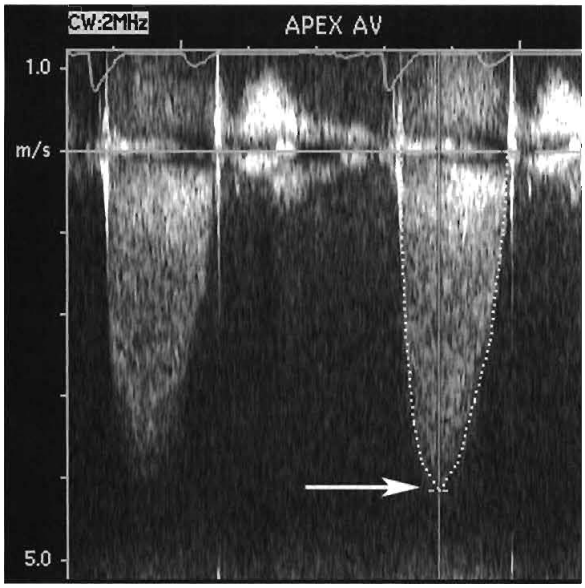


FIGURE 103–11. Continuous wave Doppler examination of the aortic valve in the patient shown in Figure 103–10 demonstrates a high-velocity signal consistent with severe aortic stenosis. The maximum velocity of 4.2 m/s corresponds to a maximum transaortic pressure gradient of 69 mm Hg and a mean gradient of 41 mm Hg. Valve area, calculated by the continuity equation, was 0.8 cm^2.

Echocardiography provides reliable evaluation of aortic stenosis severity based on the maximum velocity through the narrowed orifice and valve area, calculated with the continuity equation (Fig. 103-11). Disease severity is a continuum and velocities may be relatively low, despite severe stenosis, when cardiac output is reduced. In general, stenosis can be graded as severe (valve area < 1.0 cm^2 or jet velocity > 4 m/sec), moderate (valve area 1.0 to 1.5 cm^2 or jet velocity 3 to 4 m/sec), or mild (valve area > 1.5 cm^2 or jet velocity < 3 m/sec). Echocardiography also allows evaluation of ventricular systolic and diastolic function and any associated valve disease.[52]

MANAGEMENT

As with mitral stenosis, most patients with decompensated aortic stenosis can be managed conservatively by treating the underlying disease process that led to decompensation and restoring the patient's normal loading conditions. However, in the patient who has denied symptoms or has not been receiving medical care, the first presentation of aortic stenosis may be syncope or pulmonary edema. In these patients, aortic stenosis is the cause of decompensation, as evidenced by very severe valve obstruction, often with a low ejection fraction. Treatment is urgent aortic valve replacement. Some centers advocate the use of balloon aortic valvuloplasty in these patients, but this approach has no advantage over direct surgical intervention. A preliminary study suggests that cautious use of nitroprusside may improve hemodynamics before valve replacement in severe decompensated aortic stenosis if mean arterial pressure is greater than 60 mm Hg, but the utility and safety of this approach needs further evaluation.[53,54]

RIGHT-SIDED VALVE DISEASE

Pulmonic valve disease is nearly always congenital in origin with a chronic disease course. Tricuspid valve stenosis is rare and usually accompanies rheumatic mitral valve disease. However, tricuspid regurgitation can present acutely with severe regurgitation due to endocarditis or to blunt or penetrating chest wall trauma.[55-58] Rarely, acute tricuspid regurgitation is iatrogenic, related to a pacer wire or Swan-Ganz catheter.[59]

If due to penetrating chest wall trauma, valve dysfunction may be accompanied by pericardial effusion and tamponade physiology. Blunt chest wall trauma is accompanied by cardiac injury in 16% to 76% of cases in clinical series. The most common consequences are injury to the thoracic aorta or contusion of the right ventricle.[60] However, blunt chest wall trauma may result in valve rupture, with case reports of acute tricuspid and aortic regurgitation. Acute severe tricuspid regurgitation results in a low forward cardiac output and signs of an elevated right atrial pressure.

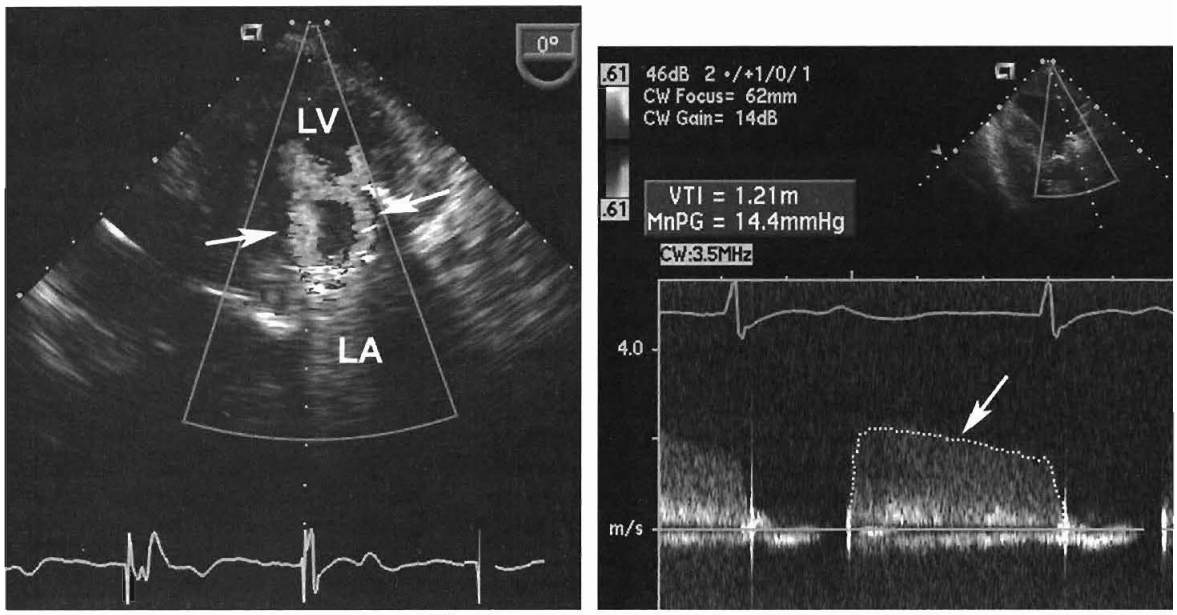
PROSTHETIC VALVES

MECHANICAL VALVES

Prosthetic mechanical heart valves are very durable, with complications most often due to valve thrombosis or paravalvular regurgitation.[61] Valve thrombosis occurs in the setting of inadequate anticoagulation and may result in functional valve stenosis if movement of the valve occluder is restricted or in valve regurgitation if clot prevents full closure of the valve. The clinical presentation of valve thrombosis is similar to that of native valve stenosis or regurgitation. Again, echocardiography provides key information on the presence and severity of valve dysfunction (Fig. 103-12).[62] TEE is especially important with mitral prosthetic valves because the valve itself blocks ultrasound penetration from a transthoracic approach.

Treatment of prosthetic valve thrombosis is controversial. When only a small thrombus and mild hemodynamic compromise is present, conservative therapy with full dose intravenous anticoagulation for several days may be adequate. With severe hemodynamic compromise, surgical intervention with repeat valve replacement may be necessary, although operative mortality is reported to be high, ranging from 17% to 40%.[9,63] Systemic thrombolytic therapy can restore valve function in some patients but is associated with death in 20%, systemic embolism due to fragmentation of the valve thrombosis in 16%, and the need for emergency surgery in 20%.[9] Thus, thrombolytic therapy typically is used only when surgical risk is high (see Fig. 103-12). The duration of thrombolytic therapy is based on Doppler echocardiographic evidence of resolution of thrombus and improvement in valve function. However, thrombolytic therapy should be stopped after 24 hours if there is no hemodynamic improvement and after 72 hours if only partial improvement. Guidelines for thrombolytic therapy for prosthetic valve thrombosis frequently are updated, so clinicians should check the latest guidelines and seek consultation from both cardiology and cardiac surgery before proceeding with therapy.[9,64]

Paravalvular regurgitation early after valve replacement may be related to suture dehiscence at a site of annular calcification. There may be associated hemolytic anemia, which can be treated conservatively if mild but may require reoperation if severe recurrent anemia is present. The new onset of paravalvular regurgitation should prompt careful evaluation for endocarditis (see Chapter 104).



A B

FIGURE 103–12. Acute prosthetic mitral valve thrombosis in an 82-year-old man 29 years after valve replacement. The patient presented acutely with pulmonary edema and a right upper extremity thrombotic occlusion after anticoagulation was temporarily discontinued owing to a gastrointestinal hemorrhage. Color Doppler imaging (**A**) shows only narrow jets *(arrows)* of flow antegrade across the mitral valve replacement and the continuous wave Doppler signal (**B**) shows a high gradient and very prolonged deceleration slope, consistent with severe obstruction to flow. After careful discussion given his high risk for surgery, he was treated with thrombolytic therapy, which resulted in normalization of his mitral valve Doppler flows and resolution of pulmonary edema. (See Color Section in this text.)

TISSUE VALVES

Tissue valves are subject to degeneration of the leaflets with superimposed calcification that may result in stenosis or regurgitation. Usually this is a slowly progressive process with presentation 10 to 15 years after valve implantation.[65,66] As with native valve disease, acute decompensation may occur in patients with chronic prosthetic valve dysfunction if there is a superimposed hemodynamic stress.

Acute regurgitation of a tissue valve can result from endocarditis or from a leaflet tear due to tissue degeneration. Tears in the valve leaflet typically occur adjacent to an area of calcification due to the increased stress on the normal leaflet tissue. As with mechanical valves, both transthoracic and transesophageal imaging are needed for full evaluation of suspected prosthetic tissue valve dysfunction. Treatment is similar to that for native valves with medical stabilization followed by surgery for repeat valve replacement.

ANNOTATED REFERENCES

Bonow RO, Carabello BA, deLeon AC, et al: ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). J Am Coll Cardiol 1998;32:1486-1588.

Consensus guidelines on the diagnosis, medical therapy, and timing of surgical intervention in valvular heart disease. Also provides a concise summary of our understanding of the natural history of valvular heart disease as the basis for an evidence-based approach to patient management. Update in progress. Most recent version available on the website of the American College of Cardiology.

Carabello BA, Crawford FA Jr: Valvular heart disease. N Engl J Med 1997;337:32-41.

Concise review of the diagnosis and therapy of aortic and mitral stenosis and of aortic and mitral regurgitation with specific attention to the issues of acute valvular regurgitation. A readable and up-to-date summary with 99 references.

Iung B: Management of ischaemic mitral regurgitation. Heart 2003;89:459-464.

Ischemic mitral regurgitation is due to alterations in the alignment of the subvalvular apparatus, not to papillary muscle dysfunction. It often is associated with a soft murmur so that quantitative Doppler echocardiography is especially important in diagnosis. Treatment often includes concurrent mitral valve surgery at the time of coronary artery bypass grafting.

Pretre R, Chilcott M: Blunt trauma to the heart and great vessels. N Engl J Med 1997;339:626-632.

Mechanisms of injury due to blunt trauma include compression of the chest, direct injury, traction or torsion, and an acute elevation in blood pressure. Types of injury include tearing of the aorta (particularly at the aortic isthmus) or myocardium, valve rupture, and myocardial contusion. The importance of rapid diagnosis with bedside echocardiography and the indications for surgical intervention are discussed.

Vongpatanasin W, Hillis LD, Lange RA: Prosthetic heart valves. N Engl J Med 1996;335:407-416.

Prosthetic valve dysfunction may be suspected based on history or physical examination, but diagnosis usually requires echocardiography and other imaging techniques. Complications of prosthetic valves include valve thrombosis, embolization, structural failure, hemolysis, paravalvular regurgitation, and endocarditis. Careful antithrombotic therapy is needed to prevent mechanical valve complications. Therapy for prosthetic valve thrombosis is controversial.

Chapter 104
INFECTIOUS ENDOCARDITIS

Michel Wolff • Jean-François Timsit

KEY POINTS

1. Infectious endocarditis can be classified into **three types that differ markedly** in terms of incidence, clinical presentation, microbiologic features, and outcome: left-sided native valve, right-sided native valve, and prosthetic valve.
2. **Modifications of the Duke criteria** were recently proposed to take into account transesophageal echocardiography and to consider all *Staphylococcus aureus* bacteremia and positive Q fever serology as major criteria.
3. According to two recent large studies conducted in the United States and in France, streptococci remain the most common etiologic agents of infectious endocarditis, accounting for 58% of all pathogens. However, the microbiologic characteristics of the subset of patients who require ICU admission differ from those of the overall population. In ICU patients with infectious endocarditis, ***S. aureus* is the leading pathogen.**
4. Patients are generally referred to the ICU for cardiogenic or septic shock, pulmonary edema caused by valvular leak or prosthetic dysfunction, neurologic events, or renal failure. **Most complications occurred early during the course of infectious endocarditis.**
5. Mounting evidence shows that, for both complicated left-sided native valve endocarditis and *S. aureus* prosthetic valve endocarditis, **valve replacement combined with medical therapy** is associated with a better outcome than medical treatment alone. Improvement of outcome requires a multidisciplinary approach to optimize medical treatment and decision-making concerning indications and optimal timing of valve replacement.

Infectious endocarditis is associated with a myriad of complications, both cardiac and extracardiac, that may require transfer to the ICU. Local progression of the infection causes destruction of valve cusps or leaflets and chordae and may extend to peri- and paravalvular structures. Hemodynamic deterioration leads to secondary organ failure. Finally, embolization of infected tissues may damage vital organs and cause peripheral abscesses. Intensivists are often confronted with complex treatment decisions, such as the indication and timing of cardiac surgery and the management of hemodynamic and neurologic complications. Therefore, treatment of patients with complicated infectious endocarditis requires close cooperation among intensivists, infectious disease specialists, cardiologists, and cardiac surgeons. This chapter focuses on the changing epidemiology and progress made during the past 3 decades in the diagnosis and management of complicated infectious endocarditis.

PATHOPHYSIOLOGY

Infectious endocarditis is a microbial infection of the endocardial surface of the heart. The process is initiated by bloodborne microorganisms that adhere directly to the endothelium or by nonbacterial thrombotic endocarditis. The most important factors facilitating nonbacterial thrombotic endocarditis are organic valvular lesions, with associated perturbation of blood flow, and prosthetic valves. Circulating microorganisms can adhere to microscopic lesions, which explains why up to 50% of patients with infectious endocarditis have no previously known valvular abnormality.[1]

In simple infectious endocarditis, infection is limited to the valve cusps or leaflets and chordae and consists of vegetations, which are formed by pathogens, platelets, fibrin, and inflammatory cells. In advanced infectious endocarditis, deep tissue invasion results in the destruction or invasion of valvular and perivalvular structures. The infection may spread as cellulitis with the formation of an abscess or pseudoaneurysm, which can rupture to another heart chamber or even the pericardium. Infectious endocarditis can also occur at the site of a septal defect or on the mural endocardium.

In prosthetic valve endocarditis, lesions may differ according to the type of prosthesis. With biologic prostheses or homografts, the infection may be limited to cusps, whereas with mechanical prostheses, involvement of the sewing ring and the valve annulus is the rule.[2] Bacterial adherence to the prosthesis results from a complex relationship among the biomaterial, plasma proteins (e.g., fibronectin, laminin, thrombospondin, fibrinogen), and bacterial adhesion proteins. *Staphylococcus aureus* and coagulase-negative staphylococci express numerous surface factors: clumping factors A and B, which promote their adhesion to fibrinogen and fibrin, and fibronectin-binding proteins A and B, which permit adhesion to fibronectin.[3] In addition, once staphylococci have escaped the microbicidal effects of platelet peptides, they can bind to the platelet surface by a series of pathogenetic steps, including direct binding to the platelet surface, up-regulation of platelet surface receptors for fibrinogen, and interaction between specific bacterial proteins and platelet surface receptors.[4]

INCIDENCE AND CLASSIFICATION

The overall annual incidence of infectious endocarditis in Europe and the United States is between 15 and 60 cases per million. In a recent study conducted in France, the crude annual incidence of infectious endocarditis was 30 (95% confidence interval, 27 to 33) per million inhabitants. In the United States, the yearly incidence is estimated to be 15,000 to 20,000 cases.[5] Infectious endocarditis can be classified into three groups that differ markedly in terms of incidence, clinical presentation, microbiologic features, and outcome: left-sided native valve, right-sided native valve, and prosthetic valve endocarditis.

Left-sided native valve infectious endocarditis traditionally occurs in patients with underlying heart disease but may affect patients with no known valvular disease, especially when endocarditis is caused by highly virulent bacteria such as *S. aureus* or *Streptococcus pneumoniae*. Most infections are community acquired, but nosocomial cases are becoming more common.

Right-sided native valve infectious endocarditis is usually associated with intravenous drug use and has an estimated incidence of 1.5 to 20 per 1000 addicts.[6] Nosocomial cases are frequently a consequence of catheter-related infections. In most cases of pacemaker infectious endocarditis, vegetations are located only on leads, but tricuspid valve involvement occurs in at least 10% of patients.[7]

Prosthetic valve endocarditis accounts for 7% to 25% of infectious endocarditis episodes,[8] with a risk of approximately 1% at 12 months after valve implantation and 2% to 3% at 60 months.[9,10] The risk persists throughout follow-up, at a rate of approximately 0.4% yearly. The rates of endocarditis associated with mechanical versus biologic prostheses are controversial; some authors have found that bioprostheses present a greater risk of infection after the first postoperative year. Cases of prosthetic valve endocarditis occurring within 2 months of prosthesis implantation are called early and are usually of nosocomial origin; those developing more than 1 year after valve replacement are called late and are predominantly community acquired. Intermediate prosthetic valve endocarditis occurs between 60 days and 6 months after valve replacement and may be community or hospital acquired.[11] Proportional hazards functions based on 4189 consecutive patients indicated a significant decline in early prosthetic valve endocarditis and a slight increase in late prosthetic valve endocarditis.[12]

DEMOGRAPHICS AND ETIOLOGIC PROFILES

CLASSIC AND CHANGING PATIENT CHARACTERISTICS

The demographic characteristics of patients who develop infectious endocarditis have changed over the last few decades. Today, patients tend to be older, and their underlying diseases have changed.[13,14] In France, the infectious endocarditis incidence rises sharply for patients older than 50 years and peaks at 145 cases per million for men 70 to 80 years old.[1] In developing countries, rheumatic heart disease remains the most frequent underlying cardiac condition predisposing patients to infectious endocarditis. In contrast, in the United States and western Europe, nonrheumatic heart abnormalities, including mitral valve prolapse, aortic valve calcification, aortic bicuspid valve, and hypertrophic obstructive cardiomyopathy, are the main risk factors. For patients with mitral valve prolapse, risk factors include mitral regurgitation and thickened mitral leaflet. However, results of a recent 1-year survey of infectious endocarditis in France showed a significantly lower incidence of known underlying heart disease between 1991 and 1999.[1] This confirmed data from a Spanish study of native valve infectious endocarditis in nonaddicts, in which the percentage of patients with no prior heart disease increased from 22% in 1975-1985 to 46% in 1984-1992.[15] This trend can be explained, in part, by the markedly fewer postrheumatic valvular complications and improved antimicrobial prophylaxis. Nowadays, congenital heart diseases are rarely involved, except bicuspid aortic valve. Other conditions, including diabetes mellitus, long-term hemodialysis, and immunosuppression, are associated with a higher incidence of infectious endocarditis. At Duke University Medical Center, rates of hemodialysis dependence and immunosuppression among 329 patients with infectious endocarditis rose significantly between 1993 and 1999.[14] Moreover, several recent reports indicate that the incidence of nosocomial native valve infectious endocarditis is also rising.[16-18] Intravenous devices (catheters or fistulas for hemodialysis, vascular grafts) are the major sources of infection. Finally, patients with previous infectious endocarditis should be considered at risk for a new episode.

CLASSIC AND CHANGING CAUSES AND SOURCES OF INFECTION

Overall Distribution of Causative Microorganisms

Overall, streptococci remain the most common causative agent of infectious endocarditis, accounting for 58% of all pathogens in two recent large studies conducted in the United States and in France.[1,13] Changes in demographic characteristics probably explain the observed changes in organism frequency. Indeed, two major findings were lower rates of infectious endocarditis caused by oral streptococci[1,14] and higher frequencies of *S. aureus*. At Duke University, *S. aureus* was the single most common cause of infectious endocarditis in 1999, accounting for nearly 40% of episodes.[14]

Community-Acquired, Left-Sided Native Valve Infectious Endocarditis in Nonaddicts

Frequent Pathogens

Streptococci. *Streptococcus* species (mainly *Streptococcus mitis*, *Streptococcus sanguis*, *Streptococcus mutans*), which abound in the mouth and nasopharynx, are associated with dental procedures and diseases. Better application of appropriate prophylaxis for patients at risk probably explains the decreased frequency of *Streptococcus viridans*, but this organism is still responsible for 17%[1] to 36%[13] of episodes. Other factors, such as poor dental hygiene and minor or unrecognized periodontal disease, may be the source of *S. viridans* infectious endocarditis. *Streptococcus bovis*, isolated from up to 25% of patients with infectious endocarditis, may be involved in valve infection of dental or buccal origin. In addition, the association of *S. bovis* infectious endocarditis with carcinoma or other lesions of the colon (e.g., diverticulitis, polyps) is well known. Beta-hemolytic streptococci (groups A, B, C, and G) and *Streptococcus milleri* are isolated from 6% of patients with infectious endocarditis,[1] with the predominant species being group B. The majority of nonpregnant patients with group B streptococcal infectious endocarditis have an underlying condition such as diabetes mellitus, breast cancer, decubitus ulcer, or cirrhosis.[19]

Enterococci. Enterococci (mainly *Enterococcus faecalis* and *Enterococcus faecium*) account for only 8% to 11% of cases of infectious endocarditis.[1,13] These pathogens affect older patients, as demonstrated by a recent description of 93 episodes of enterococcal infectious endocarditis occurring in patients with a mean age of 74 years.[20] The portals of entry are the gastrointestinal and urogenital tracts through a lesion or a procedure (e.g., injection sclerosis of esophageal varices, transurethral prostate resection, urethral dilatation) resulting in transient bacteremia, in which case the infection is hospital acquired.

Staphylococcus aureus. *S. aureus* is implicated in approximately 30% of all cases of left-sided native valve infectious endocarditis[13] and is the causative agent in most acute infections, with about half of patients having no previously known heart disease. A clinically identifiable focus of infection (e.g., carbuncle, cellulitis, bursitis, ulcer, burn, osteomyelitis) may be present. However, in 50% to 60% of cases, no obvious portal of entry is detected, although the skin is probably the source in many of them. The relationship between *S. aureus* nasal carriage and infection has been established in specific subsets of patients, especially in intravenous drug users and patients with diabetes mellitus or on hemodialysis.[14]

Infrequent Pathogens

Enterobacteriaceae and HACEK Group. Despite the high frequency of Enterobacteriaceae bacteremia leading to severe sepsis or septic shock, infectious endocarditis caused by these pathogens is extremely uncommon, perhaps because Gram-negative bacilli adhere less avidly to the endothelium than Gram-positive cocci do. Most cases of infectious endocarditis develop in patients with severe comorbidities, including cirrhosis or immunosuppression. Bacteria of the HACEK group (fastidious organisms) originate from the oropharyngeal or urogenital flora and include *Haemophilus aphrophilus* or *paraphrophilus* (H), *Actinobacillus actinomycetemcomitans* (A), *Cardiobacterium hominis* (C), *Eikenella corrodens* (E), and *Kingella* species (K). These HACEK pathogens are implicated in less than 3% of cases of infectious endocarditis on either native or prosthesic valves.

Streptococcus pneumoniae. Pneumococcal infectious endocarditis occurs more commonly in alcoholics, but other patients, such as those with diabetes, malignancy, or chronic obstructive pulmonary disease, may be affected. Approximately 65% to 80% of patients have no known predisposing cardiopathy. The primary infection focus is the lungs, and meningitis is present in 40% to 60% of cases.[21]

Coagulase-Negative Staphylococci. Although they are the most common pathogens responsible for early prosthetic valve endocarditis, coagulase-negative staphylococci are also a well-documented cause of native valve infectious endocarditis. Most patients have documented valvular abnormalities, especially mitral valve prolapse. A substantial subset of coagulase-negative staphylococci infective endocarditis has been identified as being due to *Staphylococcus lugdunensis*, which causes destructive cardiac lesions, and its differentiation from other coagulase-negative staphylococci species in the laboratory may be difficult.[22]

Infectious Endocarditis in Intravenous Drug Users

It has been estimated that up to 76% of the infectious endocarditis cases in intravenous drug users are right sided, versus 9% in nonaddicts. The tricuspid valve is affected in 40% to 69% of episodes, a left-sided valve in 20% to 30%, and multiple valves in 5% to 10%. *S. aureus* is the most frequently isolated pathogen, especially for right-sided infectious endocarditis, where it is isolated in more than 80 % of cases.[23] Intravenous drug users are generally their own source of the infectious organism; many carry *S. aureus* in their noses or throats or on their skin. Most cases are caused by methicillin-susceptible strains. However, methicillin-resistant *S. aureus* infectious endocarditis has been reported in intravenous drug users in the United States and Europe. Other bacteria are involved much less frequently. Right-sided or left-sided infectious endocarditis caused by streptococci, enterococci, or coagulase-negative staphylococci has been reported, especially in those who inject drugs into the femoral vein. Enterobacteriaceae and *Pseudomonas aeruginosa* have also been observed to preferentially attack right-sided, previously undamaged heart valves in addicts, but these cases were attributed to preparation of the drug. Finally, although drug addiction is a classic predisposing factor for fungal endocarditis, a recent analysis of 270 cases of fungal endocarditis incriminated drug use in only 13%.[24]

Hospital-Acquired Native Valve Infectious Endocarditis

Several reports have indicated that hospital-acquired infectious endocarditis unrelated to cardiac surgery is a growing problem. Because intravascular devices are the main source of infection, the predominant role of *S. aureus* is not surprising. Other sources of nosocomial infectious endocarditis are gastrointestinal and urogenital procedures and surgical wounds. Other pathogens are Gram-negative bacilli, enterococci, coagulase-negative staphylococci, and fungi.[16,17] It should be emphasized that the diversification of care structures (long-term-care facilities, day-care centers) sometimes makes the distinction between community-acquired and nosocomial infection difficult, or even meaningless; this is particularly true for infections in hemodialysis patients. Infectious endocarditis developing in such circumstances is now included with the so-called health care–associated infections.

Prosthetic Valve Endocarditis

Although a broad spectrum of microorganisms may be involved in prosthetic valve endocarditis, staphylococci and streptococci predominate, with their frequency depending on the time interval after valve implantation. Coagulase-negative staphylococci and *S. aureus* are frequently responsible, regardless of interval. For late prosthetic valve endocarditis, microorganisms resemble those responsible for native valve infectious endocarditis, with a predominance of streptococci. Gram-negative bacilli are usually encountered in early and late prosthetic valve endocarditis; fungi, mainly *Candida* species, are responsible for approximately 8% and 3% of early and intermediate prosthetic valve endocarditis, respectively (Table 104-1).[8]

Specific Microbiologic Characteristics of Infectious Endocarditis in ICU Patients

The microbiologic characteristics of infectious endocarditis in patients who require ICU admission differ from those in the overall population. Analysis of a large series of infectious endocarditis patients hospitalized in two medical ICUs in a Parisian teaching hospital between 1994 and 2001 showed that *S. aureus* was the leading pathogen responsible for left-sided native valve and prosthetic valve endocarditis (see Tables 104-1 and 104-2). In a previous series of 122 ICU patients with prosthetic valve endocarditis, *S. aureus* was almost as frequent

TABLE 104–1. CAUSATIVE AGENTS OF PROSTHETIC VALVE ENDOCARDITIS (PVE)

Microorganism	Early and Intermediate PVE (%)		Late PVE (%)	
	International Studies[26,44] *(202 Patients)*	*Bichat Claude-Bernard ICUs (39 Patients)*	*International Studies*[26,44] *(326 Patients)*	*Bichat Claude-Bernard ICUs (34 Patients)*
Staphylococcus aureus	22	59	18	35
MSSA	NR	31	NR	32
MRSA	NR	28	NR	3
CoNS	33	5	16	6
Streptococci	3	5	25	26
Enterococci	9	8	14	3
HACEK	3	0	7	3
Gram-negative bacilli	10	1	NR	6
Fungi	8	8	3	3
Polymicrobial	2	0	1	0
Other	5	5*	9	9†
Culture negative	5	9	7	8

**Corynebacterium* species in 2 patients.
†*Corynebacterium* species in 2 patients; *Listeria monocytogenes* in 1 patient.
CoNS, coagulase-negative staphylococci; HACEK, *Haemophilus aphrophilus* or *paraphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; NR, not related.

as streptococci in late-onset infections.[25] Those figures were confirmed by an Austrian study of 33 ICU patients with infectious endocarditis: *S. aureus* was isolated from 36% of them, versus 15% *S. viridans* and 12% enterococci.[26] Clearly, these findings are largely explained by *S. aureus* causing valve destruction, septic shock, and emboli to vital organs such as brain.

Patients with Negative Blood Cultures

Common causes of culture-negative infectious endocarditis have been reported in detail elsewhere.[5,8] Five main points should be emphasized: (1) *Abiotrophia* species (previously classified as nutritionally variant streptococci) are the main cause of culture-negative infectious endocarditis in patients who have recently received antibiotics. (2) Only 5% to 7% of patients who have not recently taken antibiotics have negative blood cultures. Polymerase chain reaction (in blood, excised vegetation, or systemic emboli) can be used to identify the causative organism, such as *Bartonella* species,[27] *Tropheryma whiplei*, or *Coxiella burnetii*. (3) Serologic tests are useful to diagnose infectious endocarditis caused by those organisms or by *Brucella* and *Legionella* species. (4) HACEK organisms may require prolonged incubation and subculturing. (5) *Candida* (but not *Aspergillus*) species are usually isolated from routine blood cultures, but in some cases, fungi are recovered only from excised vegetations or peripheral emboli.

TABLE 104–2. CAUSATIVE AGENTS OF LEFT-SIDED NATIVE VALVE INFECTIOUS ENDOCARDITIS

Microorganisms	Connecticut Hospitals[13] (513 Patients): Number* (%)	Bichat-Claude Bernard ICUs (122 Patients): Number (%)
Streptococci	240 (47)	42 (34)
Staphylococcus aureus	143 (28)	52 (43)
Enterococci	58 (11)	3 (2)
CoNS	38 (7)	2 (2)
Gram-negative bacilli	NR	4 (3)
Streptococcus pneumoniae	NR	5 (4)
Other	21 (4)	7 (6)
Negative blood cultures	29 (6)	7 (6)

*The number of microorganisms exceeds the number of patients because some cases were polymicrobial.
CoNS, coagulase-negative staphylococci; NR, not reported.

CLINICAL CHARACTERISTICS AND DIAGNOSIS

In 1994, a new set of diagnostic criteria for the diagnosis of infectious endocarditis, including two major and six minor criteria—known as the Duke criteria—was proposed.[28] Modifications of these criteria were recently proposed to take into account transesophageal echocardiography and to consider all *S. aureus* bacteremias and positive Q fever serology as major criteria.[29]

CLINICAL CHARACTERISTICS

In ICU patients, the clinical presentation of infectious endocarditis often includes extracardiac manifestations or findings associated with cardiac complications. Patients are generally referred to the ICU for cardiogenic or septic shock, pulmonary edema caused by valvular or prosthetic dysfunction, neurologic events, acute renal failure, or respiratory failure in the setting of pulmonary emboli complicating right-sided infectious endocarditis. Two salient features, usually associated with high-grade fever, strongly suggest the diagnosis of infectious endocarditis: a heart murmur (most commonly preexisting) or a prosthetic valve, and petechiae on the skin (especially the extremities; Fig. 104-1) and conjunctivae. A typical ICU candidate has an acute febrile and toxic illness with heart murmur, petechiae, and meningeal signs. Cerebrospinal fluid examination finds pleocytosis and Gram-positive cocci. Blood cultures yield *S. aureus*, and echocardiography confirms left-sided infectious endocarditis.

The onset of nosocomial infectious endocarditis is usually acute, and suggestive signs are often absent.[18] The diagnosis of infectious endocarditis is suggested by bacteremia persisting 3 to 5 days after the onset of antimicrobial treatment and removal of an infected catheter.

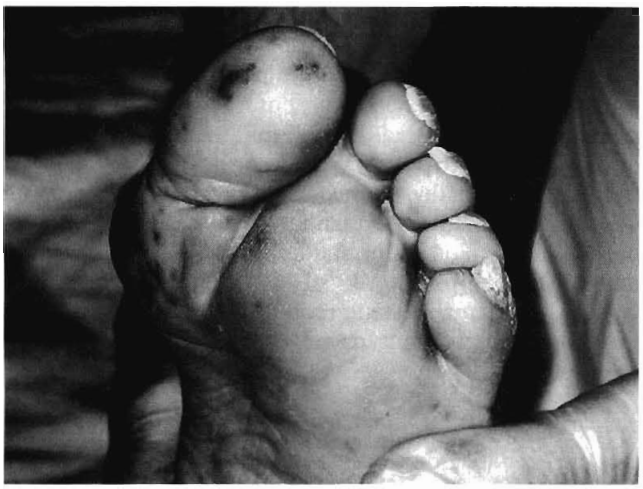


FIGURE 104–1. Typical purpuric lesions in a patient with *S. aureus* mitral valve endocarditis.

ECHOCARDIOGRAPHY

Echocardiography has the following objectives: (1) to detect vegetations and determine their size, (2) to diagnose paravalvular extension of the infection, (3) to evaluate myocardial function, (4) to detect pericardial effusion, and (5) if cardiac surgery is being considered, to measure the valve ring to choose the appropriate prosthetic valve for replacement. Transthoracic echocardiography is rapid and noninvasive, but its overall sensitivity is only about 65%. False-negative results are obtained when the examination is inadequate (in those with obesity or chronic obstructive pulmonary disease) or when vegetations are less than 5 mm. Transesophageal echocardiography associated with color Doppler techniques is more invasive, but its sensitivity for detecting vegetations is 90%.[18] Transesophageal echocardiography is particularly useful in patients with suspected valve perforation or extension of perivalvular infectious endocarditis and in those with prosthetic valve endocarditis. Its sensitivity and specificity for the detection of cardiac abscess are 80% and 95%, respectively. This technique is necessary for all patients undergoing valve surgery and may be repeated at close intervals to help the physician decide when to operate. However, transesophageal echocardiography should be used cautiously in nonintubated critically ill patients with respiratory failure.

COMPLICATIONS

Cardiac complications and hemodynamic failure, central nervous system (CNS) complications, and acute renal failure are the leading causes of ICU admission for patients with infectious endocarditis. Other complications are not addressed in detail.

CARDIAC COMPLICATIONS AND HEMODYNAMIC FAILURE

Congestive heart failure (CHF) is usually caused by infection-induced valvular damage or prosthesis dysfunction. In native valve infectious endocarditis, acute CHF is more frequently associated with aortic than mitral disease. CHF caused by aortic failure may require urgent valve replacement. Perivalvular extension of infectious endocarditis is frequently associated with CHF, and spread into the septum may lead to heart block. Erosion of a mycotic aneurysm of the sinus of Valsalva can cause hemopericardium and tamponade or can create fistulas to the right or left ventricle. Myocardial infarction due to coronary artery embolization is a rare event. Hemodynamic failure can also be caused by septic shock, especially during the bacteremic phase of *S. aureus* infectious endocarditis. All these complications may require the administration of positive inotropes or vasoconstrictors and the use of mechanical ventilation before valve replacement.

NEUROLOGIC COMPLICATIONS

CNS complications of infectious endocarditis occur frequently. They may be the first or predominant manifestation of the disease and can arise through several mechanisms. CNS complications are a leading cause of death due to infectious endocarditis, and their specific management may be complex.

Frequency, Microbiology, and Timing

In most series, CNS involvement during the course of infectious endocarditis occurs in 20% to 40% of cases, with an average of 30%; this figure has not changed much over time. Among 1329 episodes of infectious endocarditis from seven series described between 1985 and 1993, 437 (33%) were accompanied by CNS manifestations.[30] In a Finnish teaching hospital, 55 of 218 infectious endocarditis episodes (25%) were associated with neurologic complications.[31] Among 228 episodes of infectious endocarditis requiring ICU admission in our institution, 84 (37%) involved CNS complications. However, two other studies had lower rates: in France, strokes occurred in 17% of 264 infectious endocarditis cases caused by staphylococci or streptococci[1]; in the United States, among 513 episodes of complicated, left-sided native valve infectious endocarditis, focal neurologic signs or altered mental status were observed in 18% and 16% of cases, respectively.[13] Neurologic complications are a hallmark of left-sided abnormalities of either native or prosthetic valves. Despite some reported discrepancies, the infectious site does not influence the occurrence of neurologic complications. When neurologic complication rates were assessed as a function of the causative agent, the frequency of CNS involvement was two to three times higher with *S. aureus* than with other pathogens.[31,32]

Most neurologic complications are already evident at the time of hospitalization or develop within a few days. Indeed, neurologic manifestations were the first sign of infectious endocarditis in 47% of episodes and occurred in less than 1 week in another 29% of episodes.[31] The probability of developing these complications decreases rapidly once antimicrobial therapy has been started. Moreover, recurrent neurologic events, although possible even late, are uncommon.

Pathogenesis and Distribution

Neurologic complications of infectious endocarditis can arise through various mechanisms. Cerebral emboli result from dislodgment or fragmentation of cardiac vegetations, followed by vessel occlusion; this results in various degrees of ischemia and infarction, depending on the vessels and the collateral blood flow. Occlusion of cerebral arteries, with either stroke or transient ischemic attack, accounts for 40% to 50% of the CNS complications of infectious endocarditis.[30,31] Diffusion-weighted magnetic resonance imaging (Fig. 104-2)

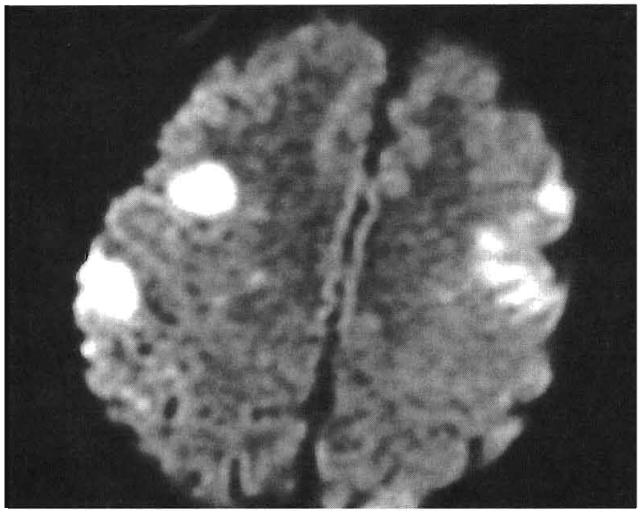


FIGURE 104–2. Diffusion-weighted magnetic resonance imaging showing multiple cerebral emboli in the same patient as in Figure 104-1.

has revealed a variety of patterns, including disseminated punctate lesions.[33] Cerebral hemorrhage may be the consequence of different mechanisms, each of which accounts for one third of bleeding complications: rupture of an intracranial aneurysm; septic erosion of the arterial wall, without a well-delineated aneurysm (acute necrotizing arteritis); or hemorrhagic transformation of ischemic brain infarcts, especially in anticoagulated patients. Overall, intracranial hemorrhage represents 10% of CNS complications (Fig. 104-3). Brain hemorrhage is more frequent during the bacteremic phase of *S. aureus* infectious endocarditis and is made more likely by severe thrombopenia and anticoagulant therapy.[34] Meningitis, occurring in 5% to 40% of patients with CNS manifestations of infectious endocarditis, can be the consequence of a wide variety of mechanisms; the cerebrospinal fluid may be purulent with positive cultures, clear with moderate pleocytosis, or hemorrhagic. Brain abscesses associated with infectious endocarditis are uncommon; they account for less than 5% of CNS events, but the rate depends on the imaging technique used. In addition, many small abscesses or areas of cerebritis resolve with antibiotics alone. Finally, toxic encephalopathy, defined as mental changes or stupor without focal neurologic manifestations and without computed tomographic abnormalities, is often included among the CNS complications of infectious endocarditis. Obviously, this manifestation can have different causes, such as subtle cerebral lesions, or may be present in the setting of severe sepsis.

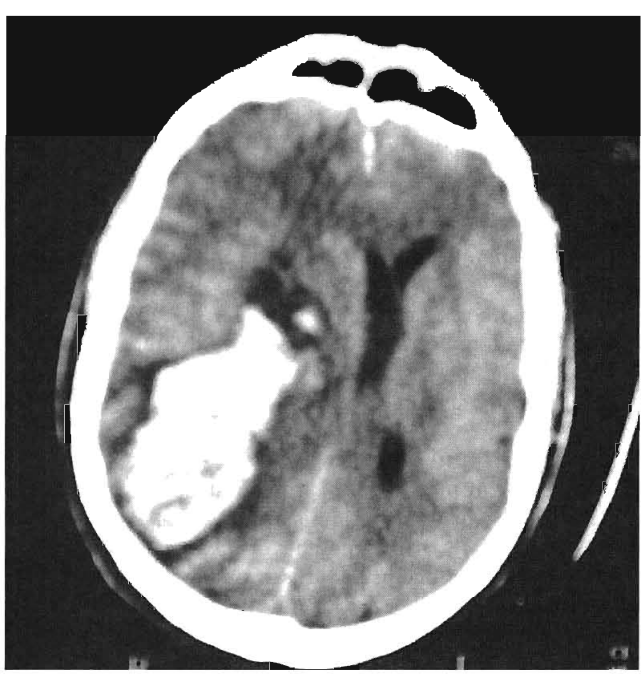


FIGURE 104–3. Cerebral hematoma in a patient with *S. aureus* prosthetic valve endocarditis.

Specific Management

Infectious endocarditis occurring in patients receiving anticoagulant therapy poses a difficult problem. In the absence of CNS complications or in patients with nonhemorrhagic neurologic lesions, warfarin should be discontinued and replaced by heparin. However, in the presence of brain hemorrhage, anticoagulant therapy should be temporarily discontinued. Computed tomography scanning is essential for the diagnosis and management of CNS events associated with infectious endocarditis. In addition, it may be the only technique available for unstable ICU patients, especially those on mechanical ventilation. Computed tomography may show intracranial bleeding, ischemic lesions, or a pattern consistent with cerebral abscess. Magnetic resonance imaging is more sensitive for most lesions, except hemorrhage. Although conventional four-vessel angiography remains the gold standard for the evaluation of mycotic aneurysms, magnetic resonance angiography is a promising technique. In the absence of randomized trials, which are difficult (if not impossible) to organize, the respective roles of medical, endovascular, and neurosurgical treatment of intracranial aneurysms are not easily assessable. Endovascular treatment (coil embolization) seems to be a reliable and safe technique that should be considered when cerebral mycotic aneurysms are diagnosed.[35]

ACUTE RENAL FAILURE

Acute renal failure occurs in up to 40% of complicated infectious endocarditis cases necessitating ICU admission[26] and may result from several mechanisms. It is often the consequence of cardiogenic or septic shock (with or without multiorgan failure) leading to acute tubular necrosis. Drugs, such as the combination of a glycopeptide and an aminoglycoside, and the use of iodine contrast medium for radiologic investigations may further deteriorate renal function. In some patients with streptococcal or staphylococcal infectious endocarditis, acute renal failure is caused by severe glomerulonephritis. Acute renal failure may require the initiation of dialysis.

OTHER COMPLICATIONS

Systemic embolism can involve many organs, such as the spleen and kidneys; rarely, the liver or the iliac, mesenteric, or peripheral arteries are involved. Splenic abscesses are caused mainly by *S. aureus* or *S. viridans*. Abdominal computed tomography is the best procedure to detect splenic abscesses, which may require percutaneous drainage or splenectomy. Pulmonary emboli, the hallmark of right-sided

TABLE 104–3. ANTIBIOTIC TREATMENT OF COMPLICATED INFECTIOUS ENDOCARDITIS AS A FUNCTION OF VALVE TYPE, PATHOGEN, AND SUSCEPTIBILITY

Microorganism	Native Valve Infectious Endocarditis	Prosthetic Valve Endocarditis
Penicillin-susceptible streptococci (MIC ≤0.1 mg/L)	Penicillin G, amoxicillin, or ceftriaxone for 4 wk*	Penicillin G or amoxicillin for 4-6 wk + gentamicin for 2 wk*
Relatively penicillin-resistant streptococci (MIC >0.1-0.5 mg/L)	Penicillin G or amoxicillin for 4 wk + gentamicin for 2 wk*	Penicillin G or amoxicillin for 4-6 wk + gentamicin for 4 wk*
Streptococci with penicillin G MIC >0.5 mg/L, enterococci, and *Abiotrophia* spp	Penicillin G or amoxicillin for 4-6 wk + gentamicin for 4 wk*	Penicillin G or amoxicillin for 6 wk + gentamicin for 6 wk*
MSSA	Nafcillin or oxacillin for 4-6 wk + gentamicin for 3-5 days†	Nafcillin or oxacillin + rifampin for 6 wk + gentamicin for 2 wk†
MRSA	Vancomycin + rifampin for 4-6 wk + gentamicin for 3-5 days	Vancomycin + rifampin for 4-6 wk + gentamicin for 2 wk
HACEK organisms	Ceftriaxone or cefotaxime for 4 wk	Ceftriaxone or cefotaxime for 6 wk
Enterobacteriaceae	Ceftriaxone or cefotaxime for 4 wk + gentamicin or amikacin for 1 wk‡	Ceftriaxone or cefotaxime for 6 wk + gentamicin or amikacin for 2 wk‡
Bartonella spp	Amoxicillin or ceftriaxone for 4 wk + gentamicin for 1 wk	Amoxicillin or ceftriaxone for 4 wk + gentamicin for 1 wk
Coxiella burnettii	Doxycycline + rifampin + hydroxychloroquine for ≥ 18mo	Doxycycline + rifampin + hydroxychloroquine for ≥18 mo
Candida spp	Amphotericin B + flucytosine for 4-6wk + long-term suppressive treatment with fluconazole§	Amphotericin B + flucytosine for 6-8 wk + long-term suppressive treatment with fluconazole§

*Vancomycin or teicoplanin therapy is indicated for patients who are allergic to beta-lactam antibiotics. Optimal antimicrobial therapy is not available for high-level aminoglycoside-resistant and vancomycin-resistant enterococci. Eradicating these pathogens requires consultation with an infectious disease specialist or a microbiologist.

†A first-generation cephalosporin is indicated for patients who are allergic to penicillin, except for those with immediate-type hypersensitivity reactions to beta-lactam antibiotics, who should be treated with a glycopeptide.

‡The results of susceptibility tests might indicate the need to adapt the initial regimen.

§New molecules such as voriconazole and caspofungin should be evaluated.

HACEK, *Haemophilus aphrophilus* or *paraphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

endocarditis, may be responsible for respiratory failure or even acute respiratory distress syndrome, especially in intravenous drug users with *S. aureus* infectious endocarditis.[23]

MEDICAL AND SURGICAL TREATMENT

In the absence of large prospective, randomized studies, which present a considerable challenge, the overall strategy for infectious endocarditis treatment is derived mainly from retrospective series, clinical judgment, and expert recommendations.

ANTIBIOTIC TREATMENT

Certain general principles underlie the current guidelines for infectious endocarditis treatment.[36,37] In cases of streptococcal infectious endocarditis, determination of the minimal inhibitory concentration of penicillin is necessary to choose the best regimen. Parenteral antibiotics are recommended over oral drugs because of the importance of sustained antibacterial activity, which requires high dosages (e.g., 150 to 200 mg/kg of amoxicillin for streptococcal infectious endocarditis). However, oral antibiotics may be considered for right-sided infectious endocarditis after a few days of parenteral antibiotics when intravenous administration is not possible because of poor venous access. In that case, a combination of a fluoroquinolone and rifampin is an acceptable regimen. Many experts recommend using a combination of agents with activities against the cell wall (beta-lactams or glycopeptides) plus an aminoglycoside for most cases of infectious endocarditis, especially complicated cases such as those in ICU patients. The duration of aminoglycoside use depends on the pathogen and the presence of a prosthesis (Table 104-3). Although a shorter course of aminoglycosides has been proposed for enterococcal infectious endocarditis,[20] no controlled study has confirmed the safety of this strategy. For staphylococcal infectious endocarditis, a triple regimen including rifampin is recommended,[38] especially for patients with prosthetic valve endocarditis. Short-term therapy (15 days) was shown to be effective in selected cases of noncomplicated *S. aureus* right-sided infectious endocarditis or left-sided native valve infectious endocarditis caused by highly susceptible streptococci. However, most current recommendations emphasize prolonged antibiotic administration (4 to 6 weeks, or even 8 weeks) for *S. aureus* prosthetic valve endocarditis. Valve cultures, but not positive Gram staining, should be taken into account to decide how long to continue antimicrobial therapy after valve replacement.[39]

SURGICAL MANAGEMENT

In recent series, 45% to 50% of patients (up to 75% in specialized medical-surgical centers) undergo valve replacement during the acute phase of infectious endocarditis before the completion of antibiotic treatment.

Indications for and Timing of Cardiac Surgery

Absolute indications are CHF caused by valvular insufficiency, prosthesis obstruction or dehiscence, periannular abscess, or *S. aureus* or fungal prosthetic valve endocarditis. These microorganisms cannot be eradicated without removal of the prosthesis. Development of CHF in the setting of infectious endocarditis generally requires cardiac valve replacement regardless of the number of days on antibiotics.

Relative indications, requiring case-by-case evaluation, are persistent bacteremia beyond 7 days, despite appropriate

antibiotic therapy; non–*S. aureus* prosthetic valve endocarditis; and difficult-to-treat organisms such as *C. burnetii*, *Bartonella* species, multiresistant enterococci, or *P. aeruginosa*, especially in patients with prosthetic valve endocarditis.

With regard to other potential indications, contraindications, and timing of valve replacement, the following factors should be emphasized: (1) Although the risk of systemic embolization is higher in patients with large vegetations on the mitral valve, vegetation characteristics alone rarely justify valve surgery.[8] The decreasing risk of emboli with time, especially after the first week of effective antibiotic therapy, should be considered when deciding whether to operate. (2) In patients with neurologic complications, a conservative approach is to delay cardiac surgery for 2 or 3 weeks after an embolic event[40] and for at least a month after cerebral bleeding.[8] However, in the case of CHF, the valve can be replaced within 7 days or less after an embolic infarct, especially when it is of limited size and the patient's good mental status prevails. (3) True contraindications of valve surgery are rare and include uncontrolled septic shock, unhealed sternal wound infection, and severe coagulation disorders.

Surgical Technique

Surgery includes complete removal of all infected and necrotic tissue, followed by valve reconstruction. In selected cases, good results have been achieved with conservative mitral valve valvuloplasty. In most patients, valve replacement with a mechanical or biologic prosthesis or a homograft is necessary. An aortic homograft may be associated with a lower risk of relapse for patients operated on during the very early phase of infectious endocarditis.

OUTCOME AND PROGNOSTIC FACTORS

In a recent 1-year survey of infectious endocarditis in France, the overall in-hospital mortality rate was 16.6%.[1] This figure includes all types of infectious endocarditis and needs to be refined according to different categories of disease. Another recent cohort of 513 patients with complicated, left-sided native valve infectious endocarditis had a 6-month mortality rate of 26%.[13] Mortality rates for prosthetic valve endocarditis are much higher; rates of 33% and 44% have been reported,[41,42] and mortality may be higher than 50% for early prosthetic valve endocarditis.[25] Among 228 patients with infectious endocarditis referred to the two ICUs in our hospital, the in-hospital mortality rate was 45%. Nosocomial infectious endocarditis is associated with up to 68% mortality.[17] In contrast, the prognosis of right-sided infectious endocarditis in intravenous drug users is much better, with mortality being less than 10%.[23]

Prognostic factors of survival have been studied by several authors. In most cases, these reflect the site of infectious endocarditis (see earlier), comorbidities, causative agent, and type of complications. CHF, septic shock, neurologic events, and *S. aureus* are associated with a poor prognosis in most studies.[13,25,26] The hemodynamic status of the patient at the time of valve replacement is the main determinant of perioperative mortality, with a poorer prognosis for patients with pulmonary edema or impaired left ventricular function.[43] Neurologic events markedly increase the risk of death, which can reach 50% in patients with altered mental status.[13] Among microorganisms, *S. aureus* is associated with higher mortality rates than streptococci for left-sided native valve and prosthetic valve endocarditis.[13,25] Finally, mounting evidence shows that, for both complicated left-sided native valve infectious endocarditis and *S. aureus* prosthetic valve endocarditis, valve replacement combined with medical therapy is associated with a better outcome than medical treatment alone.[13,25,42,45] The reoperation rate, mainly for prosthesis dehiscence or new infectious endocarditis, is 2% to 3% per year, and the 5-year survival rate is approximately 80% to 90% for native valve infectious endocarditis and 60% for prosthetic valve endocarditis. A scoring system taking into account mental status, comorbidity, CHF, microbiology, and the use of surgical treatment in left-sided native valve infectious endocarditis was recently published.[13]

CONCLUSION

Despite advances in both diagnosis and treatment, infectious endocarditis still carries high morbidity and mortality rates, especially for patients requiring ICU admission. Improvement of outcome requires a multidisciplinary approach to optimize medical treatment and decision-making concerning valve surgery.

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Le T, Bayer AS: Combination antibiotic therapy for infective endocarditis. Clin Infect Dis 2003;36:615-621.

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Li JS, Sexton DJ, Mick N, et al: Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633-638.

The authors have reevaluated the Duke criteria. The main modifications are: redefinition of "possible endocarditis"; proposed clarifications and modifications of minor criteria; and redefinition of major criteria to take into account transesophageal echocardiography. Bacteremia due to S. aureus *is a major criterion, regardless of whether the infection is nosocomially acquired or whether a removable source of infection is present. Positive Q fever serology is also changed to a major criteria.*

Mylonakis E, Calderwood SB: Infective endocarditis in adults. N Engl J Med 2001;345:1318-1330.

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Vickram HR, Buenconseyo Y, Uasbun R, et al: Impact of valve surgery on 6-month mortality in adults with complicated, left-sided native valve endocarditis: A propensity analysis. JAMA 2003;290:3207-3214.

This study suggests that valve surgery for patients with complicated, left-sided native valve endocarditis is independently associated with reduced 6-month mortality. The protective effect of surgery is more evident among patients with congestive heart failure.

Chapter 105
HYPERTENSIVE CRISIS AND URGENCY

Catherine Lee Kelleher • Stuart L. Linas

KEY POINTS

1. Hypertensive crisis is defined as an elevated blood pressure associated with evidence of acute end-organ damage to vital organs, such as the kidney, heart, and brain. The absolute level of blood pressure and the rate of blood pressure elevation determine the development of hypertensive crisis.
2. Hypertensive encephalopathy is a distinct clinical syndrome that occurs when rapidly increasing central perfusion pressure exceeds the ability of the central nervous system to autoregulate.
3. Patients with hypertensive crisis are best treated parenterally with intensive care monitoring by arterial cannulation or automated blood pressure cuff measurement. The primary goal of blood pressure therapy is to lower the pressure at a rate that arrests or alleviates end-organ damage without causing ischemia of vital organs.
4. As a general rule, the choice of blood pressure medication and the rate at which the blood pressure is decreased are determined by the clinical setting.

Hypertension is a common problem in the United States affecting nearly 28.7% of adults in 1999 and 2000 (age-adjusted hypertension prevalence).[1] An analysis of self-reported rates of hypertension in the United States suggests that the incidence of hypertension may be increasing in adults.[1] Of hypertensive individuals, 30% are not aware of their diagnosis.[2] Of the 59% of hypertensive individuals being treated for hypertension, only 34% have a blood pressure less than 140/90 mm Hg.[2] The exact risk of hypertensive crisis is not clear; however, most authors estimate the risk to be less than 1%.[3,4] Data from the United States suggest that the hospital admissions for malignant or accelerated hypertension has doubled.[3]

Hypertensive crisis is defined as an elevated blood pressure associated with evidence of acute end-organ damage. With acute damage to vital organs, such as the kidney, heart, and brain, there is a significant risk of morbidity in hours without therapeutic intervention. The absolute level of blood pressure and the time course of blood pressure elevation determine the development of hypertensive crisis. In general, with hypertensive crisis, the diastolic blood pressure is greater than 130 mm Hg. In children, gravid women, and previously normotensive individuals, hypertensive crises may occur with relatively minor increases in blood pressure. It is important to identify this syndrome early to prevent end-organ damage and to institute appropriate therapy as soon as the diagnosis is made. Malignant hypertension is a specific syndrome in which a markedly elevated blood pressure is associated with hypertensive neuroretinopathy.

Individuals with hypertensive urgency have an elevated blood pressure (diastolic pressure often >115 mm Hg) without evidence of acute end-organ damage. Hypertensive urgency may be associated with chronic stable complications, such as stable angina, previous myocardial infarction, chronic congestive heart failure, chronic renal failure, previous transient ischemic attacks, or previous cerebrovascular accident with no threat of an acute insult. Complications from hypertensive urgency are not immediate. In contrast to hypertensive crisis, a more gradual blood pressure reduction over hours is recommended.

An increased blood pressure can occur in the absence of acute or chronic target organ dysfunction. When the cause of hypertension is not identified, the blood pressure is lowered over days to weeks. Occasionally an elevated blood pressure may result from drug use, including over-the-counter medications such as pseudoephedrine and illicit substances such as cocaine. In these situations, the blood pressure is lowered rapidly. The focus of this chapter is hypertensive emergencies, including hypertensive crisis and hypertensive urgency.

PATHOPHYSIOLOGY OF HYPERTENSIVE CRISIS

The precise pathophysiology of hypertensive crisis is unknown. An abrupt increase in blood pressure is one of the initiating events in the transition from simple hypertension or normotension to hypertensive crisis. The product of cardiac output and peripheral vascular resistance determines blood pressure. The initial blood pressure increase is likely secondary to an increase in vascular resistance. Considerable evidence suggests that mechanical stress in the arteriolar wall leads to disruption of endothelial integrity.[5] With disruption of vascular integrity, diffuse microvascular lesions develop.[6,7] Fibrinoid necrosis of the arterioles is seen in vulnerable organs and is considered the histologic hallmark of hypertensive crisis.[6,7] It is unclear whether hypertension alone causes the development of hypertensive crisis or whether other factors are necessary. Increases in peripheral vascular resistance result in part from activation of the renin-angiotensin-aldosterone system. Evidence suggests angiotensin II may injure the vascular wall directly by activation of genes for proinflammatory

cytokines (interleukin-6) and proinflammatory mediators regulated by nuclear factor-κB.[8,9] Other vascular-toxic influences may contribute to increased peripheral vascular resistance, including hyperviscosity, immunologic factors, and other hormones (e.g., catecholamines, vasopressin, and endothelin).[10-12] The end result of these changes is a significant increase in peripheral vascular resistance with ischemia of heart, brain, and kidneys.

In considering hypertensive crisis and treatment, the impact of blood pressure on cerebrovascular physiology is important. Hypertensive encephalopathy is a distinct clinical syndrome that occurs when rapidly rising central perfusion pressure exceeds the ability of the central nervous system to autoregulate. Autoregulation of cerebral blood flow refers to the ability of the brain to maintain a constant cerebral blood flow as the cerebral perfusion pressure varies from 60 to 150 mm Hg. In chronic hypertension, the range of autoregulation is increased from 60 to 150 mm Hg to 80 to 160 mm Hg. Autoregulation of cerebral blood flow is a function of cerebral perfusion pressure (mean arterial pressure – venous pressure) and cerebral vascular resistance:

Cerebral blood flow = cerebral perfusion pressure (mean arterial pressure – venous pressure)/cerebrovascular resistance

Under normal physiologic conditions the backflow in the cerebral venous system or venous pressure is near zero, and the arterial pressure determines the cerebral perfusion pressure. With acute brain injury, as seen with subarachnoid hemorrhage, stroke, and intracranial hemorrhage, the ability of the brain to autoregulate and maintain cerebral blood flow is impaired. Inability to autoregulate cerebral blood flow also is seen in hypertensive crisis when the mean arterial pressure is greater than 140 mm Hg.

DIAGNOSIS OF HYPERTENSIVE EMERGENCIES

Hypertension from any cause may enter a "crisis" phase. Although hypertensive crisis usually occurs in individuals with a history of essential hypertension, it also is seen in individuals with secondary hypertension and in individuals with no hypertensive history, as in preeclampsia, pheochromocytoma, drug withdrawal, and acute glomerulonephritis. A medication history, including over-the-counter medications and illegal drug use, should be obtained from every patient. Malignant hypertension is a unique clinical/pathologic syndrome that is associated with hypertensive crisis. Increases in blood pressure and target organ damage are caused by changes in the vasculature characterized by fibrinoid necrosis and a proliferative endarteritis. Risk factors associated with the development of malignant hypertension include age between 30 and 50 years,[13] male gender,[6] African-American background,[14] and smoking (increases risk by 2.5-fold to 5-fold).[15]

Patients with hypertensive crisis present with a variety of symptoms. The most common is headache. It is either sudden in onset or represents a change from a usual headache pattern and is often worst in the morning. The location is generally occipital or anterior with a steady quality. Other symptoms include visual complaints (scotoma, diplopia, hemianopsia, blindness), neurologic symptoms (focal deficits, stroke, transient ischemic attacks, confusion, somnolence), ischemic chest pain, renal symptoms (nocturia, polyuria, hematuria), back pain (aortic aneurysm), and gastrointestinal complaints (nausea, vomiting). Weight loss occurs as high levels of circulating renin and angiotensin induce a diuresis.[16] These patients often present with intravascular volume depletion, which has strong implications for treatment.

The blood pressure is measured in both arms and with the patient lying and standing. In hypertensive crisis, diastolic blood pressures are usually greater than 120 to 130 mm Hg. Pathologic processes that cause stiffening of the vascular wall can prevent vessel compression by external compression with a blood pressure cuff; this results in an artificial increase (at times extreme) in the systolic and diastolic blood pressure, or "pseudohypertension." Pseudohypertension can occur in atherosclerosis, Mönckeberg's medial calcification, and metastatic calcification as experienced in end-stage renal disease. Clues to pseudohypertension include a markedly elevated blood pressure in an individual without evidence of end-organ damage. The diagnosis is suggested by a palpable radial artery after proximal compression (Osler's maneuver).[17]

A dilated funduscopic examination should be performed on all patients. Arteriolar thickening reflects chronic hypertension and is manifest by increased light reflex, vascular tortuosity, and arteriovenous nicking (grade I and II). Increased arteriole damage results in decreased blood flow manifest by a silver wire pattern to the vessels. These funduscopic findings reflect chronic hypertension and have no prognostic significance with regard to hypertensive crisis. During hypertensive crisis, there is loss of cerebral autoregulation. In malignant hypertension, additional findings are caused by the increased blood pressure and vasculitis in the retinal arteriolar and venous circulation, including flame-shaped hemorrhages, white cotton-wool spots, yellow-white exudates, and eventually, papilledema. The prognosis for these acute funduscopic findings is identical.[18,19]

With long-standing hypertension, there is often evidence of left ventricular hypertrophy. Examination of the abdomen should include evaluation for an aortic aneurysm. A careful neurologic examination should be done to rule out any evidence of a cerebrovascular accident. Alterations in mental status may indicate a stroke or hypertensive encephalopathy. Symptoms of hypertensive encephalopathy include headache, visual changes, and seizures. Focal neurologic symptoms are unusual without an associated cerebral bleed. Hypertensive neuroretinopathy is usually present but may be absent in patients in whom the pressure increase has been abrupt, such as in cases of acute glomerulonephritis or catecholamine excess states.

The initial laboratory evaluation should include serum sodium, chloride, potassium, bicarbonate, creatinine, and blood urea nitrogen levels; complete blood count (with a peripheral smear to identify schistocytes); electrocardiogram; and urinalysis. Evidence of intravascular hemolysis is common and may make it difficult to differentiate hypertensive crisis from primary vasculitis with secondary hypertension.[20,21] The renin-angiotensin-aldosterone axis is markedly activated, as evidenced by hypokalemia and metabolic alkalosis.[22,23] Blood urea nitrogen and creatinine are often elevated. Urinalysis may show small amounts of proteinuria and hematuria with occasional erythrocyte casts.[5] Marked increases in proteinuria suggest a primary glomerular process, such as glomerulonephritis, as the cause of the elevated blood pressure.

TABLE 105–1. DIFFERENTIAL DIAGNOSIS OF HYPERTENSIVE ENCEPHALOPATHY

Cerebral infarction
Subarachnoid hemorrhage
Intracerebral hemorrhage
Subdural or epidural hematoma
Brain tumor or other mass lesion
Seizure disorder
Central nervous system vasculitis
Encephalitis/meningitis
Drug ingestion
Drug withdrawal

If hypertensive encephalopathy is suspected, magnetic resonance imaging should be performed. With hypertensive encephalopathy, edema may occur in the posterior regions of the cerebral hemispheres, particularly in the parieto-occipital regions, a finding called *posterior leukoencephalopathy* on magnetic resonance imaging.[24] Brainstem involvement on magnetic resonance imaging also has been reported.[24] However, it is important to consider and eliminate other conditions with a similar clinical presentation (Table 105-1). Several important diagnostic considerations help exclude other causes of altered mental status: (1) Symptoms of generalized brain dysfunction tend to develop over time (12 to 24 hours) with hypertensive encephalopathy compared with acutely with ischemic stroke or cerebral hemorrhage; (2) focal neurologic findings are unusual with hypertensive encephalopathy, unless there is associated bleed; (3) papilledema almost always is noted with hypertensive encephalopathy and, if absent, should raise suspicion of another etiology; (4) compared with an acute central nervous system bleed, mental status with hypertensive encephalopathy improves within 24 to 48 hours of treatment.

TREATMENT OF HYPERTENSIVE CRISIS

Patients with hypertensive crisis are best treated parenterally with intensive care monitoring by arterial cannulation or automated blood pressure cuff measurement. The primary goal of blood pressure therapy is to lower the pressure at a rate that arrests or alleviates end-organ damage without causing ischemia of vital organs. Generally the rate of blood pressure control depends on conditions associated with the hypertensive crisis. In most settings, blood pressure can be reduced acutely by 20% to 25% within minutes to hours. After the patient is stabilized at this pressure, blood pressure is decreased to 160/100 to 160/110 mm Hg over the next 2 to 6 hours. If the patient is clinically stable, the blood pressure may be decreased toward a normal blood pressure over the next 24 to 48 hours. With these decreases in blood pressure, central nervous system blood flow autoregulation usually is maintained. In ischemic stroke, there are no large clinical trials to support rapid reduction of blood pressure. Rapid blood pressure reduction (e.g., 15 to 30 minutes) to the normal range is indicated with acute aortic dissection or in previously normotensive subjects with abrupt increases in blood pressure.

More rapid reduction in blood pressure also is recommended in patients with active unstable angina or congestive heart failure with pulmonary edema. In patients with malignant hypertension or hypertensive encephalopathy, a more controlled titration of blood pressure reduction over 1 to 3 hours is satisfactory. Exceptions to rapid blood pressure reduction include older patients with carotid stenosis. These individuals are particularly susceptible to central nervous system hypoperfusion. Blood pressure management in patients with stroke or intracranial bleeding is controversial because the loss of central nervous system blood flow autoregulation and the presence of brain edema require high systemic pressures to provide adequate cerebral perfusion.

Of hypertensive crises, 40% to 50% arise in patients with preexisting hypertension without identifiable secondary causes.[5,25,26] Essential hypertension is the underlying disorder in most African-American individuals.[27-29] In contrast, 50% to 60% of white patients with malignant hypertension have an identifiable cause (Table 105-2).

TABLE 105–2. SYNDROMES OF HYPERTENSIVE CRISIS

Malignant hypertension
Nonmalignant hypertension with target organ disorders
Patient requiring emergency surgery with poorly controlled hypertension
Hyperviscosity syndrome
Postoperative patient
Renal transplant patient: acute rejection, transplant renal artery stenosis
Quadriplegic patient with autonomic hyperreflexia
Severe burns
Acute aortic dissection
Intracranial hemorrhage, ischemic stroke, or subarachnoid hemorrhage
Hypertensive encephalopathy
Myocardial ischemia/acute left ventricular failure
Preeclampsia/eclampsia
Antiphospholipid antibody syndrome
Acute renal failure
Scleroderma renal crisis
Chronic glomerulonephritis
Reflux nephropathy
Analgesic nephropathy
Acute glomerulonephritis
Radiation nephritis
Ask-Upmark kidney
Chronic lead intoxication
Renovascular hypertension
Fibromuscular dysplasia
Atherosclerosis
Endocrine hypertension
Congenital adrenal hyperplasia
Pheochromocytoma
Oral contraceptives
Aldosteronism
Cushing's disease/syndrome
Systemic vasculitis
Atheroembolic renal crisis
Drugs
Oral contraceptives
Nonsteroidal anti-inflammatory drugs
Atropine
Corticosteroids
Sympathomimetics
Erythropoietin
Lead intoxication
Cyclosporine
Catecholamine excess states
Pheochromocytoma
Monoamine oxidase/tyramine interaction
Antihypertensive withdrawal
Cocaine intoxication, sympathomimetic overdose

Renovascular hypertension, secondary to either fibromuscular dysplasia or atherosclerosis, is common. Patients with underlying chronic glomerulonephritis account for 20% of cases of malignant hypertension.[30] Other renal causes include reflex nephropathy (particularly in children)[30] and analgesic nephropathy.[31]

SPECIFIC TREATMENT RECOMMENDATIONS FOR HYPERTENSIVE CRISIS BASED ON ETIOLOGY

GENERAL COMMENT ON MEDICATIONS USED TO TREAT HYPERTENSIVE CRISIS

The classes of parenteral antihypertensive agents available to treat hypertensive crisis include direct vasodilators (sodium nitroprusside, nitroglycerin), alpha/beta-adrenergic blockers (labetalol), alpha-adrenergic blockers (phentolamine), angiotensin-converting enzyme inhibitors (enalaprilat), calcium channel blockers, and dopamine agonists (fenoldopam). The advantages and disadvantages of these medications are summarized in Table 105-3. Their uses in specific clinical conditions are discussed in subsequent sections. In general, the vasodilator sodium nitroprusside is the most widely used agent because of it rapid onset of action (1 to 2 minutes) and short half-life (2 to 5 minutes). It is effective in most hypertensive emergencies, but should be used with caution in the setting of renal disease and liver dysfunction. There is no consensus on the most effective antihypertensive medications in the setting of a central nervous system insult, and there are no randomized trials comparing different agents in hypertensive crisis and central nervous system insult. Most authors now caution, however, the use of nitroprusside in the setting of increased intracranial pressure. Vasodilators increase blood volume and have the potential to increase intracranial pressure. Animal and human studies in the setting of a normal intracranial pressure show no effect of nitroprusside on intracranial pressure.[32-34] In studies on animals and humans with preexisting increased intracranial pressure, however, nitroprusside increased the intracranial pressure, likely reflecting vasodilation on the background of decreased cranial compliance.[35-37] When sodium nitroprusside is contraindicated, other treatment options include labetalol and nicardipine. Fenoldopam, which is an agonist of the vasodilator dopamine-1 receptor, shares with nitroprusside a rapid onset and short duration of action. In addition, fenoldopam, in contrast to nitroprusside, increases renal blood flow, induces natriuresis, and produces no toxic metabolites.[38-42]

MALIGNANT HYPERTENSION

Malignant hypertension is specific syndrome characterized by markedly elevated blood pressures in conjunction with hypertensive neuroretinopathy. Funduscopic examination reveals flame-shaped hemorrhages, cotton-wool spots, or papilledema. Malignant hypertension also is associated with nephropathy, encephalopathy, microangiopathic hemolytic anemia, and cardiac ischemia. Untreated malignant hypertension is a rapidly fatal disorder, with a mortality of greater than 90% within 1 year, as reported in a classic series by

TABLE 105–3. TREATMENT OF HYPERTENSIVE CRISIS: INTRAVENOUS MEDICATIONS

Drug Name and Mechanism of Action	Indications/Advantages/Dose	Disadvantages/Adverse Effects/Metabolism/Cautions
Sodium nitroprusside: nitric oxide compound, vasodilator of arteriolar and venous smooth muscle, increases cardiac output by decreasing afterload	Useful in most hypertensive crises Onset of action immediate, duration of action 1-2 min Dose: Initial dose, 0.25 μg/kg/min, maximum dose 8-10 μg/kg/min Beware: 500 μg/kg over prolonged time, rate >2mEq/kg/min, cyanide is generated more rapidly than can be taken care of.	Contraindicated in high output cardiac failure, congenital optic atrophy. Anemia and liver disease at risk for cyanide toxicity—acidosis, tachycardia, change in mental status, almond smell on breath. Renal disease at risk for thiocyanate toxicity—psychosis, hyperreflexia, seizure, tinnitus. Cautious use with increased intracranial pressure. Do not use maximum dose for >10 min. Crosses the placenta
Nitroglycerin: directly interacts with nitrate receptors on vascular smooth muscle, primarily dilates venous bed, decreases preload	Use with symptoms of cardiac ischemia, perioperative hypertension in cardiac surgery Initial dose: 5 μg/min, maximum dose 200 μg/min	Contraindicated in angle-closure glaucoma, increased intracranial pressure. Blood pressure decreased secondary to decreased preload, cardiac output—avoid when cerebral or renal perfusion compromised. Caution with right ventricular infarct
Labetalol: beta-adrenergic blockade and alpha-adrenergic blockade, alpha/beta blocking ratio 1:7	Onset of action 2-5 min. Duration 3-6 h Dose: Bolus 20 mg, then 20-80 mg every 10 min for maximum dose 300 mg. Infuse at 0.5-2 mg/min	Avoid in bronchospasm, bradycardia, congestive heart failure, greater than first-degree heart block, second or third trimester pregnancy. Use caution with hepatic dysfunction, inhalational anesthetics (myocardial depression). Enters breast milk
Esmolol: cardioselective $beta_1$-adrenergic blocking agent	Used with aortic dissection, used during intubation, intraoperative and postoperative hypertension Onset 60 sec, duration 10-20 min Dose: 200-500 μg/kg over 1-4 min, then 50 μg/kg/min for 4 min, and titer, then infuse 50-300 μg/kg/min	See labetalol. Not dependent on renal or hepatic function for metabolism (metabolized by hydrolysis in red blood cells)
Fenoldopam: postsynaptic dopamine-1 agonist, decreases peripheral vascular resistance, 10 times more potent than dopamine as vasodilator	May be advantageous in kidney disease, increases renal blood flow, increases sodium excretion, no toxic metabolites Initial dose: 0.1 μg/kg/min with titration every 15 min, no bolus	Contraindicated in glaucoma (may increase intraocular pressure) or allergy to sulfites, hypotension especially with concurrent beta blocker. Check serum potassium every 6 h. Concurrent acetaminophen may significantly increase blood levels. Dose-related tachycardia

TABLE 105–3. TREATMENT OF HYPERTENSIVE CRISIS: INTRAVENOUS MEDICATIONS—CONT'D

Drug Name and Mechanism of Action	Indications/Advantages/Dose	Disadvantages/Adverse Effects/Metabolism/Cautions
Hydralazine: primarily dilates arteriolar vasculature	Primarily used in pregnancy/eclampsia Decrease blood pressure in 10-20 min, duration of action 2-4 h Dose: 10 mg every 20-130 min, maximum dose 20 mg	Reflex tachycardia, give beta blocker concurrently, may exacerbate angina. Half-life 3 h, may affect blood pressure for 100 h. Depends on hepatic acetylation for inactivation
Phentolamine: alpha-adrenergic blockade	Used primarily to treat hypertension from excessive catecholamine excess (i.e., pheochromocytoma) Onset of action 1-2 min, duration 3-10 min Dose: 5-15 mg	Beta blockade is generally added to control tachycardia or arrhythmias. As in all catecholamine excess states, beta blockers should never be given first because the loss of beta-adrenergically mediated vasodilation leaves alpha-adrenergically mediated vasoconstriction unopposed and results in increased pressure
Nicardipine: dihydropyridine calcium channel blocker inhibits transmembrane influx of calcium ions into cardiac and smooth muscle	Onset of action 10-20 min, duration 1-4 h Initial dose: 5 mg/h to maximum of 15 mg/h	Avoid with congestive heart failure, cardiac ischemia. Adverse effects include tachycardia, flushing, headache
Enalaprilat: angiotensin-converting enzyme inhibitor	Onset of action 15-20 min, duration 12-24 h Dose: 1.25-5 mg q6h	Response not predictable, with high renin states may see acute hypotension. Hyperkalemia with reduced glomerular filtration rate. Avoid in pregnancy
Trimethaphan: nondepolarizing ganglionic blocking agent, competes with acetylcholine for postsynaptic receptors	Used in aortic dissection Dose: 0.5-5 mg/min	Does not increase cardiac output. No inotropic cardiac effect. Disadvantages include parasympathetic blockade resulting in paralytic ileus and bladder atony, and development of tachyphylaxis after 24-96 h of use

Compiled from (1) Up to Date; (2) Varon J, Marik PE: The diagnosis and management of hypertensive crisis. Chest 2000;118:214-227; and (3) Abdelwahab W, Frishman W, Landau A: Management of hypertensive urgencies and emergencies. J Clin Pharm 1995;35:747-762.

Kincaid-Smith.[6] In this series, deaths were due to renal failure (19%), congestive heart failure (13%), renal failure plus congestive heart failure (48%), stroke (20%), and myocardial infarction (1%).

Aggressive therapy to prevent progressive ischemic injury in malignant hypertension is crucial. Although the autoregulatory range of central nervous system blood flow is reset upward in chronic hypertension, the lower limit of the autoregulation remains approximately 25% less than the resting mean arterial pressure in patients with normotension and chronic hypertension.[43] When the arterial blood pressure falls below this lower limit, cerebral blood flow decreases progressively, and symptoms of low central nervous system flow, including nausea, yawning, hyperventilation, clamminess, and syncope, develop. To protect cerebral function, after initial reduction of blood pressure by 20% within the first hour, blood pressure is reduced further over the next 2 to 6 hours to the 160/110 mm Hg range as long as the patient remains stable. Nitroprusside is one of the most useful intravenous agents for hypertensive crises. Some patients are highly sensitive to treatment owing to coexisting hypovolemia; low-dose nitroprusside is used to reach goal blood pressure. Many parenteral agents have been used as successful alternatives to nitroprusside, including labetalol, fenoldopam, and nicardipine. Premature discontinuation of parenteral therapy may cause rebound hypertension. Oral therapy is started after the pressure has been stabilized on parenteral therapy. Parenteral therapy then is slowly weaned.

Renal failure is common with malignant hypertension. For patients with worsening renal failure from malignant hypertension, renal failure exacerbates the hypertension. Aggressive treatment can arrest and reverse renal damage. Because the arteriolopathy of malignant hypertension includes fixed anatomic lesions, initial lowering of blood pressure may worsen renal function. Dialysis may be required in patients with a presenting creatinine greater than 4.5 mg/dL.[44] In most patients, renal function begins to improve after 2 weeks of therapy. Of patients who require dialysis, 50% regain sufficient function to discontinue dialysis.[45] Recovery of renal function is predicted when the combined length of both kidneys is 20.2 cm or more, but is thought to be unlikely when the length is 14.2 cm or less.[46] The mean time to recovery is approximately 2 to 3 months, but recovery after 26 months has been reported.[47] In patients with malignant hypertension secondary to glomerulonephritis, eventual deterioration to end-stage renal disease may occur despite blood pressure control.[48] In contrast, renal function tends to remain well preserved in patients without underlying glomerulonephritis if blood pressure is well controlled. Nitroprusside is one of the preferred agents to treat hypertension and renal failure. The metabolism of nitroprusside results in the production of cyanide, which is taken up by red blood cells and conjugated to thiocyanate in the liver. Cyanide toxicity occurs in patients with anemia or liver disease, whereas thiocyanate toxicity is seen in renal disease (see Table 105-3). Thiocyanate levels should be monitored, and the duration of therapy should be kept to less than 72 hours whenever possible. Fenoldopam has no toxic metabolites and may protect renal function.[38-42]

Controversy exists regarding the management of relatively asymptomatic malignant hypertensive patients (i.e., with neuroretinopathy alone).[49-51] Although oral medication under close observation has been used successfully,[52] we prefer initial parenteral therapy. The progressive breakdown of central nervous system autoregulation in these patients

enhances the sensitivity to ischemia with abrupt decreases in blood pressure. Of the oral agents, calcium antagonists and minoxidil are effective and safe. Angiotensin-converting enzyme inhibitors may cause hyperkalemia in undialyzed patients with significant renal insufficiency.

HYPERTENSIVE ENCEPHALOPATHY

In hypertensive encephalopathy, the mean arterial pressure exceeds the limits of autoregulation, and brain edema develops from extravasation of plasma proteins. If hypertensive encephalopathy is untreated, coma and death may follow.[53] The challenge of hypertensive encephalopathy is appropriate lowering of blood pressure in the setting of central nervous system ischemia and edema. The hallmark of hypertensive encephalopathy is improvement within 12 to 24 hours of adequate blood pressure reduction. The mean arterial pressure should be reduced cautiously by no more that 15% over 2 to 3 hours. Neurologic complications have been reported from reductions in mean arterial pressure of 40% or more.[54] In previously normotensive patients, including patients with eclampsia, blood pressure should be normalized. If the mental status worsens with treatment, the pressure should be allowed to increase until neurologic symptoms resolve, then be reduced to within the normal range over several days, to allow restoration of autoregulation.

ISCHEMIC CEREBRAL INFARCTION

When the cerebral perfusion pressure decreases below the level of autoregulation, ischemia develops. In response, there is a marked elevation in arterial blood pressure, which tends to return spontaneously to baseline 24 to 48 hours after the acute event. The role of blood pressure treatment in this setting is controversial. Data from animal studies show in the area surrounding the ischemic infarct that there are "neurons at risk" that rely on collateral circulation to maintain perfusion.[55] These neurons are nonfunctional, are not dead, and potentially can be "rescued" by reperfusion, a phenomenon referred to as *ischemic penumbra*.[55] The degree to which this phenomenon occurs in humans is unknown.[55] In addition, in acute stroke, autoregulation is impaired, and cerebral blood flow is not preserved in a predictable manner. As a result of these changes, acute reductions in blood pressure potentially could increase the area of infarct, resulting in severe clinical consequences. Recommendations from the American Stroke Association are as follows: In individuals with a recent ischemic infarct and a blood pressure greater than 220/120 to 220/140 mm Hg, the blood pressure may be decreased by 10% to 15%. During this reduction, the patient is monitored cautiously for any neurologic sequelae. If the diastolic blood pressure is greater than 140 mm Hg, the blood pressure is reduced with sodium nitroprusside by 10% to 15%.[56] Most clinicians do not treat hypertension in the setting of ischemic stroke, unless the blood pressure elevation is extreme (systolic blood pressure >220 mm Hg, diastolic pressures >120 mm Hg), or there is acute ischemic damage to vital organs (cardiac ischemia, aortic dissection). Hypotensive agents used in this setting include nitroprusside and labetalol. Intravenous labetalol may not elevate intracranial pressure as much as nitroprusside.[57,58]

SUBARACHNOID HEMORRHAGE

Approximately 10% of cerebrovascular accidents are due to subarachnoid hemorrhage.[59] Mortality rates are estimated at 40% to 50%.[60,61] Ruptured congenital berry aneurysms are the most common cause of subarachnoid hemorrhage. Subarachnoid hemorrhage increases intracranial pressure and decreases cerebral perfusion, causing global ischemia. Complications include an intracerebral hemorrhage or the development of hydrocephalus. The treatment of choice is surgical clipping. There is a significant risk of rebleed in the first 24 hours. Management of these patients is significantly different from patients with ischemic stroke. In contrast to ischemia, intracranial bleed induces intense vasospasm in neighboring vessels 4 to 12 days after the initial bleed, increasing the risk for significant cerebral ischemia. The mental status evaluation may be used to guide therapy. An intact mental status is evidence of adequate cerebral perfusion.

Markedly elevated pressures increase the risk of rebleeding. The goal is a 20% to 25% reduction in mean arterial pressure over 6 to 12 hours, but to not less than 160/100 to 180/100 mm Hg.[62] Labetalol is the preferred agent because there are no significant adverse effects on intracranial pressure or cerebral perfusion pressure.[58] Given the potential increase in cerebral blood volume and intracranial pressure associated with vasodilators, sodium nitroprusside and nitroglycerin are not usually first-line treatments. There are clinical data to show that treatment with oral nimodipine within 4 days of the acute event decreases vasospasm and cerebral ischemia.[63] Nimodipine also may directly protect nerve cells from ischemic damage by blocking calcium uptake into cells.

INTRACEREBRAL HEMORRHAGE

Intracerebral hemorrhage accounts for 10% to 20% of all strokes.[64] Hypertension is a major risk factor; 75% of affected individuals have preexisting hypertension.[65] Although patients with intracerebral hemorrhage may present with nausea, vomiting, change in mental status, hypertension, headache, and a focal neurologic examination, the definitive diagnosis must be made by neuroimaging. In contrast to ischemic stroke, in which blood pressure generally returns to normal in 24 to 48 hours, in intracerebral hemorrhage, although the most rapid decline in blood pressure occurs in the first 24 hours, the blood pressure may remain elevated for 7 to 10 days.[55,57] The hematoma compresses normal tissue, creating an area of ischemia, increasing intracranial pressure and further decreasing cerebral perfusion pressure. Autoregulation is altered, making cerebral perfusion critically dependent on systemic blood pressure.[57] There is no consensus on the treatment of hypertension in this setting, and no randomized studies have been done to look at the impact of blood pressure control on outcome. Some authors argue that decreasing blood pressure decreases risk of hemorrhage extension, edema, and associated systemic complications, particularly when systolic blood pressure exceeds 200 mm Hg, a level shown to be associated with hematoma growth.[57,64,65] Other authors argue that not treating hypertension allows continued perfusion of areas at risk from low blood flow.[57] It was thought previously that rebleeding was rare in the first 24 hours. More recent data suggest that rebleeding is more common than thought, occurring in one third of affected individuals.[65,66]

The greatest risk is in the first few hours after the initial insult.[66,67] An increased risk of bleed is associated with an initial large irregular bleed,[68] coagulopathy, liver disease,[69] and a low platelet count.[69] No studies have shown a clear relationship between acute hypertension after an intracerebral bleed and the risk of rebleed.[57] Extreme elevations of pressure (mean arterial pressure > 130 mm Hg) probably should be treated with reduction of blood pressure limited to 20%.[65] There is no consensus on the agent of choice.

Concern revolves around the impact of different antihypertensives on intracranial pressure. Common to all agents is a decrease in mean arterial pressure and a decrease in cerebral perfusion pressure. Vasodilating agents may increase cerebral blood flow and in the setting of decreased cranial compliance potentially may increase intracranial pressure, further decreasing cerebral perfusion pressure.[36,57] The combination of decreased cerebral compliance, decreased cerebral blood flow, and altered autoregulation as occurs in chronic hypertension makes the administration of any antihypertensive agent potentially dangerous. No large randomized studies are available to guide therapy. Combination alpha and beta blockers are recommended when antihypertensive treatment is indicated in intracerebral hemorrhage. Risks of this therapy include worsening of bradycardia associated with the Cushing response. In the setting of normal cranial compliance and an increased intracranial pressure, however, vasodilators are probably safe. Because of the high levels of circulating catecholamines with intracerebral bleed, beta blockade is added when vasodilator therapy alone is ineffective. In one study, barbiturates were found to reduce mean arterial pressure modestly, while markedly reducing the intracranial pressure, and should be considered in cases of severe hemorrhage.[70]

HEAD TRAUMA

Head trauma complications include skull fractures, epidural hematomas, subdural hematomas, intracerebral hematomas, and diffuse axonal damage. With trauma, there is often edema. Acute increases in intracranial pressure are prevented initially by flow of blood and cerebrospinal fluid from the cranial vault. With increasing edema, however, intracranial pressure eventually increases. In most trauma centers, intracranial pressure monitoring has become the standard of care.[71] Defective autoregulation may occur in 31% to 61% of patients with a closed-head injury.[71] If autoregulation is intact, increasing the mean arterial pressure causes vasoconstriction and produces no change in intracranial pressure. With altered autoregulation, increasing the mean arterial pressure may cause vasodilation, increasing blood volume, causing edema and increased intracranial pressure. The goal is to maintain a minimal cerebral perfusion pressure of 70 mm Hg and a mean arterial pressure greater than 90 mm Hg. If an antihypertensive agent is needed, a major consideration is its impact on intracranial pressure. A combination alpha and beta blocker may be preferred when there is decreased intracranial compliance and increased intracranial pressure. In the absence of increased intracranial compliance, vasodilators may be preferred.

AORTIC DISSECTION

Aortic dissection begins with a tear in the intima of the aorta that is propagated by the aortic pulse wave (dP/dt). Myocardial contractility, heart rate, and blood pressure contribute to the aortic pulse wave. There are two types of aortic dissection—type A and type B. Type A dissections often are associated with a tear in the intima of the proximal aorta next to a coronary artery and may extend to the aortic arch.[73] Type B dissections occur in the descending aortic arch and usually begin with an intimal tear next to the subclavian artery.[74] Risk factors for dissection include advanced atherosclerosis, Marfan syndrome, Ehlers-Danlos syndrome, and coarctation of the aorta.[75] Symptoms occur as the expanding hematoma causes pressure on the vasculature; this may cause myocardial infarction, stroke, spinal cord/bowel infarction, and acute renal failure. Ischemic kidney may develop leading to refractory hypertension.[76] Dissection to the aortic root can precipitate acute aortic insufficiency.[77] Rupture of the ascending aorta leads to hemopericardium and tamponade.[77]

Both types of dissection may present with severe, often tearing, pain in the chest, back, or abdomen, accompanied by diaphoresis, nausea, or vomiting. They are often, but not always, associated with hypertension.[78] Discrepancies in peripheral pulses may be observed. The chest x-ray may show widening of the mediastinum. An analysis showed a widened mediastinum was present in only half of individuals with type B dissection.[79] The diagnosis may be confirmed with computed tomography or magnetic resonance imaging.[78] Multiplane transesophageal echocardiography also is used.[78]

Type A dissections usually require surgery to prevent the catastrophic consequences of great vessel occlusion, aortic insufficiency, or tamponade. Type B dissections usually may be treated medically.

Treatment for type A and type B dissections is initiated based on clinical suspicion alone given the high mortality associated with this entity. The goal of treatment is first to decrease myocardial contractility and heart rate with beta blockade. Propranolol often is used. Labetalol also may be used, although its longer duration of action poses a disadvantage in patients going for emergency surgery. Next, the blood pressure is reduced to the lowest tolerable level until pain is relieved. Relief of pain suggests arrest of ongoing aortic dissection. The most widely used agent is nitroprusside. Nitroprusside is titrated to systolic pressure of 100 to 120 mm Hg or to diastolic pressure of 70 to 80 mm Hg. Prior treatment with beta blockade prevents reflex cardiac stimulation and a potential increase in the aortic pulse wave seen with nitroprusside.

An alternative regimen, preferred by some because of a more potent reduction in the steepness of the pulse wave contour, involves use of the ganglionic blocking agent trimethaphan.[79] This agent prevents increases in cardiac output and left ventricular ejection rate.[76,79] The rapid onset and short duration of action of this drug allow precise pressure control. Any mild reflex increase in heart rate may be treated with subsequent beta blockade. Hydralazine is avoided because it causes unwanted reflex cardiac stimulation. Even normotensive individuals should be treated with antihypertensive medications to keep the heart rate and shear forces low.

PULMONARY EDEMA

Many patients who present with pulmonary edema have long-standing antecedent hypertension with concentric left ventricular hypertrophy and well-preserved systolic contraction.[80,81] They develop acute diastolic dysfunction in response to abrupt increases in cardiac afterload secondary

to increased systemic blood pressure.[82] With poor diastolic relaxation, the left ventricle requires markedly elevated filling pressures, leading to pulmonary venous hypertension and edema. The therapeutic goal is to decrease afterload, improve diastolic relaxation, and decrease pulmonary pressure. Vasodilators are the agent of choice because they improve diastolic relaxation and lower pulmonary venous pressure. A beta blocker also may be used. Nitroprusside often is used because it reduces preload and afterload, improving left ventricular function, and reduces myocardial oxygen demand. Modest decreases in pressure improve symptoms markedly. In less emergent settings, angiotensin-converting enzyme inhibitors or calcium channel antagonists have been shown to improve diastolic function and cause regression of concentric ventricular hypertrophy.[83]

In patients with left ventricular failure secondary to poor systolic function, vasodilators are the agents of choice. Nitroglycerin is preferred with cardiac ischemia. Nitroprusside may be used in patients refractory to nitrites. Although nitroglycerin dilates intercoronary collateral vessels more than small resistance arterioles and improves perfusion of ischemic myocardium, nitroprusside dilates resistance arterioles predominantly, resulting in a potential steal of blood flow away from ischemic areas. Diuretics are used to reduce left ventricular end-diastolic volume.

In acute myocardial infarction, acute catecholamine release and sympathetic outflow contribute to hypertension. The hypertension usually resolves in a few hours with sedation and pain control alone. Diastolic blood pressures greater than 100 mm Hg should be treated with nitroglycerin. The pressure is rapidly, but cautiously, reduced to near normotensive levels because overshoot hypotension can worsen coronary perfusion. Therapy usually can be stopped within 24 hours. There is considerable evidence that the early use of beta-blocking agents may reduce ultimate infarct size independent of blood pressure control.[84]

PERIOPERATIVE HYPERTENSION

Perioperative hypertension is a major risk factor for the development of postoperative hypertension.[85] It is recommended that elective surgery be deferred until the diastolic pressure is controlled at less than 110 mm Hg because patients with less severe hypertension do not seem to carry an increased risk.[86] The exception is in patients with end-organ damage secondary to hypertension, as with congestive heart failure, in which there seems to be an increased risk of adverse cardiac outcome.[87] In patients with chronic hypertension on adequate treatment, oral medications should be taken the morning of surgery.

Induction of anesthesia increases sympathetic activity, causing elevated blood pressure, a response that may be exaggerated in uncontrolled hypertension.[86] As anesthesia continues, there is generally a decrease in blood pressure. Rapid and wide fluctuations in blood pressure, leading to intraoperative hypotension, stroke, myocardial ischemia, or acute renal failure, are more common in individuals with a hypertensive history.

Patients taking hypertensive therapy before surgery should continue treatment after surgery, changing to an equivalent intravenous medication if they are unable to take oral medications. If patients have been on a beta blocker or clonidine, this medication should be continued postoperatively to prevent rebound hypertension. If intravenous medication is necessary, propranolol or methyldopa may be used. The high incidence of increased blood pressure results from the decreased use of "deep" anesthesia and absence of prolonged sedation after surgery. As a result, there is increased sympathetic response to surgical stimuli, such as pain, hypoxia, and the anesthetic agents themselves. Effective pain control and avoidance of hypoxia are sufficient to treat the hypertension. Adequate blood pressure control reduces the risk of bleeding from suture lines, premature graft closure, and ischemic damage to organs at risk. Nitroprusside is widely used. Nitroglycerin is preferred for post–coronary bypass patients. Fenoldopam, with its impact on increasing renal blood flow, also is recommended, especially in clinical settings where renal ischemia is a risk.

CATECHOLAMINE-ASSOCIATED HYPERTENSION

Hypertensive crisis related to excess catecholamine secretion can result from the ingestion of sympathomimetic agents, such as cocaine, amphetamines, phencyclidine, and phenylpropanolamine (diet pills); decongestants, such as ephedrine and pseudoephedrine; and other agents, including atropine, ergot alkaloids, and tricyclic antidepressants. It also may be caused by tyramine ingestion in conjunction with monoamine oxidase inhibitor therapy, autonomic dysfunction, withdrawal from certain antihypertensive medications, and pheochromocytoma. Critically elevated pressures can result and cause myocardial infarction, aortic dissection, and stroke.

Pheochromocytoma is a rare cause of hypertension.[88] Excess catecholamine secretion by the tumor results in a sustained elevation of blood pressure in most cases, whereas peripheral catecholamine uptake and storage lead to paroxysmal symptoms when the catecholamines are released in response to stimuli. Symptoms of pheochromocytoma include headache, palpitations, hypertension, anxiety, abdominal pain, and diaphoresis. Patients may present with orthostatic changes in blood pressure, a clue to the diagnosis.[89] For patients with hypertensive emergency, the treatment of choice is the short-acting parenteral alpha antagonist, phentolamine. After blood pressure reduction, beta blockade generally is added to control tachycardia or arrhythmias. As in all catecholamine excess states, beta blockers should not be used as initial therapy. Loss of beta-adrenergically mediated vasodilation leaves alpha-adrenergically mediated vasoconstriction unopposed and results in increased pressure. An oral regimen of the nonselective alpha antagonist, phenoxybenzamine, can be used in less critical situations. Labetalol has been effective in treating hypertension related to pheochromocytoma in selected patients. Because its beta-blocking effect exceeds its alpha-blocking effect, however, severe hypertension has been reported.[90]

Significant rebound hypertension may develop 12 to 72 hours after abrupt discontinuation of chronic beta-blocker therapy or a centrally acting alpha-agonist antihypertensive, such as clonidine or methyldopa, from increased sympathetic outflow. With severe hypertension, headache, diaphoresis, anxiety, nausea, tachycardia, and abdominal pain are reported. In cases of moderate hypertension, simply restarting the antihypertensive agent may control the blood pressure. With more severe blood pressure elevations, intravenous therapy should be started.

TABLE 105–4. TYRAMINE-CONTAINING FOODS

Chianti wine
Soy sauce
Avocados
Bananas
Coffee
Chocolate
Pickled herring
Chicken liver
Yeast
Fermented sausage
Canned figs
Certain beer
Unpasteurized cheese

In patients on monoamine oxidase inhibitor therapy, ingestion of foods containing tyramine or sympathomimetic amines can result in hypertension (Table 105-4). Tyramine is metabolized by an alternative pathway to octopamine, which releases catecholamines from peripheral sites by acting as a false neurotransmitter. Nitroprusside or phentolamine is used, with the addition of beta blockade as needed for tachycardia. The episodes are self-limited and last 6 hours or less.

GESTATIONAL HYPERTENSION, PREECLAMPSIA, AND ECLAMPSIA

Gestational hypertension is defined as a systolic blood pressure of at least 140 mm Hg and a diastolic blood pressure of at least 90 mm Hg on two separate blood pressure measurements done 6 hours apart. It occurs after 20 weeks of pregnancy in patients known to be previously normotensive.[91] Fifty percent of these women develop preeclampsia if gestational hypertension develops before 30 weeks of gestation.[94] *Preeclampsia* is defined as gestational hypertension with 300 mg of protein on a 24-hour urine (urine dipstick 1+).[91] A 24-hour urine is necessary because urine protein on dipstick correlates poorly with 24-hour urine protein in gestational hypertension.[92] Preeclampsia also should be suspected in patients with hypertension developing after 20 weeks of gestation and associated with nausea, vomiting, cerebral symptoms, abnormal liver function tests, and thrombocytopenia even in the absence of proteinuria. Preeclampsia develops in 7% of all pregnancies—70% in null gravidas and 30% in multigravidas. In the setting of molar pregnancy, it is seen in 70% of individuals.[93] During normal pregnancy, blood pressure initially is decreased, then slowly increases toward the normal range during the third trimester. In preeclampsia, intravascular volume is low despite peripheral edema, and the renin-angiotensin system is activated. Progression to seizures defines *eclampsia*, which may occur with diastolic pressures of 100 mm Hg. Clinical treatment includes bed rest and parenteral magnesium. With preeclampsia, to avoid compromise of placental blood flow, the goal is to keep the systolic blood pressure between 140 mm Hg and 150 mm Hg and diastolic blood pressure between 90 mm Hg and 105 mm Hg.[94] Hydralazine is the preferred agent. Labetalol also may be used. Nitroprusside should be avoided because of the risk of cyanide toxicity in the fetus. Angiotensin-converting enzyme inhibitors also should be avoided because of their potential impact on the fetus' kidney.

OTHER HYPERTENSIVE SITUATIONS

The renal crisis of scleroderma is an aggressive form of malignant hypertension in which proliferative endarteritis precedes hypertension. Ischemia-induced activation of the renin-angiotensin system causes hypertension. The incidence of this condition among patients with scleroderma ranges from 8% to 13%, and it is more common among blacks.[95] Progression to end-stage renal disease occurs in 1 to 2 months without treatment. Aggressive pressure control with angiotensin-converting enzyme inhibitors leads to a long-term survival of about 50% to 70%.[96]

Hypertension is a feature of primary and secondary antiphospholipid antibody syndromes, occurring in 93% of patients.[97] Malignant hypertension occurs in this syndrome secondary to microvasculopathy and emboli to the renal artery. Antihypertensive treatment is similar to malignant hypertension. Successful treatment outcomes have been reported with anticoagulation.[97]

One fourth of patients with extensive second-degree or third-degree burns develop severe hypertension in the first few days, likely owing to high levels of circulating catecholamines and renin. Nitroprusside and phentolamine are other treatments.

Patients with transverse spinal cord lesions at the T6 level or higher, including patients with Guillain-Barré syndrome, have dysreflexia, in which noxious stimuli in dermatomes below the level of the lesion trigger a massive sympathetic discharge. This discharge leads to severe hypertension, bradycardia, diaphoresis, and headache. In 90% of patients, distention of the bladder or bowel causes dysreflexia, and prompt decompression leads to resolution of hypertension.[98] Drugs that have been used successfully in treating this condition include nitroprusside, phentolamine, and labetalol.

Hypertension in the renal transplant recipient may be caused by acute rejection, vascular anastomotic stenosis, obstructive uropathy, corticosteroid use, cyclosporine, and native kidney renin release.[99] Oral calcium channel antagonists are effective and well tolerated in these patients. Other rare causes of hypertension include erythropoietin-associated hypertension. This condition is treated with phlebotomy and dose reduction in conjunction with antihypertensive drug.[100] Diabetics on beta blockers can experience severe hypertension with hypoglycemic episodes, presumably due to catecholamine release.

HYPERTENSIVE URGENCY

Hypertensive urgency refers to patients in whom blood pressure is severely elevated, but based on detailed history, physical examination, and laboratory evaluation, there is no evidence of acute end-organ damage. This clinical situation is different from that of patients with severe hypertension and chronic stable complications, such as patients with stable chronic renal failure or stable angina. The decision to treat the latter group in the inpatient or outpatient setting often depends on the associated end-organ involvement (Table 105-5) and reliability of patient follow-up.

The most common treatment category, termed *severe uncomplicated hypertension* (see Table 105-5), is used to describe patients with severe blood pressure elevation but no end-organ involvement. Despite markedly elevated pressures (e.g., diastolic pressures of 140 mm Hg at times), these patients are at low risk of immediate complications.

TABLE 105–5. SEVERE UNCOMPLICATED HYPERTENSION

Severe hypertension (diastolic >115 mm Hg) in association with one or more of the following:
- Chronic renal failure
- Chronic congestive heart failure
- Stable angina
- Previous myocardial infarction
- Transient ischemic attacks
- Previous cerebrovascular accident

Hypertension-related morbidity tends to occur over months to years. The treatment of choice is gradual pressure reduction over a few days in the outpatient setting. The major risk of therapy is rapid pressure reduction. The choice of antihypertensive agent is based on ease of administration and side-effect profile rather than on rapid blood pressure reductions. Frequently, restarting a previously effective regimen is all that is necessary. It is crucial to follow these patients over the next 24 to 48 hours to ensure the blood pressure is appropriately reduced. Although medicolegal issues may pressure physicians into loading these patients with medication to observe on-the-spot control of blood pressure, this practice has been questioned as having no clear rational scientific basis.

ANNOTATED REFERENCES

Hajjar I, Kotchen TA: Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1999-2000. JAMA 2003; 290:199-206.

Contrary to earlier reports, hypertension prevalence is increasing in the United States. Hypertension control rates, although improving, continue to be low. Programs targeting hypertension prevention and treatment are of utmost importance.

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Blumenfeld JD, Laragh JH: Management of hypertensive crisis. Am J Hypertension 2001;14:1154-1167.

This article provides a detailed treatment algorithm to guide drug selection in patients presenting with a hypertensive crisis.

Adams HP Jr, Adams RJ, Brott T, et al: Guidelines for the early management of patients with ischemic stroke: A scientific statement for the Stroke Council for the American Stroke Association. Stroke 2000;34:1056-1083.

The management of patients with acute ischemic stroke is multifaceted, and indications for specific therapies vary among patients. There is strong evidence that outcomes after stroke can be improved and that death or disability from stroke can be reduced with appropriate treatment. This statement aims to provide guidance to physicians for the early treatment of patients.

Chapter 106

CARDIAC SURGERY: INDICATIONS AND COMPLICATIONS

Jacques P. Goldstein • Pierre Wauthy

KEY POINTS

1. Cardiac surgery includes mainly coronary and valve surgery. Indications for coronary artery bypass surgery are mainly based on symptoms and the presence of myocardial ischemia. Surgery is recommended in the presence of specific anatomical coronary lesions such as left main stenosis, triple vessel disease, or significant proximal left anterior descending stenosis.
2. Concerning aortic valve stenosis, aortic valve replacement is indicated when the effective valve area is $\leq 1 cm^2$. Aortic valve regurgitation requires surgery as left ventricular systolic dysfunction develops. Indications for mitral valve surgery have increased with the development of mitral valve repair.
3. Complications after cardiac surgery mainly include cardiac arrhythmias, bleeding, myocardial dysfunction, infectious problems such as mediastinitis, and pulmonary dysfunction. Neurologic complications and renal dysfunction also may develop. Acute complications such as aortic dissection after cardiac surgery or left ventricular rupture after mitral valve replacement are rarely observed but require early diagnosis and emergency reoperation.

Since the first clinical use of the heart-lung machine, developed by Gibbon in 1953, cardiac surgery has become a worldwide standard technique for the treatment of congenital and acquired cardiac diseases.[1] Over a period of more than 50 years with trials and errors, indications for surgical treatment of cardiac diseases have been well defined. The introduction of new surgical techniques, such as beating-heart surgery or new ministernotomy approaches, may improve some surgical results and may be applied to patients not suitable for the standard therapies. This chapter reviews the specific indications for cardiac surgery in patients with coronary and valvular diseases and discusses some of the most frequent complications encountered after cardiac surgery.

SURGICAL INDICATIONS FOR CORONARY ARTERY DISEASES

Chest pain is usually evaluated with a combination of noninvasive and invasive tests. Symptoms should be characterized in terms of duration, location, and severity using the Canadian Cardiovascular Society Classification System.[2]

Noninvasive tests, including resting and exercise electrocardiogram in combination with more complex isotope studies, confirm the presence of ischemic myocardial diseases. For the cardiac surgeon, coronary angiography remains the essential invasive test to describe the exact location and the extent of the coronary artery narrowing. Left ventricular function also should be evaluated using noninvasive or invasive tests. Because the aim of coronary artery bypass surgery is to eliminate symptoms and to prolong life, indications for surgery are based on symptoms (Canadian classification), left ventricular function, extension of regional ischemia, and anatomic localization of the coronary artery stenosis.

In the early 1990s, three large multicenter randomized trials were undertaken in Europe and in the United States: the Veterans Administration Cooperative Study, the European Coronary Surgery Study, and the Coronary Artery Surgery Study. Among all patients, patients who underwent coronary artery bypass grafting (CABG) always had extended survival compared with medically treated patients. Referring to the natural history of coronary artery disease and these three large multicenter randomized trials, Gibbons and colleagues[2] made some specific recommendations for myocardial revascularization, published by the American College of Cardiology/American Heart Association task force.[2] Anatomic criteria remain the key factors in favor of myocardial revascularization. The benefit of CABG is correlated with specific coronary lesions such as the following:

- Left main stenosis of more than 50% or a left main equivalent disease (>70% stenosis in the proximal left anterior descending and the proximal circumflex arteries)
- Triple-vessel diseases defined as significant lesions (>70%) in all three coronary territories (right, anterior, and lateral)
- Significant proximal left anterior descending stenosis with two-vessel disease

The improvement of long-term survival is even more striking when left ventricular function is depressed before surgery.[3] Since these three randomized trials were performed, however, several important factors have changed. The patient population is getting older, but patients older than age 65 were excluded from the early trials. Improvements in surgical

techniques with systematic use of arterial grafts (intrathorax arteries, radial arteries) in combination with new medical therapies (platelet inhibitors or lipid-lowering agents) have been shown to improve the long-term survival rates after CABG.[2]

Besides specific coronary lesions, CABG should be evaluated taking into account some incremental risk factors that may increase morbidity or mortality, such as hemodynamic instability, older age, diabetes mellitus, and chronic obstructive pulmonary disease.[4] Nashef and coworkers[5,6] developed a simple and effective scoring system for the prediction of early mortality after cardiac surgery (Euroscore). Using the Euroscore online (www.euroscore.org), predictive mortality can be calculated according to several risk factors, including age, sex, chronic pulmonary disease, extracardiac arteriopathy, neurologic dysfunction, previous cardiac surgery, serum creatinine level, critical preoperative status, left ventricular function, pulmonary hypertension, and emergency operation.

New, less invasive CABG procedures may broaden the indications for surgery by reducing morbidity and mortality. Currently, evolving technology can be divided into three categories:

1. Off-pump CABG performed via sternotomy on a beating heart, avoiding cardiopulmonary bypass (CPB)
2. Minimally invasive CABG performed via a small left thoracotomy without CPB
3. Port-access CABG with femorofemoral CPB using thoracoscopic instruments

Early studies confirm the feasibility of these new techniques. Long-term benefits need to be evaluated, however.

SURGICAL INDICATIONS FOR AORTIC VALVE SURGERY

AORTIC STENOSIS

Echocardiography is the most efficient investigation to evaluate the degree of stenosis, degree of left ventricular hypertrophy, and evolution of left ventricular function in patients with aortic valve stenosis. The American College of Cardiology/American Heart Association Task Force on Practice Guidelines has graded the degree of aortic stenosis as mild (effective valve area >1.5 cm^2), moderate (area >1 to 1.5 cm^2), or severe (area ≤1 cm^2).[7] When stenosis is severe and cardiac output is normal, the mean transvalvular pressure gradient is generally greater than 50 mm Hg. Most patients with aortic stenosis are symptomatic, mainly with angina pectoris and dyspnea.

Because aortic valve replacement is the only effective treatment for severe aortic stenosis, surgery is indicated in virtually all symptomatic patients except for patients with severe comorbid conditions. Cases involving patients undergoing CABG with mild-to-moderate aortic stenosis are controversial.[7-9] For asymptomatic patients with mild aortic stenosis (mean gradient ≤25 mm Hg) who require CABG, it may be reasonable to perform only revascularization given the slow evolution of aortic stenosis and the improvement in reoperation mortality and morbidity.[9]

AORTIC REGURGITATION

Patients with chronic aortic regurgitation are mainly asymptomatic for many years. During this period, increased volume and pressure are compensated by left ventricular hypertrophy. This balance between volume overload and hypertrophy may deteriorate, however, with a reduction in contractility. Patients develop dyspnea, orthopnea, and pulmonary edema, usually New York Heart Association functional class III or IV, which is a good indication for valve replacement.[7] Surgery also is indicated in patients with left ventricular systolic dysfunction (ejection fraction <0.25 or end-systolic dimension >60 mm or both).

Surgical treatment of asymptomatic patients with aortic regurgitation is controversial. Patients with aortic regurgitation and mild-to-moderate left ventricular dysfunction at rest (ejection fraction 0.25 to 0.49) also should be candidates for surgery knowing that most of them develop symptoms within 2 to 3 years. Aortic regurgitation also can be caused by aortic root dilation. Aortic root replacement with aortic valve replacement or aortic valve–sparing surgery should be performed when the aortic root dilation is 50 mm or greater.[10,11]

SURGICAL INDICATIONS FOR MITRAL VALVE SURGERY

Indications for mitral valve surgery have changed with the extension of mitral valve repair. With a better understanding of the specific anatomic lesions of the mitral valve associated with improvements in the surgical techniques, successful mitral repair can be achieved in specific ischemic and nonischemic mitral regurgitation.

MITRAL STENOSIS

Moderate or severe mitral stenosis (mitral valve area ≤1.5 cm^2) in symptomatic patients (New York Heart Association class III or IV) represents a good indication for surgery.[7] Mortality may be 15% in older patients, however, with calcified valves and pulmonary hypertension.

MITRAL REGURGITATION

Mitral valve repair always should be attempted to avoid problems associated with prosthetic valves. Surgery is required in symptomatic patients with normal left ventricular function or mild or severe left ventricular dysfunction. In asymptomatic patients, surgery is advised only if the left ventricular function is mildly or moderately reduced. The acute onset of atrial fibrillation in patients with mitral regurgitation also is a good indication for surgery, even with normal left ventricular function.

Ischemic mitral regurgitation represents a specific entity related to left ventricular dysfunction, anulus dilation, or papillary muscle dysfunction. CABG alone sometimes may reduce left ventricular dysfunction and reduce mitral regurgitation. Echographic data were able to evaluate the regurgitated volume (proximal isovelocity surface area).[12] Mitral valve plasty should be undertaken when the regurgitated volume is greater than 35 mL. Usually, mitral ring annuloplasty is performed with a downsized ring enabling better mitral valve coaptation.[13,14]

COMPLICATIONS AFTER CARDIAC SURGERY

Most patients after cardiac surgery under CPB have a normal convalescence without complications. Convalescence may be

abnormal, however, requiring intensive observation and prompt intervention if required. Numerous complications may occur after cardiac surgery; the most common are described here.

CARDIAC ARRHYTHMIAS

Postoperative cardiac arrhythmia is a major cause of morbidity and mortality in cardiac surgery. These arrhythmias may occur with normal cardiac function and in postoperative cardiac failure. Inotrope administration may increase the risk of such complications. Atrial and ventricular arrhythmias can occur in the postoperative period. Systemically, ventricular pacing wires are placed during the operation and left until patient discharge or a maximum of 10 postoperative days. Frequently, atrial and ventricular epicardial pacing wires are placed at the end of surgery. Pacing wires may help in the diagnosis and treatment of postoperative arrhythmias. To detect such arrhythmias, electrocardiogram monitoring is mandatory at least during the first 5 postoperative days.

Atrial Arrhythmias

Atrial fibrillation and flutter are common after cardiac surgery. After open cardiac procedures, 40% of patients may present with atrial fibrillation.[15] Flutter generally is recognized to be more difficult to treat than fibrillation. These complications rarely result in major morbidity or death, however. Age older than 65 years, history of intermittent atrial fibrillation, atrial pacing, male sex, and white race are risk factors of postoperative atrial fibrillation.[15] Intraoperative variables may influence the occurrence of atrial arrhythmias, such as Guiraudon atrial incision in mitral surgery. A postoperative increase in creatinine is also an independent risk factor for occurrence of atrial fibrillation.[16] Treatment of atrial fibrillation in the postoperative period is required. Beta blockers (sotalol) and amiodarone reduce the risk of postoperative atrial fibrillation with no marked difference between them.[17] Acquired long Q-T syndrome induced by class 3 antiarrhythmic agents may lead to spontaneous torsades de pointes, however, a fatal arrhythmia.[18] Acute administration of amiodarone is mandatory if the arrhythmia induces hemodynamic instability.[19] A bolus of 5 mg/kg is given initially over 20 minutes, followed by 15 mg/kg during the first 24 hours. This treatment is generally considered as the most appropriate after cardiac surgery.

Ventricular Arrhythmia

Ventricular electrical instability may occur after cardiac surgery. This instability may place the patient at high risk for sudden death from ventricular fibrillation. Electrocardiogram monitoring is mandatory during the first 48 hours after major cardiac procedures. The management of ventricular electrical instability is problematic; drugs generally used to treat these arrhythmias are often considered to induce these arrhythmias.[20,21] Electrophysiologic studies are essential in the immediate and long-term management of patients presenting with ventricular tachycardia in the postoperative period if the left ventricular ejection fraction is less than 40%.

BLEEDING AND CARDIAC TAMPONADE

Hemostasis is deeply altered after cardiac surgery under CPB. Altered platelet numbers and qualitative changes occur. The fibrinolytic cascade and coagulation are activated, and the formation of fibrin clots is inhibited. All of these factors, associated with cytokine activation and kallikrein stimulation of neutrophils, lead to a propensity for patients to bleed after the procedure.[22] Continuous blood loss must be monitored as long as the drains are in place. Platelets and fresh frozen plasma administration may be considered if coagulation parameters are altered. Supplementary protamine administration must be considered if required. If bleeding persists despite correct coagulation tests, however, prompt reoperation must be considered if the bleeding rate exceeds 300 mL/h for 3 consecutive hours or 1000 mL/h during the first 4 to 5 hours after the procedure in adult patients. Early reexploration for bleeding is mandatory in 0.5% to 5% of cardiac surgery patients, essentially depending on institutional criteria. Using these parameters, early reoperation generally stops the bleeding, even if no bleeding origin is found. Reduction of homologous blood transfusion, cardiac tamponade, and easier patient subsystem management is the key point of early reoperation. Patience during the final steps of the primary procedure generally reduces the need for revision to nearly 0%.

Cardiac tamponade may occur if excessive bleeding persists. To prevent such a complication, chest drainage tubes must be placed properly in the operating room, and early suction is mandatory to avoid blood accumulation in the pericardium and the pleural space. Massive bleeding during the hours after the procedure and clot obstruction of the drains may lead to cardiac tamponade. Meticulous monitoring of drainage is required. If cardiac tamponade occurs, prompt reoperation is required. Delayed cardiac tamponade also may occur within the days after cardiac surgery. Clinical signs and symptoms must be tracked before patient discharge, including unexplained weakness; orthopnea and dyspnea; aggravation during exertion; and peripheral edema with hepatomegaly, ascites, and venous turgescence. Pulsus paradoxus must be checked, and a prompt chest radiograph must be done. A widened cardiac silhouette generally appears before clinical signs and symptoms. A large pericardial effusion develops postoperatively in 30% of patients after cardiac surgery and is more common if early postoperative bleeding is excessive.[23] Maximal effusion appears at approximately 10 days. Cardiac echocardiography generally is performed before patient discharge to exclude important pericardial effusion requiring drainage. If required, drainage is performed via a reopening of the incision below the xyphoid process. The pericardial fluid is evacuated using a surgical sucker. A chest tube may be placed if required to avoid early recurrence of the tamponade.

MYOCARDIAL DYSFUNCTION AFTER CARDIAC SURGERY

Low cardiac output after cardiac surgery when atrial pressures are elevated above usual postoperative values may be attributed to myocardial dysfunction in the absence of any other likely causes. Ventricular wall motion evaluation and end-diastolic and end-systolic ventricular volumes assessed by echocardiography are key in the diagnosis of myocardial dysfunction. Patients with normal preoperative left ventricular contractility and patients with depressed contractility are more likely to develop this complication. Chronic preoperative

impairments of ventricular preload, afterload, or contractility by any mechanism are risk factors for postoperative myocardial dysfunction. Perioperative myocardial damage must be considered in the absence of preoperative risk factors in patients with postoperative contractility dysfunction. Incomplete operations, accuracy of myocardial protection management, and duration of global myocardial ischemia are intraoperative risk factors of further myocardial dysfunction. Poor postoperative function that reduces coronary blood flow explains the particular vulnerability of the heart in the early postoperative period. This coronary malperfusion may worsen myocardial function further. It generally is considered that heart vulnerability after cardiac surgery persists during the first 24 to 48 postoperative hours.

In the presence of postoperative myocardial dysfunction, the possibility of cardiac tamponade or cardiac compression (i.e., by pericardial restriction) must be excluded. If cardiac tamponade is diagnosed, prompt reoperation must be undertaken to relieve cardiac compression from blood accumulation in the pericardium. If cardiac dilation is observed at echocardiography, such as is observed during pulmonary hypertensive crisis, external heart compression by the sternum or the pericardium should be considered. The sternum and the pericardium must be opened rapidly if they were closed. This complication can be prevented in patients with increased risk factors for postoperative myocardial dysfunction by leaving the sternum open for the first 24 to 40 hours after the procedure. If cardiac restriction is believed not to be present, treatment is directed at increasing the cardiac output by manipulating preload and afterload, heart rate, and myocardial contractility. Preload may be manipulated by infusion of appropriate fluids. If the left ventricular wall thickness is unusually great or its compliance is restricted, as usually observed in aortic stenosis, the left atrial pressure may be elevated to 20 mm Hg. Left ventricular afterload should be reduced if required by vasodilator administration (e.g., nitroglycerin or nitroprusside). Nitroprusside is generally considered the drug of choice because of its short half-life and its potent arterial and lesser venous dilator effect. Heart rate must be optimally adapted by atrial pacing, sequential atrioventricular pacing, or ventricular pacing if the patient is in atrial fibrillation. If all these simple measures are not sufficient to restore cardiac performance, a catecholamine infusion must be started, although the disadvantages are recognized, particularly in the presence of a hypertrophic myocardium.

When all of these measures fail, the use of devices to support the circulation is indicated. All devices have advantages and risks. They generally are used as a last resort when the patient would not survive with standard approaches. The first device generally considered, if non contraindicated, is the intra-aortic balloon pump.[24] Contraindications include aortic insufficiency, severe aortic arteriosclerosis, and severe cardiac arrhythmias. Important complications do not exceed 3%.[24] Others devices must be considered if the intra-aortic balloon pump fails, including ventricular assist devices[25-27] and extracorporeal membrane oxygenation.[28] These supports generally require anticoagulation to avoid embolic complications and may induce severe hemorrhagic complications.

MEDIASTINITIS AND STERNAL DEHISCENCE

Wound complications and infections are uncommon in cardiac surgery and generally concern sternal dehiscence and mediastinitis. Deep sternal wound infection occurs in 1% to 4% of patients after cardiac surgery and has an overall mortality around 25%. Risk factors of mediastinitis are imperfect aseptic technique, prolonged operative time, harvesting both internal mammary arteries, undrained retrosternal hematoma, insecure sternal closure, obesity, diabetes mellitus, chronic obstructive pulmonary disease, prolonged mechanical ventilation, long-term corticosteroid treatment, and male gender. Early diagnosis is one of the cornerstones in the management of mediastinitis. Sternal puncture may facilitate the diagnosis of mediastinitis.[29] The gold standard treatment in early diagnosed mediastinitis includes early radical débridement to remove all the infected tissue and closed drainage techniques.[30] Severe mediastinitis necessitates complete sternal resection and associated techniques using omental[31,32] or bilateral pectoralis major flap transposition[33] to achieve chest stabilization and to restore pulmonary function.

PULMONARY DYSFUNCTION AFTER CARDIAC SURGERY

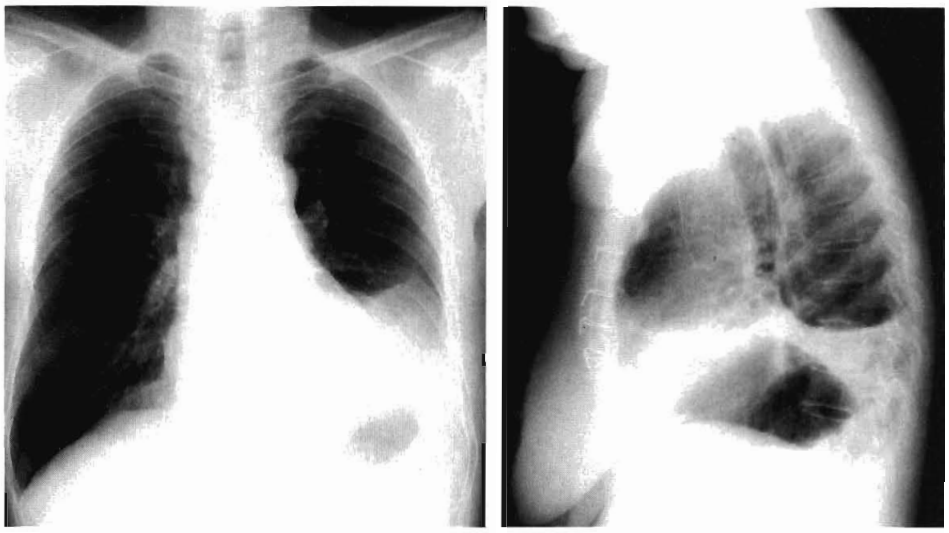
After the heart, the lungs are the organs that commonly have dysfunction after cardiac surgery. Nearly all patients after cardiac surgery with extracorporeal circulation have an increased alveolar-arterial oxygen gradient, resulting from right-to-left shunting in 3% to 15%.[34-36] Reasons for post–cardiac surgery lung dysfunction include the following:

1. During CPB, there is no blood flow in the pulmonary arteries.
2. The lungs are subject to an intense inflammatory reaction after CPB.
3. The alveolar-capillary barrier becomes more permeable after CPB.[37]
4. Atelectasis tends to develop, partially explained by the absence of pulmonary ventilation during CPB. Left lower lobe atelectasis is the most common.
5. Direct trauma to the lung or phrenic nerve paralysis by the surgeon may lead to pulmonary dysfunction.

Risk factors for acute pulmonary dysfunction after cardiac surgery include young age (particularly <2 years old),[38] which is associated with an increased tendency to develop whole-body edema; older age (>60 years old)[39]; pulmonary arterial hypertension; chronic obstructive pulmonary disease[40]; Down's syndrome[41]; amiodarone therapy[42-44]; elevated postoperative left atrial pressure; prolonged mechanical ventilation; and phrenic nerve paralysis.[45] In the presence of risk factors, pulmonary dysfunction may lead to acute respiratory distress syndrome. Mild pulmonary dysfunction generally resolves slowly after the patient is extubated and treated with ambulation and breathing exercises, but residual dysfunction may persist 10 days after operation.[46]

PHRENIC NERVE INJURY AND PARALYSIS

Phrenic nerve paralysis may enhance the tendency toward postoperative pulmonary dysfunction (Fig. 106-1).[47] Consequences of postoperative phrenic nerve palsy range from asymptomatic radiographic abnormality to severe pulmonary dysfunction requiring prolonged mechanical ventilation to other associated morbidities and even mortality.[48]



A B

FIGURE 106–1. A, Posteroanterior chest x-ray of a left phrenic nerve injury after coronary bypass surgery. **B,** Lateral chest x-ray of a left phrenic nerve injury after coronary bypass surgery.

Several conditions in cardiac surgery may injure the phrenic nerve. The most common is a transient paralysis of the left phrenic nerve related to topical cooling application on the heart.[49] In the presence of topical cooling in contact with the pericardium containing the phrenic nerve, particularly on the pleural side of the pericardium, the phrenic nerve may be injured, and transient paralysis may result. The chest radiograph shows that when the patient was extubated, an elevation of the diaphragm related to this paralysis. At 1 week after surgery, radiologic evidence of diaphragm paralysis occurs in 30%[49] to 60%[50] if topical ice slush cooling is used. This paralysis may persist in 75% at 1 month and 30% at 1 year[49] after the procedure.

Transient or definitive phrenic nerve injury may be the result of internal mammary artery pedicle mobilization, ductus arteriosus closure, and aortic coarctation surgery. Reoperations in cardiac surgery enhance the risk of phrenic nerve injury, leading even to double phrenic nerve injury.[51]

NEUROLOGIC COMPLICATIONS

Neurologic complications after cardiac surgery under extracorporeal circulation may be attributed to hypoxia, metabolic abnormalities, emboli, or hemorrhage. Two types of complications, occurring in the same proportions, have been reported: A type 1 complication is major focal deficit, stupor, or coma, and a type 2 complication is intellectual dysfunction. After cardiac surgery with extracorporeal circulation, 6% of patients have been reported to develop an adverse cerebral outcome. Risk factors for developing neurologic impairment are advanced age and history of severe hypertension. Predictive factors for type 1 neurologic complications include severe proximal aortic atherosclerosis, history of prior neurologic disease, use of intra-aortic balloon pump, diabetes, hypertension, unstable angina, and increased age. Predictive factors for type 2 neurologic complications include history of excess alcohol consumption, arrhythmia (including atrial fibrillation), hypertension, prior CABG, peripheral vascular disease, and congestive heart failure.

RENAL DYSFUNCTION

Of patients who undergo cardiac surgery under extracorporeal circulation, 8% develop renal dysfunction in the postoperative period. Serum creatinine levels greater than 2 mg/dL are generally considered as the limit of appearance of renal dysfunction; 20% of these patients require dialysis. The overall mortality in patients who develop postoperative renal dysfunction is 20% and increases to 75% in patients who require dialysis. Predictive factors of renal dysfunction include advanced age, history of congestive heart failure, prior bypass surgery, type 1 diabetes, prior renal disease, and preoperative advanced renal dysfunction. The association between preoperative renal dysfunction and adverse events after cardiac surgery has been reported to be stronger if renal dysfunction is defined using creatinine clearance rather than the plasma creatinine level, particularly in patients with normal plasma creatinine levels.[52]

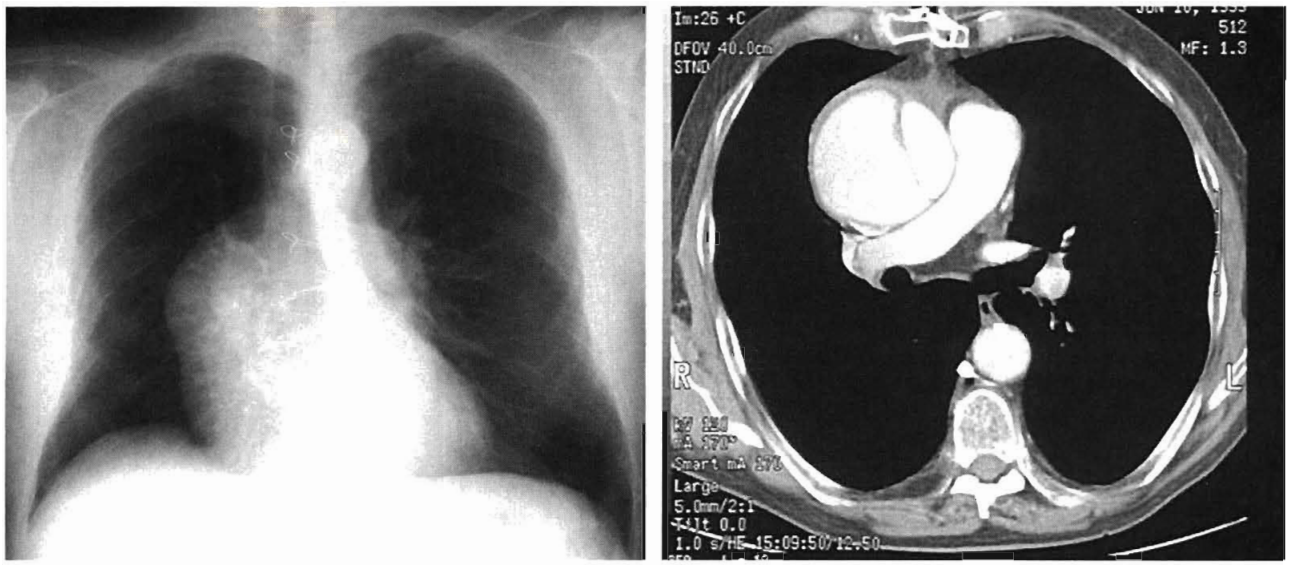
AORTIC DISSECTION AFTER CARDIAC SURGERY

Acute aortic dissection after cardiac surgery is a feared complication in which the blood leaves the normal aortic channel, the true lumen, and dissects the media to produce a false lumen (Fig. 106-2). An intimal tear generally is considered to be at the origin of this phenomenon.

Risk factors for spontaneous aortic dissection are systemic arterial hypertension, cystic medial necrosis of the aorta, Marfan syndrome, bicuspid aortic valve,[53] aortic coarctation (probably because it is associated with systemic arterial hypertension and aortic bicuspid valve), Turner's syndrome,[54] and Noonan's syndrome.[55] Cardiac surgery also may lead to aortic dissection. Aorta cannulation or partial clamping in the presence of excess aortic blood pressure may induce shear stress and subsequent intimal tears.

Diagnosis

Symptoms generally are induced by vessel occlusion. Cardiac ischemia and arrest may occur secondary to coronary arteries shearing off from their aortic origin after aortic dissection.



A B

FIGURE 106–2. A, Chest x-ray of a patient with aortic dissection after aortic valve replacement. **B,** Computed tomography scan of a patient with aortic dissection after aortic valve replacement.

Massive hemorrhage after free rupture of the false lumen into the pericardium, the pleura, or the peritoneum also may occur. Aortic valvular incompetence may appear secondary to aortic valve involvement by the dissection. Oliguria or anuria also may appear. Neurologic complications, including stroke (secondary to aortic arch vessel occlusion) and paraplegia (secondary to intercostal arteries), may be observed. During or immediately after cardiac surgery, signs induced by aortic dissection and surgeon visualization of an important adventitial hematoma are important. The gold standard test to confirm aortic dissection is transesophageal echocardiography,[56] which is easily applicable in the operating room or in the ICU at the patient's bedside. The intimal flap is easily identified in the aortic lumen, and Doppler evaluation may help in identification and localization of the entry point of the dissection. This echocardiography may help to identify aortic valve regurgitation, left ventricular contractility, and eventually pericardial effusion. Computed tomography with contrast injection also has been used for the diagnosis of aortic dissection and evaluation of the extent of the dissection, including involvement of the abdominal aorta. Complications including stroke, renal hypoperfusion, and mesenteric ischemia also may be diagnosed using computed tomography.

Treatment

After diagnosis of an acute postoperative dissection, an aggressive surgical approach is mandatory. Surgery is performed to prevent death from hemorrhage and to reestablish blood flow in nonperfused organs. Limited ascending aortic replacement, associated with intimal tear resection, if any, is the standard procedure for a DeBakey type I and II dissection.[57]

LEFT VENTRICULAR RUPTURE AFTER MITRAL VALVE REPLACEMENT

Left ventricular rupture may occur immediately after discontinuing CPB in mitral valve replacement or within the first few hours in the ICU. Risk factors for this complication are the presence of a small left ventricle, female sex, and advanced age.[58] Excessive papillary muscle traction, decalcification of the mitral annulus, and ventricular mobilization (especially if the apex is tipped up) after valve replacement generally are involved in left ventricular rupture near the posterior atrioventricular groove. The midportion of the posterior wall also may be damaged by a pillar of a stented bioprosthesis. This complication, if it occurs in the ICU, is generally fatal. Some patients may be saved, however, if reoperation can be performed promptly. The patient must be placed rapidly on CPB and internal repair of the ruptured left ventricle done.[59]

ANNOTATED REFERENCES

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With the rapid evolution in diagnostic techniques and interventional cardiologic and surgical procedures, this publication presents significant guidelines in the diagnosis, evaluation, and treatment of coronary cardiac diseases. Written by more than 20 authors under the supervision of the American College of Cardiology and the American Heart Association, these guidelines represent an excellent summary of recent articles published in the English literature.

Funk M, Richards SB, Desjardins J, et al: Incidence, timing, symptoms, and risk factors for atrial fibrillation after cardiac surgery. Am J Crit Care 2003;12:424-433.

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With the rapid evolution in diagnostic techniques and interventional cardiologic and surgical procedures, this publication presents significant

guidelines in the diagnosis, evaluation, and treatment of coronary cardiac diseases. Written by more than 20 authors under the supervision of the American College of Cardiology and the American Heart Association, these guidelines represent an excellent summary of recent articles published in the English literature.

Wang F, Dupuis JY, Nathan H, Williams K: An analysis of the association between preoperative renal dysfunction and outcome in cardiac surgery: Estimated creatinine clearance or plasma creatinine level as measures of renal function. Chest 2003;124:1852-1862.

This was a prospective study comprising 6000 patients. The authors reported that routine preoperative estimation of creatinine clearance may improve the identification of high-risk patients, particularly patients with normal plasma creatinine levels preoperatively.

Chapter 107

PATHOPHYSIOLOGY AND CLASSIFICATION OF SHOCK STATES

Mark E. Astiz

KEY POINTS

1. The development of shock is related to alterations in one or more components of the circulatory system that regulate cardiovascular performance. These are intravascular volume, cardiac function, arteriolar resistance, the capillary circulation, the venules, the venous capacitance circuit, and mainstream patency.
2. Circulatory performance can be assessed from hemodynamic parameters, which include the underlying cardiac rhythm, arterial blood pressure, cardiac filling pressures, cardiac output, and systemic vascular resistance. Although shock is frequently defined by low pressure, the level of arterial pressure is not a reliable indicator of circulatory performance and tissue perfusion.
3. Circulatory shock can be divided into four subsets: hypovolemic, cardiogenic, distributive, and obstructive shock. This classification can be simplified into two broad categories with typical hemodynamic profiles. The first category is hypodynamic shock, which includes the hypovolemic, cardiogenic, and obstructive shock subsets. The second category, hyperdynamic shock, includes distributive shock. The common features of hypodynamic shock are a low cardiac output and vasoconstriction manifested by a high vascular resistance. Hyperdynamic circulatory shock is characterized by a high cardiac output and vasodilation manifested by a low vascular resistance.
4. Critical reductions in tissue perfusion elicit a complex set of reflexes that are directed at maintaining cardiac output and arterial pressure. Progression of the shock state is marked by declines in blood pressure that compromise coronary perfusion, cardiac performance, and microcirculatory integrity.
5. The primary metabolic defect in circulatory shock is impaired oxidative metabolism. This impairment is most commonly caused by decreases in tissue oxygen supply due to either global decreases in blood flow or maldistribution of blood flow. Cellular oxidative metabolism may also be impaired by mechanisms independent of tissue hypoperfusion. Accumulation of tissue carbon dioxide parallels the development of oxygen debt in circulatory shock.
6. Controversy exists over the optimal manner in which to monitor tissue perfusion in patients with circulatory shock. Commonly utilized parameters such as heart rate, arterial pressure, and cardiac output correlate poorly with survival in critically ill patients. These observations have led to the use of indices of tissue oxygen metabolism and carbon dioxide accumulation as markers of tissue perfusion and the adequacy of resuscitative efforts.
7. The primary causes of organ dysfunction in circulatory shock are ischemic injury related to tissue hypoperfusion, mediator-related organ dysfunction, and reperfusion injury. The relative importance of these mechanisms varies with the underlying cause of the shock state and the specific organ being examined.
8. The approach to patients with circulatory shock involves a rapid assessment of the underlying disease process and restoration of cardiopulmonary stability. The patient should be assessed by history and examination for clues as to the etiology of the patient's shock syndrome and for evidence of organ hypoperfusion. Efforts to achieve cardiopulmonary stability should occur simultaneously and should focus on ventilation, fluid infusion, and cardiac function. Definitive therapy depends on the etiology of the shock state.
9. There are several areas of active experimental interest. Therapies that modulate the activity of proinflammatory mediators and cellular apoptosis are being studied. The genetic underpinning of the immune response and its role in circulatory shock is another area of active interest.

PATHOPHYSIOLOGY OF SHOCK

Circulatory shock represents a final common pathway of cardiovascular failure. The mortality rate remains high, particularly for patients in cardiogenic and septic shock, among whom the overall mortality rates are 50% and 40%, respectively.[1,2] From a physiologic perspective, circulatory shock can be defined as a syndrome in which tissue perfusion is reduced such that blood flow is inadequate to meet

cellular metabolic requirements. Clinical manifestations of shock are those of organ hypoperfusion: altered mental status; cool, clammy extremities; decreased blood pressure; decreased pulses; and oliguria.

MECHANISMS UNDERLYING IMPAIRED CARDIOVASCULAR PERFORMANCE

The development of shock is related to alterations in one or more components of the circulatory system that regulate cardiovascular performance. The first component is intravascular volume, which regulates mean circulatory pressures and venous return to the heart. Decreases in intravascular volume resulting from loss of plasma, water, or red blood cells limit venous return to the heart and cardiac output. The heart is the second component. Cardiac output is determined by heart rate, contractility, and loading conditions. Abnormalities in rhythm and heart rate may limit cardiac output. Impaired cardiac contractility decreases effective ventricular ejection and compromises stroke volume. Abnormalities in valvular function may also limit cardiac output. The third component is the resistance circuit and consists of the arteriolar bed, where the major decreases in vascular resistance occur. Arteriolar tone plays an important role in ventricular loading conditions, arterial pressure, and the distribution of systemic blood flow. Excessive decreases in arteriolar tone produce hypotension and limit effective organ perfusion, whereas excessive increases in arteriolar tone impede cardiac ejection by increasing ventricular afterload. Differences in arteriolar tone between organs can result in maldistribution of blood flow and mismatching of blood supply with tissue metabolic demands. The capillaries are the fourth component. They are the site of nutrient exchange and fluid flux between the intravascular and extravascular spaces. Increases in capillary permeability result in tissue edema and loss of intravascular volume. Decreases in capillary cross-sectional area, due to either obstruction or impairment in endothelial cell function, compromise tissue perfusion and nutrient blood flow. The opening of arteriovenous connections, which bypass the capillary network, may play a role in tissue hypoperfusion. The venules are the fifth component. They are the site of lowest shear stress in the circulatory system, and thus the site most prone to occlusion from alterations in cell rheology. Venular resistance contributes 10% to 15% of total vascular resistance. Increases in venular tone increase capillary hydrostatic pressures, thereby promoting the extravascular movement of fluid. The sixth component is the venous capacitance circuit. More than 80% of the total blood volume resides in the large capacitance vessels. Increases in venous tone decrease venous capacitance, redistributing blood volume centrally and thereby increasing venous return to the heart. Decreases in venous tone increase venous capacitance and decrease effective arterial blood volume and venous return. The seventh component is mainstream patency. Obstruction of the systemic or pulmonary circuit impedes ventricular ejection, while venous obstruction limits venous return to the ventricles.

HEMODYNAMIC ASSESSMENT

Circulatory performance can be assessed from hemodynamic parameters. A low heart rate may limit cardiac output, whereas increased heart rates can compromise stroke volumes by limiting ventricular filling times. Bradyarrhythmias indicate structural abnormalities, the effects of drugs, hypoxia, or other metabolic stimuli. Severe bradyarrhythmias can also represent reflex-mediated responses, as occurs in cases of severe hemorrhagic shock, acute inferior wall myocardial infarction, and neurocardiogenic syncope. Tachyarrhythmias may be due to underlying cardiac disease or pharmacologic or environmental stimuli. Alternatively, increases in heart rate may reflect compensatory responses to maintain cardiac output and organ perfusion.

In patients with circulatory shock, blood pressure should be monitored using intravascular measurements. Vasoconstriction due to compensatory mechanisms to maintain arterial pressure or the use of pharmacologic agents limits the accuracy of noninvasive measurements. This is particularly true in hypodynamic forms of circulatory failure.[3]

For most vital organs, autoregulatory and neuronal mechanisms maintain blood flow independent of blood pressure at a mean arterial pressure of 60 mm Hg to 130 mm Hg.[4] At either higher or lower levels of pressure, blood flow becomes linearly dependent on blood pressure. Diseases such as hypertension can shift this relationship and increase the critical level of arterial pressure required for organ perfusion. Similarly, impaired autoregulatory mechanisms present in a variety of pathologic states expand the range of pressure-dependent blood flow.

The level of arterial pressure is not a reliable indicator of circulatory performance and tissue perfusion.[5,6] In states of hypodynamic circulatory shock, hypotension is a late marker of critical hypoperfusion. As cardiac output falls, blood pressure is initially maintained by increases in peripheral vascular resistance largely mediated by the sympathoadrenal system, and it is only after these mechanisms have been exhausted that hypotension develops. In this setting, tissue hypoperfusion may be present despite normal levels of blood pressure as blood flow is redirected toward more vital organs.[7,8] Conversely, hypotension may exist without evidence of organ hypoperfusion. In some vasodilated states, increases in cardiac output maintain vital organ blood flow despite decreased levels of arterial pressure.

Pulmonary artery wedge pressure and central venous pressure are indirect measures of ventricular preload. Filling pressures are determined by ventricular compliance, venous return, and systolic function. There is a poor correlation between filling pressures and blood volume measurements.[9] Factors such as ventricular interactions, positive airway pressure, and intrinsic cardiac disease may decrease ventricular compliance and lead to an overestimation of ventricular preload.[10] Measurements of ventricular volumes using echocardiographic techniques can provide more accurate assessment of ventricular loading conditions.

Cardiac contractility can be assessed by several techniques. End-systolic pressure-volume measurements are independent of loading conditions and are the most reliable measurement of cardiac contractility. Noninvasive methods, including radionuclide studies and echocardiographic measurements, can be used to assess ventricular ejection. The relationship between stroke volume and filling pressures can also be used to determine inotropic competence. In this regard, the response of stroke volume to changes in ventricular loading during fluid infusion is a measure of cardiac contractility. The adequacy of cardiac output in meeting tissue metabolic demands must be assessed independently

TABLE 107-1. CIRCULATORY SHOCK—HEMODYNAMIC PROFILES

	MAP	PAWP	CO	SVR	Svo_2	Lactate
Hypodynamic						
Hypovolemic hemorrhage, dehydration	↓	↓	↓	↑	↓	↑
Cardiogenic myocardial infarction	↓	↑	↓	↑	↓	↑
Obstructive pulmonary embolism, pericardial tamponade, tension pneumothorax	↓	↔↑	↓	↑	↓	↑
Hyperdynamic						
Distributive sepsis, adrenal insufficiency, anaphylaxis	↓	↔↓	↔↑	↓	↔↑	↑

CO, cardiac output; MAP, mean arterial pressure; PAWP, pulmonary arterial wedge pressure; Svo_2, venous oxygen saturation; SVR, systemic vascular resistance.

by monitoring indices of organ perfusion and systemic oxygen metabolism. A low cardiac output may be adequate in settings in which metabolic requirements are decreased, for example deep sedation or hypothermia. In contrast, an increased cardiac output may not be adequate when metabolic requirements are increased or maldistribution of blood flow exists, such as in septic shock.

Systemic vascular resistance is used as an indicator of arterial tone and is calculated from cardiac output and arterial pressure. Increases in systemic vascular resistance are most commonly due to vasoconstriction and represent compensatory mechanisms directed at maintaining blood pressure in the setting of a decreased cardiac output. Excessive increases in vascular resistance increase ventricular afterload and the impedance to ejection. Decreases in vascular resistance are due to vasodilation, decreases in blood viscosity, or the presence of arteriovenous connections. Vasodilation may be pathologic, as occurs in septic shock and liver disease, or it may be adaptive, as occurs in hyperdynamic stress following major surgery and traumatic injury. Venous tone is much harder to assess clinically. In most cases, changes in venous tone will parallel changes in arterial tone. Modest increases in central venous pressures in the setting of large-volume infusion and the absence of intravascular volume loss suggest decreased venous tone.

CLASSIFICATION OF SHOCK

Hinshaw and Cox proposed a classification of circulatory shock that was divided into four subsets: hypovolemic, cardiogenic, distributive, and obstructive shock.[11] This classification can be simplified into two broad categories with typical hemodynamic profiles (Table 107-1). The first category is hypodynamic shock, which includes the hypovolemic, cardiogenic, and obstructive shock subsets. The second category, hyperdynamic shock, includes distributive shock.

The common features of hypodynamic shock are a low cardiac index and a high-resistance vasoconstricted state. Increased oxygen extraction and lactic acidosis usually parallel the decrease in cardiac output. In cases of hypodynamic shock, the development of organ dysfunction is directly related to inadequate global blood flow. Common causes of hypovolemic shock are hemorrhage, dehydration due to gastrointestinal losses, and third spacing due to burns. Acute decreases in blood volume of 25% result in tachycardia and orthostasis, whereas decreases of 40% are associated with hypotension. Decreased filling pressures are the hallmark of hypovolemic shock, in contrast to cardiogenic shock, in which situation they are elevated. Acute myocardial infarction involving 40% or more of the ventricular mass is the most common cause of cardiogenic shock.[12] Cardiomyopathies and severe valvular lesions are other important causes of cardiogenic shock. Finally, obstructive shock is related to a variety of causes, most commonly pericardial tamponade, acute pulmonary embolism, and tension pneumothorax. Since filling pressures are usually increased in these settings (due to outflow obstruction, impaired ventricular filling, and decreased ventricular compliance), distinguishing between obstructive shock and cardiogenic shock can be difficult.

Hyperdynamic circulatory shock is characterized by a high cardiac index and a low-resistance vasodilated state. Filling pressures can be increased or normal depending on the degree of volume repletion and the presence of myocardial incompetence. Common causes of hyperdynamic shock include sepsis, anaphylaxis, drug intoxications, spinal shock, and adrenal insufficiency. The underlying hemodynamic defect in each of these syndromes is maldistribution of blood flow and/or blood volume such that effective nutrient blood flow is compromised. In contrast to hypodynamic shock, oxygen extraction is normal or decreased despite evidence of hypoperfusion.[13] Direct mediator-related effects couple with tissue hypoperfusion to produce cellular injury and organ dysfunction in patients with septic shock.

Considerable overlap may exist between these different syndromes. Early in septic and anaphylactic shock, prior to fluid infusion, a significant hypovolemic component usually exists.[14] Hypovolemia may be present in a small group of patients presenting with shock due to acute myocardial infarction.[15] In the presence of severe sepsis-related myocardial depression, patients with septic shock can develop a hypodynamic profile. Similarly, patients in cardiogenic shock after cardiac surgery may demonstrate significant vasodilation due to the activation of mediator cascades while on cardiopulmonary bypass.[16]

PROGRESSION OF SHOCK

Critical reductions in tissue perfusion elicit a complex set of reflexes that are directed at maintaining cardiac output and

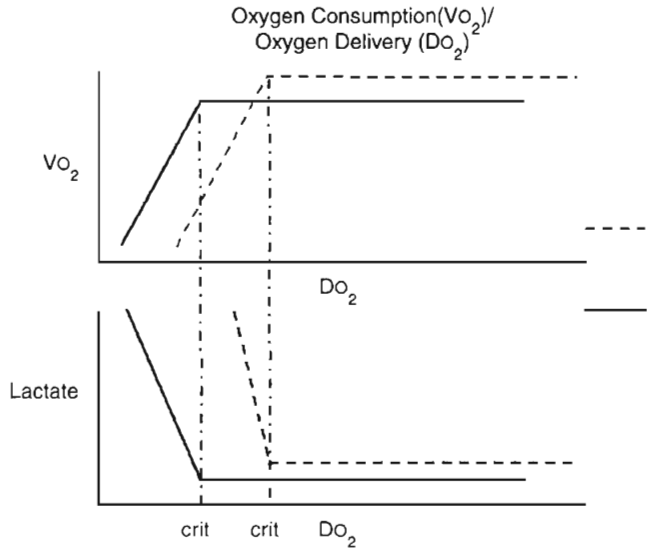

FIGURE 107–1. Oxygen consumption/oxygen delivery relationships. Oxygen consumption (Vo_2) is independent of oxygen delivery (Do_2) until a critical level of Do_2 is reached at which oxygen extraction has been maximized. At that level of oxygen delivery (Do_2crit), Vo_2 becomes linearly dependant on Do_2, and anaerobic metabolism manifested by lactic acidosis ensues. This relationship shifts upward and to the right when the ability of the tissues to extract oxygen is impaired due to alterations in the distribution of blood flow.

arterial pressure.[4] Activation of the sympathetic system increases heart rate and contractility. The release of catecholamines, angiotensin, vasopressin, and endothelins increases arteriolar and venous tone, thereby increasing arterial blood pressure and shifting blood volume from the capacitance vessels to the central circulation. In addition, blood flow is redirected from skeletal muscle, subcutaneous tissue, and the splanchnic circulation to the heart and brain. Vasopressin and activation of the renin-angiotensin system serve to enhance water and sodium retention, thereby protecting intravascular blood volume.

Progression of the shock state is marked by further declines in blood pressure that compromise coronary perfusion and cardiac performance. Increases in peripheral vascular resistance impede left ventricular ejection by increasing left ventricular afterload. Terminal phases of shock are marked by vasomotor dysfunction characterized by loss of arteriolar tone with paradoxical increased venular resistance. The resulting increase in capillary hydrostatic pressure leads to a loss of intravascular volume and worsening of the shock state. In animal models of hemorrhagic shock, a state of irreversible shock evolves from which the animals cannot be successfully resuscitated.[17]

This pathophysiology is altered in patients with hyperdynamic forms of circulatory failure such as septic shock. These patients are characterized by arterial and venous dilation, increased cardiac output, and misdistribution of blood flow. The influence of vasodilatory substances such as nitric oxide predominates over the effects of endogenous and exogenous vasopressor substances. In some forms of vasodilatory shock, inappropriately low levels of vasopressin and cortisol may contribute to vasodilation and refractoriness to catecholamines.[18,19] Progressive hypotension, which is refractory to fluid infusion and vasopressors, results in tissue hypoperfusion, acidosis, and organ failure. A hypodynamic circulation develops as a terminal event.

OXIDATIVE METABOLISM IN SHOCK

The primary metabolic defect in circulatory shock is impaired oxidative metabolism. This impairment is most commonly due to decreases in tissue oxygen supply caused by either global decreases in blood flow or maldistribution of blood flow. Systemic oxygen consumption may initially be increased yet inadequate to meet tissue metabolic requirements; however, the terminal phases of all forms of shock are characterized by decreases in oxygen consumption. In experimental studies, the risk of mortality is directly related to the total amount of accumulated oxygen debt.[20]

Oxygen delivery is determined by cardiac output, hemoglobin concentration, and the arterial oxygen saturation. Under normal circumstances, oxygen consumption is independent of oxygen delivery and cardiac output (Fig. 107-1). Increases in cellular oxygen extraction, from a normal level of 25% to a maximum of level of 80%, maintain oxygen consumption as blood flow is reduced. When oxygen extraction is maximized, a critical level of oxygen delivery (Do_2crit) is reached, oxygen consumption falls, and anaerobic metabolism ensues. Alterations in vasomotor reflexes due to sepsis or drugs limit maximal oxygen extraction, resulting in critical tissue hypoxia and anaerobic metabolism at higher levels of oxygen delivery.[21,22]

Aerobic adenosine triphosphate (ATP) generation is dependent on glycolysis occurring in the cytoplasm and oxidative phosphorylation occurring in the mitochondria (Fig. 107-2). Under anaerobic conditions, ATP generation is limited to the two ATP generated in the cytoplasm, as compared to the 38 ATP generated aerobically. The decreased entry of pyruvate into the citric acid cycle results in the accumulation of lactic acid and the generation of additional hydrogen ions from the hydrolysis of ATP. Accordingly, the presence of lactic acidosis serves as an indicator of critical deficits in high-energy phosphate metabolism. The normal level of lactate is 0.4 mEq/L to 1.2 mEq/L levels greater than 2 mEq/L are associated with an increased rate of mortality.[23]

Oxidative metabolism may also be impaired by mechanisms independent of tissue hypoperfusion. A number of inflammatory mediators, including nitric oxide, endotoxin, oxygen radicals, calcium, and tumor necrosis factor impair mitochondrial function. Mitochondrial abnormalities have been observed in animal models of septic shock and in cases of reperfusion injury. Decreased mitochondrial activity has been reported in tissue taken from patients with septic shock.[24] Serum from patients with septic shock inhibits mitochondrial respiration and decreases cellular ATP concentration in vitro.[25] A potential pathway of direct mitochondrial impairment involves nitric oxide and its metabolite peroxynitrite.[25,26] Both of these substances can directly impair mitochondrial electron

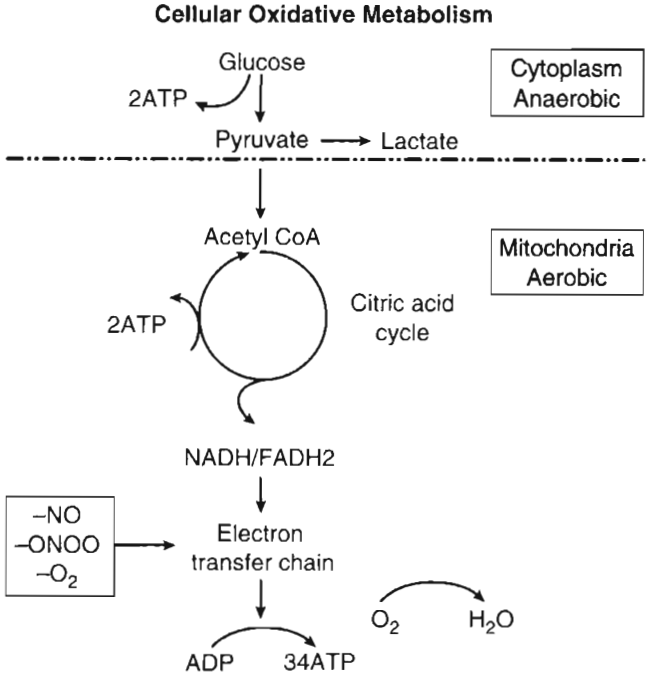

FIGURE 107–2. Cellular oxidative metabolism. Glucose is metabolized anaerobically in the cytoplasm and aerobically in the mitochondria under conditions of normal tissue perfusion. In conditions of shock, high-energy phosphate generation (ATP) is limited to anaerobic pathways. Nitric oxide (NO), peroxynitrite ($ONOO^-$), and superoxide (O_2^-) are potential inhibitors of the electron transfer chain.

chain complexes. In addition, peroxynitrite activates the mitochondrial enzyme polyadenosine-ribose-synthetase, leading to depletion of nicotine adenine dinucleotide and ATP.

Accumulation of tissue carbon dioxide parallels the development of oxygen debt in circulatory shock.[27] Clinically, increases in tissue carbon dioxide levels are manifested by venous hypercapnia and decreases in venous pH. The result is a widening of the arterial-venous carbon dioxide gradient proportional to the degree of circulatory failure. The normal gradient is less than 5 mm Hg, and it can increase to 40 mm Hg during cardiac arrest.[27] Decreased clearance of carbon dioxide generated by oxidative processes is responsible for the initial increase in tissue carbon dioxide levels. With the onset of anaerobic metabolism, tissue carbon dioxide excess is largely generated from titration of anaerobically derived acids by bicarbonate. The increase in tissue carbon dioxide levels may have physiologic significance and has been associated with impaired myocardial performance in vitro.[28]

MONITORING PERFUSION FAILURE

Controversy exists over the optimal manner in which to monitor tissue perfusion in patients with circulatory shock. Commonly utilized parameters, such as heart rate, arterial pressure, and cardiac output, correlate poorly with survival in critically ill patients.[5,6] This is particularly true in patients with septic shock and traumatic injury, in whom underlying deficits in tissue perfusion may exist despite initial resuscitative efforts.[5,29] These observations have led to the use of indices of tissue oxygen metabolism as markers of tissue perfusion and the adequacy of resuscitative efforts.

Mixed venous oxygen saturation (Svo_2), measured on blood taken from the pulmonary artery, is used as an index of tissue oxygenation. Venous blood is in equilibrium with the tissue and mixed venous blood, representing a weighted mean of all the venous effluents, and reflects overall tissue oxygenation. Mixed venous desaturation indicates the need for increased extraction to maintain oxygen consumption and the presence of tissue hypoxia. In cardiogenic shock, Svo_2 tracks cardiac function and systemic perfusion.[30] However, the same is not true in situations of septic shock and in other circumstances when the relationship between venous blood and tissue oxygenation is altered by maldistribution of blood flow.[13] In these circumstances, the ability of the tissues to extract oxygen is limited by decreases in effective nutrient flow such that Svo_2 may be increased or normal despite the presence of tissue hypoxia and anaerobic metabolism. Accordingly, although mixed venous desaturation is indicative of tissue hypoxia, normal levels do not preclude tissue hypoperfusion. Central venous oxygen saturation, measured on samples taken from the superior vena cava, may serve as an alternative measure of tissue perfusion.[31,32]

Arterial lactate concentration is a useful marker for the presence of anaerobic metabolism and therefore tissue energy deficits.[6,23] Although the initial level of arterial lactate has prognostic significance, the inability to clear lactate over time is more discriminating.[33,34] In patients with septic shock, factors other than hypoperfusion may contribute to lactate accumulation. These factors include increased hepatic flux of alanine from skeletal muscle, decreased pyruvate dehydrogenase activity, decreased hepatic clearance of lactate, and dysfunctional mitochondrial respiration. Despite these concerns, increases in lactate concentration are associated with decreases in the intracellular redox potential in patients with septic shock, suggesting that it is a useful marker of cellular energy metabolism in this setting.[35]

Oxygen consumption and oxygen delivery are global markers of systemic oxygen metabolism. Oxygen consumption, a measure of overall metabolic requirements, is calculated from cardiac index, hemoglobin, and arterial and venous oxygen saturation. It can also be measured directly from expired gases. Oxygen delivery is calculated from cardiac output, hemoglobin, and arterial saturation and is a measure of the total amount of oxygen being delivered to the tissues. Increased values of oxygen consumption and oxygen delivery have been observed in survivors and nonsurvivors, but considerable overlap exists between the two groups. Efforts to direct therapy at levels of these parameters associated with survival—"optimal goals"—have produced mixed results.[36,37] This, in part, reflects the varying metabolic requirements of individual patients.

The decrease in carbon dioxide (CO_2) clearance in circulatory shock is the basis for end-tidal carbon dioxide measurement and gastric tonometry. End-tidal CO_2 measurements are useful in monitoring perfusion during cardiopulmonary resuscitation.[38] Cardiac arrest results in marked decreases in pulmonary blood flow and accompanying decreases in carbon dioxide excretion. Consequently, end-tidal CO_2 values move toward zero during arrest and increase with successful resuscitation.

Gastric tonometry allows assessment of gastric mucosal perfusion. Because splanchnic blood flow is decreased early in patients in shock as blood flow is redirected to more vital organs, this measurement serves as an early marker of systemic hypoperfusion. Gastric tonometry measures intraluminal gastric carbon dioxide levels, which reflect mucosal carbon dioxide levels. In initial reports, intramucosal pH was calculated using arterial bicarbonate concentration.[39]

This calculation has been replaced with determination of the arterial-intramucosal P_{CO_2} gap. Widening of this gap or a decrease in the intramucosal pH is associated with an increased chance of mortality. Prospective randomized trials have not demonstrated that titration of therapy to tonometric values improves survival.[40] More recently, a technique for measuring sublingual CO_2 levels has been developed. Increases in sublingual P_{CO_2} and widening of the sublingual-arterial P_{CO_2} gradient are observed in nonsurvivors as compared with survivors.[41]

ORGAN FAILURE

The primary causes of organ dysfunction in circulatory shock are ischemic injury related to tissue hypoperfusion, mediator-related organ dysfunction, and reperfusion injury. Ischemic injury occurs when anaerobic metabolism ensues and high-energy phosphate production falls below the level required for cellular function and membrane integrity. It is the major factor contributing to organ failure in patients with cardiogenic and hypovolemic shock. The direct effect of inflammatory mediators, coupled with an ischemic injury, plays a major role in organ dysfunction in septic shock. Tumor necrosis factor, nitric oxide, and superoxide radicals are examples of mediators directly affecting cellular and organ function. Reperfusion injury occurs upon restoration of tissue perfusion following an absence of blood flow (Fig. 107-3). Activated neutrophils and oxygen radicals play important roles in this process.[42] Reperfusion injury may be important in hemorrhagic and traumatic shock; its role in cardiogenic shock and septic shock is less clear.

Cardiac dysfunction is frequently observed in patients in shock. In cases of acute myocardial infarction shock, cardiac dysfunction is related to ischemia and myocardial necrosis. Reperfusion injury may also play a role in patients who are acutely revascularized. Myocardial depressant substances cause myocardial depression in patients in septic shock and may also play a role in cases of hemorrhagic shock.[43] Down-regulation of beta-receptor density and affinity contribute to myocardial failure in sepsis and other syndromes.[44] Increases in pulmonary vascular resistance are the cause of acute right ventricular failure in patients with pulmonary embolism and may also be important in the situation of septic shock, particularly when it is complicated by the acute respiratory distress syndrome.

Minute ventilation and respiratory rate increase in patients with shock. Overt respiratory failure may result from pulmonary edema or acute lung injury and leads to additional increases in the work of breathing. Decreased respiratory muscle perfusion, coupled with hypoxia, contributes to respiratory muscle failure.[45] In patients with septic shock, inflammatory mediators may also directly impair respiratory muscle activity.

Renal dysfunction in shock is related to hypoperfusion. Initially, as cardiac output decreases, glomerular filtration is maintained by increases in efferent arteriolar tone. Release of atrial natriuretic peptide due to increased atrial pressures may help protect renal blood flow in patients with cardiogenic shock. However, as shock progresses, the increases in afferent arteriolar tone result in renal ischemia and acute tubular necrosis.[46] In septic shock, alterations in intrarenal blood flow may also impair effective glomerular filtration.

A characteristic pattern that involves centrilobar necrosis and marked transaminase elevation is observed in patients with ischemic hepatic injury associated with hypodynamic circulatory states.[47] Activation of Kupffer cells and the release of inflammatory mediators exacerbate ischemic injury in patients in septic shock and traumatic shock. In septic shock, canalicular cell function is impaired, resulting in intrahepatic cholestasis. Hepatic metabolic failure and impaired amino acid clearance are also a feature of septic shock.

Splanchnic mucosal blood flow is compromised early in shock. Intestinal injury may result from hypoperfusion or the release of oxygen radicals and activation of neutrophils during reperfusion.[48] Loss of the intestinal barrier can lead to translocation of bacteria and toxins, which in turn contributes to organ failure. Splanchnic hypoperfusion related either to shock or to the use of vasopressors also contributes to the development of stress ulceration, acalculous cholecystitis, intestinal necrosis, and pancreatitis. Pancreatic hypoperfusion may also predispose to the release of myocardial depressant factors.

Thrombocytopenia is observed in a majority of patients with septic shock. The coagulation cascade is activated in septic and traumatic shock by the cytokines, tissue factors, and bacterial toxins. Disseminated intravascular coagulation is marked by impaired fibrinolysis and increased consumption of clotting factors. Clinical manifestations are bleeding and vascular thrombosis. Large-volume asanguineous fluid resuscitation can also produce marked hemodilution of clotting factors and platelets.

Microvascular blood flow is impaired in all forms of circulatory failure.[49,50] Rheologic abnormalities of neutrophils and erythrocytes impede microvascular blood flow. Increased expression of the neutrophil integrins, platelet P-selectin, and the endothelial cell adhesion molecules result in cellular aggregation and microvascular obstruction.

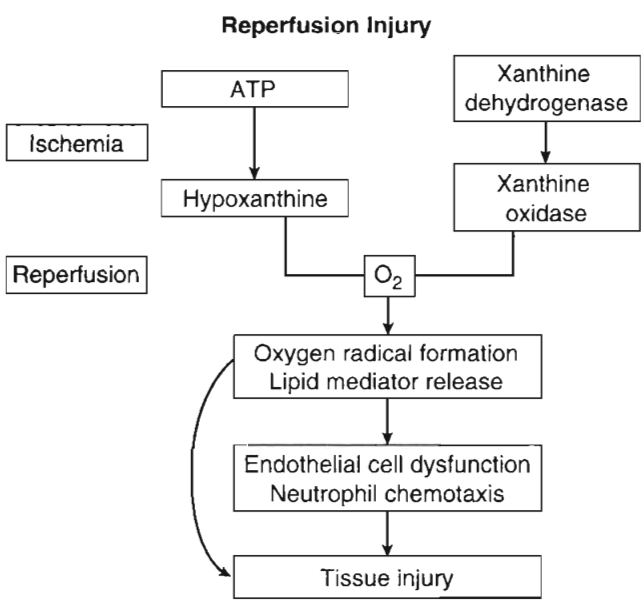

FIGURE 107–3. Reperfusion injury. Under ischemic conditions, ATP is metabolized to hypoxanthine and xanthine dehydrogenase is converted to xanthine oxidase. During reperfusion, superoxide is produced from hypoxanthine and oxygen by xanthine oxidase. Superoxide and it metabolites produce cellular injury and membrane disruption, resulting in the release of prostanoids and leukotrienes. The lipid mediators and oxygen radicals act as chemoattractants for neutrophils, which injure tissues through the release of elastases, proteases, and additional oxygen radicals.

Platelet-fibrin interactions mediated through platelet expression of glycoprotein IIB/IIIA accentuate this process.[51] Decreased endothelial cell nitric oxide synthetase activity impairs normal vasodilatory reflexes and decreases the microvascular response to hypoxia. Increased microvascular permeability and tissue edema may also impede the diffusion of oxygen from the capillaries into the cells.

Disorientation and delirium are common in patients in shock. Hypotension, metabolic abnormalities, and hypoxia all contribute to neurologic dysfunction. Alterations in cerebral vascular reactivity and direct toxic effects of inflammatory mediators may also play a role in cerebral injury.[52] Severe hypotension, mean arterial pressure well below 60 mm Hg, can result in ischemic injury of the arterial border zones in the cortex and spinal cord.

The development of shock is associated with down-regulation of immunologic function. Immunosuppressive substances, including interleukin-10, prostaglandin E_2, and adenosine, are released that decrease humoral immunity, monocyte, and neutrophil activity. An immunologic profile of decreased monocyte HLA-DR expression and impaired monocyte responsiveness to inflammatory stimuli has been associated with an increased risk of secondary infection and mortality.[53,54]

CLINICAL ASPECTS OF SHOCK

INITIAL APPROACH TO CIRCULATORY SHOCK

The approach to patients with circulatory shock involves a rapid assessment of the underlying disease process and restoration of cardiopulmonary stability. The patient should be assessed by history and physical examination for clues as to the cause of the patient's shock syndrome and for evidence of end-organ hypoperfusion. A complete blood cell count, coagulation studies, and blood gases and electrolytes measurement should be performed for all patients. Arterial lactate measurement is helpful to confirm the severity of the perfusion failure. An electrocardiogram and chest radiograph should also be obtained. The need for additional studies such as cultures, cardiac enzymes, and other tests depends on the suspected cause of the shock state. Efforts to achieve cardiopulmonary stability should occur simultaneously. The VIP approach can be used to prioritize these efforts by focusing on *v*entilation, *i*nfusion, and *p*ump activity.[55] The importance of early and vigorous resuscitation has recently been documented in patients in septic shock.[31]

Oxygenation and adequate ventilation must be ensured. High-flow oxygen systems can be employed initially; however, evidence of respiratory muscle fatigue, refractory hypoxia, or severe acidosis should prompt intubation and the initiation of mechanical ventilation. Reduction in the work of breathing may reduce physiologic stress and allow for redistribution of blood flow away from the respiratory muscles to other hypoperfused areas of the body.

Critical hypovolemia is present in the majority of patients presenting with circulatory shock in the medical-surgical setting and a significant portion of patients presenting with shock and acute myocardial infarction. Fluids should be infused in boluses and titrated to specific endpoints of heart rate, blood pressure, urine output, and clearance of arterial lactate. Attention should be given to the hemoglobin level, which will decrease with significant asanguineous fluid resuscitation. Although many patients tolerate a hemoglobin level of 7 g/dL to 9 g/dL, increased levels may be required in patients with cardiac dysfunction. Placement of a pulmonary artery catheter should be considered in patients not responding to initial efforts and those with underlying cardiac or renal disease.

Disturbances of cardiac rhythm should be addressed rapidly. Bradycardia associated with hypotension may require a pacemaker or pharmacological therapy to increase the heart rate. Tachyarrhythmias that are not compensatory may require cardioversion. In the appropriate clinical setting, consideration should always be given to possible cardiac tamponade and tension pneumothorax, since these are potentially rapidly reversible causes of shock.

Continued evidence of hypoperfusion despite initial resuscitation efforts requires the initiation of vasoactive drugs. The choice of agents should be predicated on the goal of therapy. Persistent hypotension requires the use of a pressor agent such as norepinephrine to restore blood pressure to a mean arterial pressure of 65 to 70 mm Hg, which is associated with adequate organ perfusion. When hypotension is accompanied by impaired cardiac performance, an inotropic agent should be added.

The treatment of lactic acidosis with alkali solutions remains controversial. Sodium bicarbonate solutions increase serum osmolality and potentially worsen intracellular acidosis as bicarbonate is titrated to CO_2 and water. Prospective randomized trials have not demonstrated any benefit in either oxygen metabolism or circulatory function after alkali infusion for severe lactic acidosis.[56]

Definitive therapy depends on the cause of the shock state and may require additional diagnostic and therapeutic interventions. These efforts should be pursued in a timely manner. Endoscopic or surgical interventions may be required for patients in hemorrhagic and traumatic shock. Circulatory assist devices coupled with prompt efforts at revascularization enhance outcome in patients with cardiogenic shock.[1] Antibiotics and drainage procedures are required for septic shock. Activated protein C may also benefit patients with septic shock.[57] Acute pulmonary embolism and shock can be treated with thrombolysis, catheter embolectomy, or, in more extreme circumstances, surgical embolectomy.

NEWER THERAPIES

Newer fluids such as diaspirin-linked hemoglobin and ethyl pyruvate are being studied that, in addition to their volume-expanding capacity, may have anti-inflammatory activity.[58] Therapies that modulate the activity of proinflammatory mediators such as nitric oxide and polyadenosine-ribose synthase are being tested in situations of septic and hemorrhagic shock. Interventions that scavenge oxygen radicals, limit their production, and affect neutrophil activation are being studied to attenuate reperfusion injury in patients with hemorrhagic, septic, and cardiogenic shock. The role of apoptosis in the development of immune dysfunction and organ failure is being examined, with possible interventions directed at altering this process. Interferon-gamma and other agents that enhance immune function and reduce the incidence of secondary infections in patients surviving their initial shock episode are also being tested. Finally, the genetic underpinning of the immune response and its role in circulatory shock is another area of active interest.[59] This is particularly true in situations of septic shock in which tumor

necrosis factor and interleukin-1 polymorphism have been associated with increased mortality. Progress in this important area will ultimately allow for the development of more focused interventions that have the greatest likelihood of benefiting individual patients.

ANNOTATED REFERENCES

Brealey D, Brand M, Hargreaves I, et al: Association between mitochondrial dysfunction and severity and outcome in septic shock. Lancet 2002; 360:219-223.

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The subsets of shock described in this text form the basis for all subsequent classifications of shock.

Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-1377.

This study involves septic hypotensive patients. The study illustrates the importance of an integrated approach to resuscitating patients with shock, which includes hemodynamic and perfusion-related endpoints.

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This is a classic study defining the importance of monitoring lactate in assessing perfusion failure in critically ill patients. A relationship between increased lactate levels and mortality was demonstrated. No added discrimination was observed when lactate levels were compared to lactate-pyruvate ratios.

Weil MH, Rackow EC, Trevino R, et al: Differences in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. N Engl J Med 1986;315:153-156.

This study was one of the first to reexamine the significance of carbon dioxide accumulation in patients with circulatory failure. Marked increases in mixed venous PCO_2 in patients during cardiac arrest were reported.

Chapter 108

RESUSCITATION FROM CIRCULATORY SHOCK

Benoît Vallet • Eric Wiel • Gilles Lebuffe

KEY POINTS

1. Shock often, but not only, results from circulatory failure and decreased oxygen delivery (Do_2).
2. Shock occurs when a critical cellular partial pressure of oxygen (Po_2) is reached, a state at which inadequate tissue Po_2 produces cell dysoxia (cell oxygen consumption and ATP production are Po_2 limited) and injury.
3. Initial resuscitation from circulatory shock consists of (1) addressing the global adequacy of tissue oxygenation; (2) assessing the global flow; (3) diagnosing the shock type; and (4) deciding the best probabilistic treatment.
4. Treatment aims at (1) reducing preload dependency; (2) restoring cardiac contractility; (3) improving perfusion pressure; (4) reaching oxygen supply–to–oxygen needs independency; and (5) eliminating disease sources (e.g., anaphylaxis, infection, myocardial ischemia).

Circulatory failure results in a decrease in oxygen delivery (Do_2) associated with a decrease in cellular partial pressure of oxygen (Po_2). When a critical Po_2 value is reached, oxidative phosphorylation is limited and leads to a shift from aerobic to anaerobic metabolism. The result is a rise in cellular and blood lactate concentrations, associated with a decrease in adenosine triphosphate (ATP) synthesis. Adenosine diphosphate (ADP) and hydrogen ions accumulate and together with the raised serum lactate level lead to metabolic lactic acidosis. This state is called *dysoxia* and can be accepted as a definition for "shock," a state in which inadequate tissue oxygenation produces cellular injury. Shock often, but not only, results from circulatory failure and decreased Do_2.

Resuscitation from "circulatory shock" requires an emergency and global approach that is based on limited clinical features for establishing diagnosis and probabilistic therapy. The efficacy of this initial therapeutic strategy then becomes part of the diagnostic approach: if the chosen therapy is successful, it confirms the diagnosis retrospectively. This initial diagnostic approach is essentially based on physician knowledge of global hemodynamics and oxygen-derived parameters. It can be helped by rapidly available oxygen-derived biologic markers.

UNDERSTANDING THE UNDERLYING PATHOPHYSIOLOGY OF GLOBAL FLOW AND OXYGEN DELIVERY

ADDRESSING THE GLOBAL ADEQUACY OF TISSUE OXYGENATION

Adequacy of tissue oxygenation is defined as an adapted oxygen supply (or Do_2) to oxygen demand.[1] Oxygen demand varies according to tissue type and according to time. Although oxygen demand cannot be measured or calculated, oxygen uptake or consumption ($\dot{V}o_2$) and Do_2 both can be quantified; they are linked by a simple relationship:

$$\dot{V}o_2 = Do_2 \times ERo_2$$

where ERo_2 represents oxygen extraction ratio (ERo_2 in %; Vo_2 and Do_2 in mL O_2/kg/min). Do_2 represents the total flow of oxygen in the arterial blood and is given as the product of cardiac output ($\dot{Q}$) by arterial oxygen content (Cao_2): $Do_2 = \dot{Q} \times Cao_2$, with Cao_2 being the product of hemoglobin (Hb, g/100 mL) by arterial oxygen saturation (Sao_2, %) and Hb O_2 capacity (1.39 mL O_2/g Hb): $Cao_2 = Hb \times Sao_2 \times 1.39$.

Under physiologic control, oxygen demand equals $\dot{V}o_2$ (≈2.4 mL O_2/kg/min for a 12 mL O_2/kg/min Do_2, which corresponds to a 20% ERo_2). The rate of oxygen delivered by blood is physiologically larger than the rate of $\dot{V}o_2$: Do_2 is adapted to oxygen demand. When oxygen demand increases (e.g., during exercise), Do_2 has to adapt and increase.

During circulatory shock and/or severe hypoxemia, as Do_2 declines secondary to a decrease in $\dot{Q}$ and/or a decrease in Cao_2, $\dot{V}o_2$ can be maintained by a compensatory increase in ERo_2, Vo_2 and Do_2 remaining therefore independent. But as Do_2 falls further, a critical point (Do_2crit) is reached; ERo_2 can no longer compensate for this fall in Do_2 and, at this critical level, $\dot{V}o_2$ becomes Do_2-dependent (Fig. 108-1). At this Do_2crit (4 mL/kg/min), for a $\dot{V}o_2$ of about 2.4 mL/kg/min, ERo_2 reaches its critical point (ERo_2crit) of 60%. When $\dot{V}o_2$ is higher, Do_2crit is higher as well. Increase in oxygen extraction occurs via two fundamental adaptive mechanisms[2]: (1) redistribution of blood flow among organs via an increase in sympathetic adrenergic tone and central vascular contraction (this is responsible for a decreased perfusion in organs with low ERo_2, such as the skin and splanchnic area, and a maintained perfusion in organs with high ERo_2, such as heart and brain); and (2) capillary recruitment within organs responsible for peripheral vasodilation (opposite to central vasoconstriction).

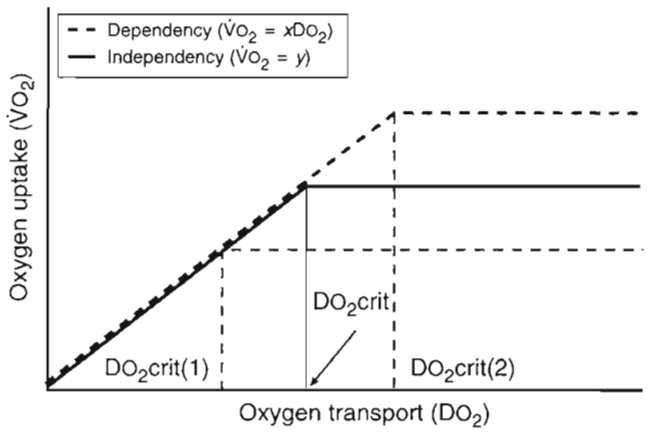

FIGURE 108–1. O_2 uptake ($\dot{V}o_2$)-to-O_2 supply (Do_2) relationship. When $\dot{V}o_2$ is supply independent ("independency") following the relation $\dot{V}o_2 = y$, whole body O_2 needs are met. When $\dot{V}o_2$ becomes Do_2 dependent ("dependency") according to the relation $\dot{V}o_2 = x\,Tao_2$, $\dot{V}o_2$ starts to be linearly dependent on Do_2 at the critical Do_2 value (Do_2crit), which corresponds to dysoxia (insufficient ATP synthesis as related to needs) and shock state. Do_2crit is influenced by global organism O_2 needs: when $\dot{V}o_2$ is decreased (e.g., by rest, sedation, hypothermia), the Do_2crit is decreased as well [lower dotted line; Do_2crit(1)]; conversely, increased $\dot{V}o_2$ (e.g., by increased muscle activity, awakening, hyperthermia, sepsis) is associated with increased Do_2crit [upper dotted line; Do_2crit(2)].

USING MIXED VENOUS OXYGEN SATURATION AS A WAY TO ASSESS ADEQUACY OF GLOBAL TISSUE OXYGENATION

In the clinical setting, mixed venous oxygen saturation (Svo_2) can be used for assessing whole body $\dot{V}o_2$-to-Do_2 relationships. Indeed, according to the Fick equation, tissue $\dot{V}o_2$ is proportional to cardiac output: $\dot{V}o_2$ = cardiac output × ($Cao_2 - Cvo_2$), where Cvo_2 is mixed venous blood oxygen content. To some extent, $\dot{V}o_2$ is approximately equal to cardiac output × ($Sao_2 - Svo_2$) × Hb × 1.39, and Svo_2 is approximately equal to $Sao_2 - \dot{V}o_2/(\dot{Q} \times Hb \times 1.39)$.

Four situations can be responsible for a decrease in Svo_2: hypoxemia (decrease in Sao_2), an increase in $\dot{V}o_2$, a fall in cardiac output, and a decrease in Hb. At Do_2crit, Svo_2 is about 40% (Svo_2crit) with an ERo_2 of 60% and a Sao_2 of 100%. This Svo_2crit has been identified in humans.[3] It is important to emphasize that for the same decrease in Cao_2 (induced by a decrease of Hb or Sao_2), the decrease in Svo_2 will be more pronounced if cardiac output cannot adapt. Hence, Svo_2 represents adequacy of global flow to Cao_2 decrease. A 40% Svo_2 can be taken as an imbalance between arterial blood oxygen supply and tissue oxygen demand with evident risk of dysoxia. In the clinical setting, a decrease of Svo_2 of 5% from its normal value (77% to 65%) is representative of a significant fall in Do_2 and/or an increase in oxygen demand (Fig. 108-2). If initial probabilistic treatment (fluid resuscitation and/or low-dose inotropes and/or red blood cell transfusion) does not allow Svo_2 to be restored to a minimal 65%, Hb, Sao_2, and cardiac output should then be individually measured to introduce the appropriate treatment.

ASSESSING GLOBAL FLOW

Global flow is dependent on preload, myocardial contractility, afterload, and heart rate. Regional flow distribution is not homogeneous and is dependent on central and peripheral vascular tone, which ultimately results in the composite systemic vascular resistances (SVR). As an oversimplification, mean arterial pressure (MAP) can be estimated as the product of cardiac output by SVR. When flow decreases, MAP remains stable when SVR increases; this corresponds to increased sympathetic adrenergic tone and central vascular contraction in low ERo_2 organs, and preserved peripheral vasodilation in high ERo_2 organs. Overall, ERo_2 increases and Svo_2 decreases.

Minimal data exist to guide selection of the threshold for blood pressure maintenance. Arbitrary values of a systolic blood pressure of 90 mm Hg or a MAP of 60 to 65 mm Hg have traditionally been chosen. MAP is a better reflection of arterial pressure-head, but in the presence of an arterial line, systolic blood pressure is likely to be a more accurate pressure measurement and is typically used.[4]

Observation of an inappropriate tissue perfusion (e.g., raised blood lactate level, metabolic acidosis, Svo_2 <40%, decreased urinary flow) and its persistence despite probabilistic therapy (fluid, low-dose inotropes, red blood cells) should lead to optimizing flow according to the Frank-Starling curve. This can be assessed by invasive and noninvasive investigative procedure (see later).

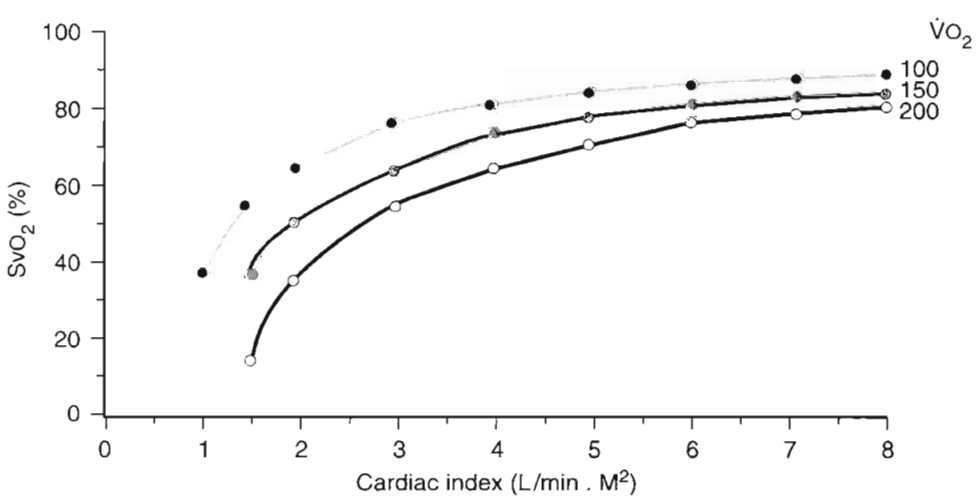

FIGURE 108–2. Venous O_2 saturation (Svo_2)-to-cardiac index (CI) relationship. According to the modified Fick equation, the relationship Svo_2/CI is curvilinear. Subsequently, when O_2 uptake ($\dot{V}o_2$) is constant, CI variations lead to large variations in Svo_2 when the initial CI value is low. In contrast, when initial CI values are already high, CI variations doe not influence Svo_2 very much. These relationships are modified when CI variations are associated with large modifications in $\dot{V}o_2$.

During circulatory shock, when ERO_2crit is reached, $\dot{V}O_2$-to-DO_2 dependency with a rise in blood lactate levels implies O_2 debt. Several authors have reported that oxygen debt is related to the likelihood of multiple organ failure and mortality in postoperative or polytrauma patients.[5,6] Patients who survive multiple organ failure have been shown to have higher cardiac index, lower SVR, higher $\dot{V}O_2$ and higher SvO_2 than nonsurvivors.[7,8] Rixen and Siegel[6] demonstrated that the degree of tissue oxygen debt is related to an enhanced inflammatory response, associated with an increased risk of acute respiratory distress syndrome, and higher mortality rates.

Recent research has emphasized the potential interest of central venous oxygen saturation ($ScvO_2$) for detecting global oxygenation impairment.[6] Experimental studies reported that changes in SvO_2 and $ScvO_2$ closely reflect circulatory disturbances during periods of hypoxia, hemorrhage, and subsequent resuscitation. Fluctuations in these two parameters correlated well, although absolute values differed.[9,10] Finally, observational data found $ScvO_2$ to be a useful parameter in detecting occult tissue hypoperfusion in both sepsis and cardiac failure.[11,12] An important feature with $ScvO_2$ monitoring is that $ScvO_2$ can be continuously provided by central venous catheters equipped with optic fibers (PreSep, Edwards Lifesciences). In initial resuscitation of circulatory shock, insertion of a central venous line is a standard, rapid, and easy approach, much easier than any other invasive or noninvasive hemodynamic monitoring, especially in patients who are not yet sedated, intubated, and ventilated.

In a recent study, patients admitted to the emergency department with severe sepsis and septic shock were randomized to standard therapy (n = 133) or to early goal-directed therapy (n = 130) targeted to achieve a central $ScvO_2$ of greater than 70%.[13] Standard therapy included antibiotics, fluid resuscitation, and vasoactive drugs to achieve a central venous pressure between 8 and 12 mm Hg, MAP greater than 65 mm Hg, and urine output greater than 0.5 mL/kg/h. The patients in the early goal-directed therapy group, in addition to the standard goals, had to reach an $ScvO_2$ of greater than 70% by optimizing fluid administration, hematocrit to greater than 30%, and/or prescription of inotrope (dobutamine to less than 20 μg/kg/min). Initial $ScvO_2$ in both groups was quite low (49 ± 12%), confirming that severe sepsis is hypodynamic before any fluid resuscitation has started. This study demonstrated a significant reduction in hospital mortality: 30.5% in the early goal-directed therapy group compared with 46.5% in the standard therapy group ($P = .009$). An important point in this study is that 99.2% of patients receiving early goal-directed therapy achieved their hemodynamic goals within the first 6 hours, compared with 86% of those receiving standard therapy. From the first to the 72nd hour, total fluid loading was not different between the two groups (approximately 13,400 mL); in contrast, from the first to the seventh hour, the amount of fluid received was significantly larger in the early goal-directed therapy patients (approximately 5000 mL vs 3500 mL). In the follow-up period between the seventh and the 72nd hour, in patients receiving early goal-directed therapy, mean $ScvO_2$ was higher (70.6 ± 10.7% vs. 65.3 ± 11.4%; $P = .02$), mean arterial pH was higher (7.40 ± 0.12 vs. 7.36 ± 0.12; $P = .02$), and lactate plasma levels were lower (3.0 ± 4.4 mmol/L vs. 3.9 ± 4.4 mmol/L; $P = .02$), as was base excess (2.0 ± 6.6 mmol/L vs. 5.1 ± 6.7 mmol/L; $P = .02$). The multiple organ failure score was significantly altered in patients receiving standard therapy when compared with early goal-directed therapy patients. This is the first study demonstrating that early identification of patients with sepsis, associated with early initiation of goal-directed therapy in order to achieve adequate tissue oxygenation by O_2 delivery ($ScvO_2$ monitoring) significantly improves mortality rates.[13]

DECIDING THE DIAGNOSTIC AND TREATMENT STRATEGY

Treatment strategy relies on shock definition (dysoxia) and starts with an early and rapid estimation of O_2 deficit, rapidly followed by an early probabilistic treatment (Fig. 108-3).

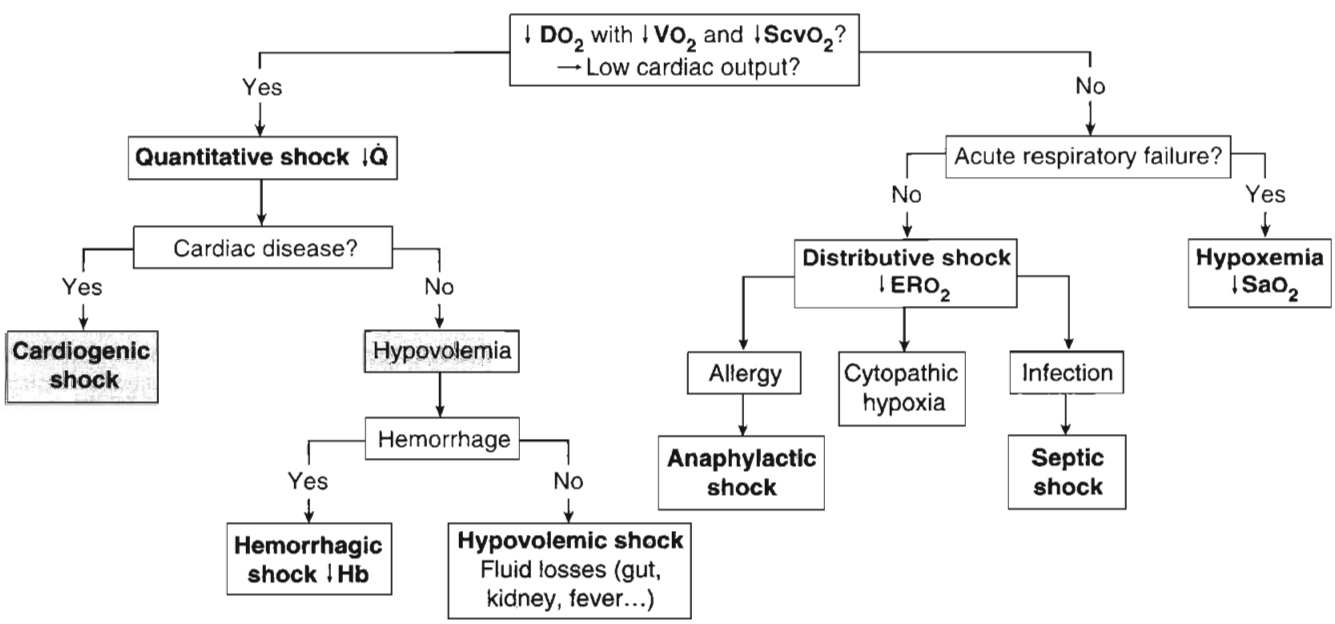

FIGURE 108–3. Initial interpretation of a shock state. Do_2, O_2 supply; $\dot{V}o_2$, O_2 uptake; Hb, hemoglobin; Sao_2, O_2 arterial saturation; $Scvo_2$, central venous O_2 saturation; $\dot{Q}$, cardiac output.

The response to this early probabilistic treatment (modification of lactate, arterial pH, Scv_{O_2} or Sv_{O_2}) then suggests which complementary investigation should be conducted (e.g., echocardiography, esophageal Doppler scan) and which type of monitoring should be installed (e.g., invasive systolic arterial blood pressure variations, Swan-Ganz catheter), which will help to refine the diagnosis and optimize treatment.

DIAGNOSING THE SHOCK TYPE

Quantitative Shock (Decreased D_{O_2})

Decreased Flow (Hypovolemic, Cardiogenic Shock)

Decrease in flow can be related to either a decrease in circulatory volume (absolute or relative hypovolemia) or to a failure of the cardiac pump.

Hypovolemia is "absolute" after severe hydration defects, plasma, or blood losses; it can be "relative" when fluid administration is insufficient to compensate a loss in vascular tone in the context of sepsis or anaphylaxis (or use of large doses of sedative drugs). In that context, there is an inadequacy between the content (volume) and the vascular capacity, and abnormal sympathetic tone is associated with an altered capillary recruitment. Relative hypovolemia is therefore often associated with altered redistribution of flow among and within organs. It is important to notice that shock can result from a mixture of quantitative and distributive features, and a mixture of absolute and relative hypovolemia.

Cardiac failure can result from either myogenic injury (infectious, viral, or ischemic disease), or "obstacle" to ventricular ejection (increased right ventricular afterload, increased vascular pulmonary resistance, increased left ventricular afterload, increased SVR), and/or a lack of ventricular filling (decreased right or left ventricular preload, valvulopathy, decrease in filling time by tachycardia).

Decreased Ca_{O_2} (Hemorrhagic Shock, Acute Respiratory Failure, Poisoning)

A decrease in Hb is not necessarily associated with hypovolemia (hemodilution in which decreased D_{O_2} remains modest). When associated with an acute hemorrhage (hypovolemia), the decrease in D_{O_2} is higher inasmuch as the decrease in flow is larger.

Hemoglobin capacity to carry O_2 can also be limited. During carbon monoxide poisoning, a decrease in D_{O_2} results from a loading competition on Hb between carbon monoxide and O_2, and is "maximized" by abnormal O_2 utilization (carbon monoxide interacts with oxidative phosphorylation) and a decrease in ER_{O_2} capabilities. In this particular case, shock is both quantitative and distributive.

In an acute respiratory disorder (altered gas exchange or abnormal central or peripheral respiratory control), decreased Sa_{O_2} leads to a decreased Ca_{O_2} and D_{O_2} as soon as cardiac output can no longer compensate.

Distributive Shock (Decreased ER_{O_2})

This type of shock is linked to

- An altered flow redistribution among organs secondary to inflammation, anaphylaxis, or abusive use of sedation;
- A decrease in capillary recruitment secondary to altered vascular reactivity, increased intravascular coagulation, increased blood cell adhesion, and/or endothelial edema;
- An abnormal mitochondrial function (mitochondrial injury or dysfunction) such as described in "cytopathic hypoxia."[14]

Distributive shock often coexists with hypovolemic and/or cardiogenic shock.

DECIDING WHEN TO ADMIT THE PATIENT TO THE INTENSIVE CARE UNIT

Admission to the intensive care unit is requested when hemodynamic instability is present and requires use of inotropes (inoconstrictors or inodilators); this occurs when shock does not respond to initial therapy (fluid administration, low-dose inotropes, red blood cell infusion), requires ventilatory support (with a noninvasive interface or after intubation), or imposes hemofiltration (severe electrolyte disorder, fluid overflow, poisoning), and more generally when invasive procedures become necessary (invasive blood pressure monitoring). A patient becomes eligible for an intensive care unit bed at the time failure of one or more organs develops.

CHOOSING THE APPROPRIATE MONITORING

The discussion on monitoring type does not have any meaning until the cardiorespiratory emergency has been treated. The minimal monitoring device consists of an electrocardioscope, pulse oximeter, and rapid arterial pressure recordings (every 5 minutes and at the best continuous and invasive). A central venous catheter allows measurement of central venous pressure, which often cannot help much in deciding fluid administration (it is indicative at least when it remains lower than 5-8 mm Hg), but which facilitates infusion of drugs, crystalloids, or colloids. The central venous line also allows for monitoring and/or sampling of Scv_{O_2} (a surrogate for mixed Sv_{O_2}) if the catheter is not equipped with optic fibers. Central venous catheters are easier, should be cheaper, and carry less iatrogenic risk than Swan-Ganz catheters.

A Swan-Ganz catheter (at the best with continuous cardiac output and Sv_{O_2} monitoring) and/or any noninvasive flow assessment (transesophageal echography, esophageal Doppler echography) is recommended when optimized cardiac output is doubtful according to the Frank-Starling curve. This requires that some preliminary cardiorespiratory stability has been obtained. In that context, fluid administration should be continued (the heart is preload-dependent) until cardiac output increases no further (becomes preload-independent); when cardiac output is not sufficient to maintain MAP or urine output, when Sv_{O_2} remains low, or when lactate concentration remains elevated, an inotrope should be given. Cardiac echography must be done in the context of congestive heart failure and/or myocardial ischemia to diagnose ventricle or valve dysfunction. In the sedated, intubated, and ventilated patient, recordings of systolic pressure variation or pulse pressure variation can be helpful: the heart remains preload-dependent until systolic pressure variation is smaller than 10 mm Hg or pulse pressure variation is less than 10%, or both.[15] Arrhythmia limits this type of evaluation.

Iterative blood gas analysis (another approach justifying insertion of an arterial line), metabolic acidosis and lactate concentration evaluation, is a way to assess global tissue oxygenation and completes Scv_{O_2} or Sv_{O_2} information.

THERAPEUTIC PRINCIPLES: SYMPTOMATIC AND ETIOLOGIC TREATMENTS

SYMPTOMATIC TREATMENT

Emergency therapeutic principles of care need to be decided at the time the initial diagnostic strategy is considered. It is necessary to give supplemental O_2 and ventilatory support in response to acute respiratory failure (acute lung injury, mechanical failure, respiratory distress) either through a face mask or by endotracheal intubation and ventilation. Acute circulatory failure is treated by initial fluid loading in the absence of left ventricular failure (see later). If decreased global contractility is present, inotropic support is considered with either dobutamine or dopamine. In case of anaphylactic shock, emergency treatment is to give intravenous epinephrine to treat allergy-induced vasodilation.

Fluid loading is the first step in treatment.[16] Its first goal is to optimize left ventricular preload to improve Do_2 by increasing cardiac output.[17] There is, however, an associated risk of interstitial edema, in particular pulmonary edema. Unless the patient has an acute lung injury, fluid loading aims at maximizing cardiac output[17] according to the Frank-Starling relationship, decreased lung gas exchange being detected by a decrease in Sao_2 (or by a decrease in its surrogate, pulse oximetry).

Swan-Ganz catheter derived pulmonary artery occlusion pressure has long been the most used static clinical variable for guiding fluid infusion. In septic shock, it was accepted that maximal cardiac output was obtained for values between 12 and 15 mm Hg.[17] To better estimate left ventricular preload, left ventricular end-diastolic surface has now been proposed. In fact, in the sedated, intubated, and ventilated patient, ventilatory-induced systolic pressure variation predicts increased systolic ejection volume to fluid loading much better than pulmonary artery occlusion pressure.[18]

Synthetic colloids are first-line agents. They may induce less pulmonary edema than crystalloids, especially in patients in septic shock. Crystalloids are recommended as first-line agents during anaphylactic shock. Normalization of hemoglobin concentration, [Hb], by red blood cell transfusion is not required. However, a [Hb] between 8 and 10 g/dL[117] might be preferred in patients with severe sepsis and/or coronary disease and/or decreased cardiac contractility. In those latter cases, decreased [Hb] is not compensated by increased cardiac output, and Do_2crit is reached more rapidly.

Catecholamines help in restoring perfusion pressure and maintaining cardiac output, thus allowing sufficient Do_2; this should allow regional flow distribution and improved ERo_2. All catecholamines are inotropes; they can be divided into (1) inodilators when they combine inotropic and vasodilatory properties (low-dose dopamine, any dose of dobutamine or dopexamine); or (2) inoconstrictors when they combine inotropic and vasoconstricting properties (high-dose dopamine, any dose of epinephrine or norepinephrine). Inodilators increase flow; inoconstrictors increase perfusion pressure. Because of variable individual sensitivity to catecholamines, dose titration is strongly recommended.[17] More potent vasopressors, such as vasopressin and derivatives, are now being tested.[19] It is important to emphasize that a rise in blood pressure may not be a surrogate of clinical benefit. Indeed, in a large placebo-controlled clinical trial, administration of the nonselective nitric oxide inhibitor N^G-methyl-L-arginine in septic shock produced both significant increases in blood pressure and significant increases in mortality.[20]

In septic shock, one study demonstrated that increasing MAP from 65 to 85 mm Hg was associated with no difference in organ perfusion variables.[21] Because increasing blood pressure through vasoconstriction may be associated with a decrease in flow, a trade-off may exist between raising blood pressure and decreasing cardiac index that will vary depending on the specific vasopressor or combined inotrope/vasopressor.[4]

OTHER THERAPEUTIC PRINCIPLES

The importance of correction of metabolic acidosis and the use of intravenous bicarbonate for shock-induced anion gap acidosis have been overemphasized in the past. Indeed, clinical studies, including one randomized, prospective trial, failed to show any hemodynamic benefit from bicarbonate therapy either to increase cardiac output or to decrease vasopressor requirements, regardless of the degree of acidemia. Cardiac function does not appear to be decreased for arterial pHs higher than 7.00. Bicarbonate infusion, apart from renal or digestive losses, is therefore not recommended, unless the patient requires hemodialysis or hemodiafiltration for hyperkalemia.[22]

In patients with septic shock, stress-dose (low-dose) steroid therapy (hydrocortisone 200 mg/day) needs to be considered, especially if the decrease in blood pressure requires high concentrations or an increasing concentration of vasopressors, once appropriate antibiotics are being given or the infectious site is controlled.[23] Intravenous hydrocortisone is administered after the serum cortisol level has been assessed (before and after corticotropin stimulation test). The duration of treatment is 5 days minimum when a positive clinical response is present. Beyond 72 hours, absence of any hemodynamic improvement suggests the hydrocortisone treatment is futile.

The place for high-volume hemofiltration in the treatment for septic shock remains to be defined. Although not oriented toward better circulatory efficacy, a number of treatments are essential in septic shock.[16] Control of the infectious source and eradication of it are essential. Empirical or probabilistic antibiotics need to be directed against gram-negative microorganisms but also against potentially resistant pathogens. This justifies double or triple antibiotherapy; it theoretically offers the following advantages: widening of the spectrum of activity, antibacterial synergy, increased bactericidal speed, and decreased risk for emergent resistant germs.

PROGNOSIS

The main prognostic factors for circulatory shock are the number of organ failures present on admission, the delay to start of treatment, and the response to symptomatic treatment; in cases of septic shock, control of the infectious source and its sensitivity to medical and surgical treatment is essential. The early timing of goal-directed therapy certainly influences the severity of multiple organ failure and the prognosis. This point has been clearly demonstrated by the recent trial from Rivers and colleagues.[13]

ANNOTATED REFERENCES

Dellinger RP, Carlet JM, Masur H, et al: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Intens Care Med 2004; 30:536-555.

The objective of the Surviving Sepsis Campaign, an international effort to increase awareness and improve outcome in patients with severe sepsis, was to develop management guidelines for severe sepsis and septic shock that would be of practical use for the bedside clinician. The process included a modified Delphi method, a consensus conference, several subsequent smaller meetings of subgroups and key individuals, teleconferences, and electronic-based discussion among subgroups and among the entire committee. Evidence-based recommendations were made regarding many aspects of the acute management of sepsis and septic shock that will hopefully translate into improved outcomes for the critically ill patient. The impact of these guidelines will be formally tested and guidelines updated annually.

Dünser MW, Mayr AJ, Ulmer H, et al: Arginine vasopressin in advanced vasodilatory shock. A prospective, randomized, controlled study. Circulation 2003;107:2313-2319.

Arginine vasopressin was tested as a potent vasopressor agent to stabilize cardiocirculatory function even in patients with catecholamine-resistant vasodilatory shock. Forty-eight patients with catecholamine-resistant vasodilatory shock were prospectively randomized to receive a combined infusion of arginine vasopressin and norepinephrine or norepinephrine infusion alone. The combined infusion of arginine vasopressin and norepinephrine proved to be superior to infusion of norepinephrine alone in the treatment of cardiocirculatory failure in catecholamine-resistant vasodilatory shock.

Lopez A, Lorente JA, Steingrub J, et al: Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: Effect on survival in patients with septic shock. Crit Care Med 2004;32:21-30.

This multiple-center, randomized, double-blind, placebo-controlled study assessed the safety and efficacy of the nitric oxide synthase inhibitor N^G-methyl-L-arginine (546C88) in patients with septic shock. The trial was stopped early after review by the independent data safety monitoring board. Day-28 mortality rate was 59% (259/439) in the N^G-methyl-L-arginine group and 49% (174/358) in the placebo group ($P < .001$). The overall incidence of adverse events was similar in both groups, although a higher proportion of the events was considered possibly attributable to N^G-methyl-L-arginine. Most of the events accounting for the disparity between the groups were associated with the cardiovascular system (e.g., decreased cardiac output, pulmonary hypertension, systemic arterial hypertension, heart failure). There was a higher proportion of cardiovascular deaths and a lower incidence of deaths caused by multiple organ failure in the N^G-methyl-L-arginine group.

Michard F, Boussat S, Chemla D, et al: Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 2000;162:134-138.

In mechanically ventilated patients with acute circulatory failure related to sepsis, the authors investigated whether the respiratory changes in arterial pulse pressure (ΔPP) could be related to the effects of volume expansion (VE) on cardiac index. It was concluded that in that particular population of patients, analysis of ΔPP is a simple method for predicting and assessing the hemodynamic effects of VE.

Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-1377.

Goal-directed therapy involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the intensive care unit. Early goal-directed therapy provided significant benefits with respect to outcome in patients with severe sepsis and septic shock.

Ronco JJ, Fenwick JC, Tweeddale MG, et al: Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. JAMA 1993;270:1724-1730.

The critical O_2 delivery for anaerobic metabolism was identified from the biphasic relationship between O_2 delivery and O_2 consumption in individual humans.

Chapter 109

INOTROPIC THERAPY IN THE CRITICALLY ILL

Jean-Louis Teboul • Xavier Monnet • Christian Richard

KEY POINTS

1. Inotropic therapy is often considered for patients with cardiogenic shock or for those with advanced heart failure whose condition is refractory to standard therapy. In these conditions, clinicians expect short-term positive effects of intravenous inotropic drugs, allowing cardiovascular stabilization.
2. Inotropic therapy can also be considered in high-risk surgical patients, even in the absence of a reduced myocardial contractility, to achieve supranormal levels of oxygen delivery during the perioperative period to prevent the onset of tissue hypoxia and organ dysfunction. Such a therapeutic attitude is not recommended for critically ill patients with established circulatory shock.
3. Most inotropic agents enhance myocardial contractility by increasing the Ca^{2+} concentration in the cytosol of cardiomyocytes after producing an increase in cytosolic cyclic adenosine monophosphate (cAMP) concentration. Synthetic and natural catecholamines enhance cAMP formation after fixing $beta_1$-adrenergic receptors at the cellular surface while phosphodiesterase inhibitors decrease cAMP degradation.
4. The $beta_1$-adrenergic agents, such as dobutamine, dopamine, and epinephrine, are the most potent inotropic agents.
5. Because of down-regulation of $beta_1$-adrenergic receptors, the myocardial effects of exogenous catecholamines are attenuated after a few days of administration.
6. Sepsis-induced decreased responsiveness of the myocardium to beta-adrenergic stimulation also results in attenuation of cardiac effects of exogenous catecholamine administration in patients suffering from septic shock.
7. The drugs given to increase cardiac contractility may also exert vasoactive effects that may interfere with vasoregulation of regional blood flow. The extent to which this interference is beneficial in increasing oxygen supply in hypoxic areas remains speculative. This emphasizes the need to monitor, as far as possible, perfusion and function of critical organs when such agents are given to patients in shock.

RATIONALE FOR USING INOTROPIC THERAPY IN CRITICALLY ILL PATIENTS

Two different objectives for using inotropes in critically ill patients have been considered: (1) the attempt to improve cardiac function in patients with low blood flow related to reduced myocardial contractility; and (2) the attempt to achieve supranormal values of cardiac output and oxygen delivery to prevent or reduce oxygen debt; in this situation, inotropes could be given after volume resuscitation, even in patients with normal myocardial contractility.

USE OF INOTROPES FOR REVERSING IMPAIRED MYOCARDIAL CONTRACTILITY

The first category of situations in which inotropic therapy is generally considered includes cardiogenic shock, acute heart failure, or acute exacerbation of chronic heart failure. However, although the use of such therapy in these clinical conditions seems logical on a classic pathophysiologic basis, no demonstration of a beneficial impact on morbidity and mortality can be found in the literature. Moreover, almost all the commercially available inotropes have been shown to be associated with an increased mortality rate when given on a long-term basis to patients with chronic heart failure. It has been postulated that the long-term use of inotropes may lead to deterioration of left ventricular function through acceleration of myocardial cell apoptosis.[1] Additionally, the beneficial effects on mortality of agents known to have negative inotropic effects, such as beta-blockers, is now well established in patients with chronic heart failure.[2,3] Therefore, inotropic therapy is generally reserved for patients with cardiogenic shock or for patients with advanced heart failure whose condition is refractory to standard therapy including diuretics, digoxin, beta-blockers, and angiotensin-converting enzyme inhibitors. Under these conditions, clinicians can expect short-term positive effects of intravenous inotropic therapy allowing cardiovascular stabilization. In patients with refractory heart failure who are candidates for cardiac transplantation, this therapy can be used as a bridge to transplantation. In those with potentially reversible causes of acute heart failure (such as myocardial infarction or acute myocarditis), short-term inotropic therapy must be considered as an appropriate bridge to coronary revascularization or recovery. The development of bedside echocardiography in the intensive care unit (ICU) should allow appropriate use of inotropic therapy, since this method provides a more accurate assessment of systolic

cardiac function than traditional invasive methods such as pulmonary artery catheterization.

USE OF INOTROPES TO ACHIEVE SUPRANORMAL LEVELS OF OXYGEN DELIVERY

High-Risk Surgical Patients

The concept of attempting to achieve supranormal hemodynamic endpoints emerged from studies in high-risk surgical patients. In a preliminary study, Shoemaker and colleagues[4] examined the changes in hemodynamic patterns occurring during the perioperative period in survivors and nonsurvivors. Although during the first 12 postoperative hours there were minimal changes in the usual vital signs of both groups, the mean values of cardiac output, oxygen delivery, and oxygen consumption increased only in surviving patients.[4] The median postoperative values of cardiac index, oxygen delivery, and oxygen consumption observed in survivors were 4.5 L/min/m^2, 600 mL/min/m^2, and 170 mL/min/m^2, respectively.[4] The authors hypothesized that the higher hemodynamic values in survivors indicate a physiologic compensation for the increase in postoperative metabolic and oxygen requirements. In a prospective study in high-risk patients undergoing surgery, the same group showed that the use of these supranormal hemodynamic values as therapeutic endpoints was associated with a reduction in mortality from 33% to 4%.[5] In the protocol group, dobutamine and dopamine were given as inotropic drugs, even in the absence of evidence of reduced cardiac contractility, when volume resuscitation (and packed red blood cells, if necessary) failed to achieve supranormal values of oxygen delivery.[5] In another randomized study performed in high-risk patients undergoing surgery, the deliberate perioperative increase in oxygen delivery above supranormal values using dopexamine was associated with decreased rates of mortality and postoperative complications.[6] It is noteworthy that, in this study, oxygen consumption did not change significantly over the study period in any group, suggesting that the beneficial effects of dopexamine could have resulted from mechanisms other than prevention of global tissue hypoxia.[7] A reduction in the mortality rate was also reported in two other randomized studies performed in high-risk surgical patients.[8,9] In these studies, various inotropic agents, including dopexamine, epinephrine, and dobutamine, were given to achieve supranormal hemodynamic targets. However, in a multicenter randomized trial, dopexamine at doses that resulted in increased cardiac output after preoperative stabilization with fluids did not improve outcome after abdominal surgery as compared with fluids alone.[10] It is likely that in this study the patients had fewer risk factors than in the studies that demonstrated a beneficial effect of perioperative hemodynamic optimization. From all these findings, it is reasonable to consider the increase of cardiac output and oxygen delivery toward values higher than normal during the perioperative period in high-risk patients undergoing elective surgery.

CRITICALLY ILL PATIENTS

Whether this therapeutic approach could also be applied to patients admitted to the ICU for established acute illnesses has been a matter of debate. It was first postulated that critically ill patients could also benefit from aggressive hemodynamic treatment for at least two reasons: (1) the observation of higher median values of cardiac output and oxygen delivery in survivors in comparison with nonsurvivors in studies performed in patients with acute respiratory distress syndrome and sepsis[11-14]; and (2) the presence, in critically ill patients with sepsis,[15-17] acute respiratory distress syndrome,[18,19] and acute liver disease,[20,21] of an oxygen consumption/supply dependency occurring for supranormal values of oxygen delivery. Such a phenomenon was reported to correlate with the presence of increased blood lactate, a marker of global tissue hypoxia[15-17] and to be associated with a poor outcome.[22] This so-called pathologic oxygen consumption/supply dependency—ascribed to impaired oxygen extraction capacities associated with acute illnesses—would incite the clinician to increase oxygen delivery toward supranormal values to exceed its critical level. However, such an aggressive therapeutic approach has been seriously questioned for at least two major reasons. First, some authors using two independent methods to obtain oxygen consumption and oxygen delivery measurements no longer found any pathologic oxygen consumption/supply dependency in critically ill patients.[23-26] It has been suggested that a mathematical coupling of the shared variables (cardiac output and arterial oxygen content) could have explained the finding of oxygen consumption/supply dependency in the previous studies in which oxygen consumption and oxygen delivery were calculated using the same reverse Fick method.[27] Second, numerous randomized clinical trials performed in patients with acute illnesses did not demonstrate any benefit from deliberate manipulation of hemodynamic variables toward values higher than physiologic values.[14,26-31] In one of these studies, the mortality rate was even higher in the group of patients assigned to receive an aggressive treatment aimed at achieving supranormal values of oxygen delivery.[29] It was postulated that deleterious consequences of the use of high doses of dobutamine in patients of the protocol group were responsible for the increased mortality. It has to be noted that (1) the patients of the protocol group received high doses of the inotropic agent despite no evidence of any deficit of inotropic function, and (2) in most of these patients, the aggressive inotropic support failed to achieve the target value of oxygen consumption (170 mL/min/m^2). The later analysis of the subgroup of septic patients of this study showed that the survivors were characterized by ability to increase both oxygen delivery and oxygen consumption regardless of their group of randomization.[13] The nonsurviving patients were characterized by inability to increase oxygen consumption despite the increase in oxygen delivery, suggesting a more marked impairment of peripheral oxygen extraction in nonsurvivors than in survivors.[13] In addition, the ability to increase cardiac output and oxygen delivery was also significantly reduced in nonsurvivors in comparison with survivors, suggesting a decrease in cardiac reserve in those patients who will die.[13] This is not a surprising finding, since the degree of myocardial dysfunction in septic shock correlates with increased risk of death. In this regard, it has been suggested that the response to a dobutamine challenge could have a prognostic value in septic patients, since, in two prospective studies, survivors were able to increase both oxygen consumption and oxygen delivery in response to dobutamine, whereas nonsurvivors were not able to increase either oxygen delivery or oxygen consumption.[32,33]

From all the results of randomized controlled studies, the deliberative attempt to achieve supranormal hemodynamic targets in the general population of critically ill patients is no longer recommended.[34-36] However, in the early phase of septic shock when blood flow and oxygen delivery are generally low, an aggressive hemodynamic therapy, including inotropes, aimed at rapidly normalizing oxygen delivery, was demonstrated to result in a better outcome in a randomized controlled trial.[37] Thus, in the early phase of septic shock and maybe in other acute illnesses, it is essential to rapidly restore normal global blood flow conditions to avoid further deleterious consequences of systemic hypoperfusion. In later stages of the disease, with inflammatory processes and organ dysfunction already developed, no evidence of benefit from a further increase in oxygen delivery has been shown in the literature. However, it seems to be likely that cardiac output should be kept in the normal range by using volume and/or inotropes to prevent worsening of the insult.

PHARMACOLOGIC PROPERTIES OF INOTROPIC AGENTS

Different inotropic drugs are available. Most of them act on adrenergic receptors located at the surface of the cardiomyocytes.

ADRENERGIC SIGNAL TRANSDUCTION IN CARDIOMYOCYTES

Natural as well as synthetic catecholamines enhance the Ca^{2+} cytosolic amount, which is directly related to the force of contraction (Fig. 109-1). Ca^{2+} fixes on the troponin C Ca^{2+}-specific binding site, inducing a conformational change that leads to the fixation of the myosin head to the actin filament.

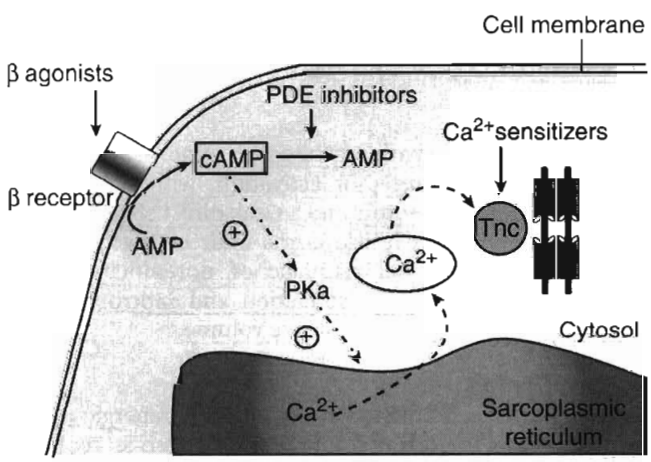

FIGURE 109–1. Mechanisms of action of inotropic agents at the cellular level. Schematic representation. Beta-agonist agents fix the beta receptor and stimulate the formation of cyclic adenosine monophosphate (cAMP) from AMP through adenylate cyclase. cAMP activates protein kinase A, which provokes the extrusion of Ca^{2+} from the sarcoplasmic reticulum into the cytosol through phosphorylated ryanodine receptors. Ca^{2+} fixes troponin C and finally activates the fixation of actin on myosin filaments. Phosphodiesterase (PDE) inhibitors also increase the cAMP concentration by inhibiting its degradation. The mechanism by which Ca^{2+} sensitizers increase inotropism is the enhancement of troponin C sensitivity for Ca^{2+}.

Hydrolysis of the adenosine triphosphate (ATP) molecule located on the myosin head to adenosine diphosphate (ADP) simultaneously induces the flexion of the myosin neck and the shortening of the contractile apparatus.

A rapid overview of the physiologic response to adrenergic receptor stimulation is essential to understand the pharmacologic properties of these drugs. Receptors of the adrenergic system are classed as α_1, α_2, β_1, β_2, and dopaminergic receptors.[38]

Beta$_1$-Adrenergic Receptors

Beta-adrenergic receptors are transmembrane proteins located in the sarcolemma. The beta$_1$-receptor subtype is mainly represented in the human heart. Its stimulation induces inotropic, lusitropic, chronotropic, and dromotropic effects, and all these effects result from the enhancement in Ca^{2+} cytosolic concentration. Binding of a beta$_1$-agonist agent to its receptor stimulates the G_s protein. The guanosine diphosphate, normally fixed to the stimulatory α_s subunit of G_s protein, is replaced by guanosine triphosphate and the α_s-guanosine triphosphate complex binds to adenyl cyclase, which then becomes activated. Cyclic adenosine monophosphate (cAMP) is formed from ATP and activates protein kinase A. Protein kinase A phosphorylates and activates several cellular structures, as follows:

- The ryanodine receptors of the sarcoplasmic reticulum, leading to enhanced extrusion of Ca^{2+} out of the sarcoplasmic reticulum. Indeed, the main part of the Ca^{2+} cytosolic content needed for contraction is provided by the sarcoplasmic Ca^{2+} store. The entry of Ca^{2+} through the membrane L-type channels modifies the molecular conformation of the ryanodine receptor of the sarcoplasmic reticulum. Parts of these ryanodine receptors are Ca^{2+} channels that enable massive release of Ca^{2+} out of the sarcoplasmic reticulum (see Fig. 109-1).
- The sarcolemmal L-type Ca^{2+} channels, increasing their opening time. This leads to an increased amount of cytosolic Ca^{2+} available for sarcoplasmic reticulum Ca^{2+} release and for contraction.

The increase in intracytosolic Ca^{2+} concentration also leads to the activation of calmodulin. This ubiquitous protein enables the phosphorylation of other proteins once it has fixed Ca^{2+}, as follows:

- The myosin light chain through the myosin light chain ATPase. This phosphorylation enhances the responsiveness of the cardiac contractile protein to Ca^{2+} and helps to increase the affinity of myosin for actin, thus participating in the inotropic effect.
- The phospholamban and the sarcolemmal Na^+/Ca^{2+} exchanger, leading to a faster decrease of Ca^{2+} cytosolic concentration after contraction and accounting for the lusitropic effect. Indeed, relaxation is dependent on Ca^{2+} reuptake by the sarcoplasmic reticulum through the sarcoendoplasmic reticulum calcium ATPase pump. The activity of the sarcoendoplasmic reticulum calcium ATPase pump is normally inhibited by the phospholamban located in the sarcoplasmic reticulum membrane near the Ca^{2+} pump. Phosphorylation of phospholamban relieves this inhibition and Ca^{2+} uptake by the sarcoplasmic reticulum is thus stimulated.

Beta$_2$-Adrenergic Receptors

The beta$_2$ receptor subtype is mainly represented in noncardiac structures. Beta$_2$-adrenergic stimulation induces arterial and venous relaxation. The effects of beta$_2$ stimulation in vascular smooth muscle result from a different activation pathway: once Ca^{2+} intracytosolic amount increases, it fixes the calmodulin regulatory protein, and the Ca^{2+}-calmodulin complex activates the myosin light chain kinase, leading to inhibiting phosphorylation of the myosin light chain, and finally smooth muscle relaxation.

Alpha-Adrenergic Receptors

When an agonist fixes the alpha$_1$ receptor, G_h, part of the G-protein family, stimulates phospholipase C, which splits phosphatidyl inositol into inositol triphosphate and 1,2-diacylglycerol. Inositol triphosphate stimulates the release of Ca^{2+} from the sarcoplasmic reticulum. Alpha$_2$-adrenoreceptor stimulation inhibits adenylate cyclase and reduces the cAMP intracellular content. Alpha-adrenoreceptors are not prominent in the cardiac tissue but are in the vascular wall. The cardiac alpha$_1$-stimulation induces a positive inotropic effect; alpha$_1$ and alpha$_2$ stimulation induces a potent arterial and venous constriction.

PHARMACOLOGIC PROPERTIES OF THE INOTROPIC AGENTS USED IN CLINICAL PRACTICE

Norepinephrine

Norepinephrine is the physiologic mediator released by the post-ganglionic adrenergic nerves.[38] It is a potent alpha$_1$ and beta$_1$-adrenergic agonist but has little activity on beta$_2$-receptors. Through its alpha-adrenergic effects, norepinephrine induces potent arterial and venous constriction. It increases systolic as well as diastolic blood pressure, left ventricular afterload, venous return, and cardiac filling pressures. The beta$_1$-stimulation results in a positive inotropic effect and an increase in stroke volume. However, the chronotropic effect is counteracted by baroreflex stimulation following vasoconstriction. Consequently, the heart rate is unchanged or reduced, and the cardiac output is generally unchanged. The coronary blood flow is enhanced by norepinephrine, because of coronary vasodilation secondary to enhanced cardiac metabolism and because of normalization of diastolic blood pressure when low.

Epinephrine

Epinephrine is the main physiologic adrenergic hormone of the adrenal medullary gland.[38] It is a potent stimulator of alpha, beta$_1$, and beta$_2$ receptors. The alpha-adrenergic effect is responsible for a marked arterial and venous vasoconstriction. Epinephrine increases systolic arterial pressure, but its effect on vasculature is partly counteracted by the beta$_2$-mediated vasodilation. The diastolic blood pressure is thus only slightly affected by epinephrine, and the increase in mean arterial pressure (MAP) is less than with norepinephrine. Through cardiac beta$_1$ stimulation, epinephrine increases heart rate and inotropism. The combination of the latter effects and the alpha-mediated venous constriction promoting venous return and cardiac preload results in an increase in cardiac output. Epinephrine also facilitates ventricular relaxation and enhances coronary blood flow through the increase in myocardial oxygen consumption.

Dopamine

Dopamine is the immediate physiologic precursor of norepinephrine and epinephrine. The cardiovascular effects of dopamine are mediated by several types of receptors that are activated at different levels of dopamine concentration and by norepinephrine produced by the transformation of dopamine.

At low rates of administration (<5 µg/kg/min), dopamine activates D1 receptors located in renal, mesenteric, cerebral, and coronary vessels and induces vasodilation without affecting arterial blood pressure. At higher and intermediate rates of administration (5-10 µg/kg/min), dopamine predominantly stimulates beta$_1$-adrenergic receptors and thus enhances inotropism and increases heart rate. At such rates of infusion, dopamine increases systolic blood pressure without altering diastolic blood pressure, because stroke volume is enhanced and arterial vascular tone only slightly altered.[38] Norepinephrine resulting from dopamine transformation contributes to these cardiovascular effects. At higher rates of administration (10-20 µg/kg/min), dopamine predominantly activates vascular alpha$_1$-adrenergic receptors and induces arterial and venous vasoconstriction, counteracting the D_1-receptor mediated vasodilation. This vasoconstriction increases arterial blood pressure, venous return, and cardiac filling pressures. At higher rates of administration, dopamine's hemodynamic effects are similar to those of norepinephrine.

Dobutamine

Dobutamine is a synthetic adrenergic agonist derived from dopamine. Its effects on adrenergic receptors are complex but do not result from endogenous transformation to norepinephrine.[38] Dobutamine simultaneously activates different adrenergic receptors with some opposite effects. In fact, the clinically used drug is a racemic mixture of a (–) enantiomer, activating alpha$_1$-adrenergic receptors, and of a (+) enantiomer activating beta$_1$ and beta$_2$ receptors.[39] The alpha$_1$- and beta$_1$-adrenergic stimulation results in inotropic and chronotropic effects. Dobutamine does not exert any intrinsic vascular effects, because the vasoconstriction induced by alpha$_1$ stimulation is counteracted by the beta$_2$ vasodilating effect.

Dopexamine

Dopexamine is a synthetic catecholamine inducing beta$_2$ and dopaminergic receptor activation, with no effect on alpha-adrenergic receptors and a weak direct effect on beta$_1$-adrenergic receptors. It also exerts indirect effects through inhibition of neuronal reuptake of norepinephrine. Its administration induces vasodilation and inotropic effects with substantially increased stroke volume.[38]

Isoproterenol

Isoproterenol is a potent synthetic beta-adrenergic agonist with a very low affinity for alpha-adrenergic receptors. Through its potent beta$_2$-vasodilating effects it induces a fall in diastolic and mean blood pressure, whereas systolic blood pressure is increased owing to the increase in stroke volume related to its beta$_1$-adrenergic activation.[38] The combination of the latter effect and the marked increase in heart rate leads to an enhanced cardiac output. The resulting increase in myocardial oxygen consumption is not compensated by coronary blood flow enhancement so that isoproterenol infusion may lead to myocardial ischemia, especially if there is preexisting coronary artery disease. Because of its

proischemic and hypotensive effects, isoproterenol is no longer used as an inotropic agent in clinical practice.

Phosphodiesterase Inhibitors

Despite the major role of catecholamines in the management of critically ill patients with inadequate cardiac output, problems such as tachycardia, arrhythmias, increased myocardial oxygen consumption, excessive vasoconstriction, or loss of effectiveness may occur with prolonged exposure to beta-agonists. Thus, other inotropic drugs, such as phosphodiesterase inhibitors (amrinone, milrinone, and enoximone) have been proposed for the management of myocardial dysfunction. These synthetic drugs inhibit the peak III isoform of phosphodiesterase, which catalyzes cAMP (see Fig. 109-1). By increasing intracellular cAMP concentration, they induce a potent vasodilation of the arterial and venous systems through relaxation of vascular smooth muscle. The left ventricular preload is reduced to a greater extent than with dobutamine. At the cardiac level, phosphodiesterase inhibitors induce an inotropic effect similar to that induced by dobutamine. The heart rate is increased only at high rates of administration. The resulting effect is an increase in cardiac output. Because the enhancement of cAMP intracellular concentration also promotes the reuptake of Ca^{2+} by the sarcoplasmic reticulum, phosphodiesterase inhibitors facilitate ventricular relaxation. Finally, since beta-agonists exert their action by increasing the production of cAMP, phosphodiesterase inhibition could enhance their adrenergic effects. This is the pharmacologic basis for the synergic association of beta-agonists and phosphodiesterase inhibitors.

Calcium Sensitizers

Calcium sensitizers represent a new pharmacologic class of inotropic drug.[40] To date, levosimendan is the only calcium sensitizer approved for clinical use.[41] These drugs increase the sensitivity of troponin C for Ca^{2+} and hence the force of contraction (see Fig. 109-1). Their advantage over catecholamines would be to increase the force of contraction without enhancing the influx of Ca^{2+} into the cytosol and thus without increasing the risk of arrhythmias related to this ionic alteration. However, some degree of phosphodiesterase III inhibitory activity probably also contributes to their inotropic effect. These drugs also induce vasodilation by opening ATP-dependent K^+ channels.[40,41]

DECREASE IN BETA-ADRENERGIC RESPONSE

It is well recognized that response to beta-adrenergic stimulation is decreased in chronic cardiac failure. This may be a response to increased activity of the sympathetic nervous system, which may itself be a response to reduced cardiac output. Therefore, this negative retrocontrol of the beta-adrenergic response could act as a protection against excessive adrenergic stimulation. The cellular mechanisms involved are a down-regulation of $beta_1$-adrenergic receptors and a stimulation of the G_i protein of the adenyl cyclase system. The decrease in $beta_1$-adrenergic receptors could result from a decrease in beta-adrenergic receptor messenger RNA and to an increased internalization and degradation of these receptors. These latter mechanisms are mainly related to the phosphorylation of $beta_1$-adrenergic receptors by the beta-adrenoreceptor kinase, which is activated. The high level of nitric oxide (NO) production during heart failure also contributes to attenuation of beta-adrenergic response. During exacerbations of chronic heart failure, the effects of exogenous catecholamines may thus be reduced.

Similarly, there is evidence for a decreased responsiveness of the myocardium to beta-adrenergic stimulation during septic shock.[42] This may be explained by the inhibition of adenyl cyclase activation due to an overexpression of G_i protein[43] at the gene level.[44]

HEMODYNAMIC EFFECTS OF INOTROPIC AGENTS IN CRITICALLY ILL PATIENTS

EFFECTS ON CARDIAC OUTPUT

Dobutamine and Dopamine

Dobutamine and dopamine are the beta-adrenergic agents most widely used in critically ill patients when an increase in cardiac output through an increase in myocardial contractility is desired. In patients with acute heart failure, the effects of these two agents were compared in a cross-over trial.[45] Whereas dobutamine (2.5-10 µg/kg/min) increased cardiac output through an increase in stroke volume in a dose-response fashion, dopamine increased stroke volume and cardiac output at 4 µg/kg/min but not at higher doses, presumably because of an increase in left ventricular afterload. It was also reported that pulmonary artery occlusion pressure decreased with dobutamine while it increased with dopamine. Similar findings were observed in patients with respiratory failure in whom dopamine also increased the left ventricular end-diastolic volume measured using isotopes while dobutamine did not.[46] This suggests an increase in left ventricular preload only with dopamine.

In cases of cardiogenic shock, dopamine is recommended as the inotropic agent of choice in the presence of severe hypotension whereas dobutamine is considered as a first-line therapy in the presence of predominant pump failure and volume overload but normal or moderately reduced blood pressure.[47,48] Accordingly, the SHOCK trial registry (1190 patients) reported that dopamine and dobutamine were used in 89% and 70%, respectively, of patients with cardiogenic shock due to massive acute myocardial infarction.[49] The combination of dopamine and dobutamine at low doses can be a therapy of interest when dobutamine alone fails to restore an adequate MAP.[50]

In patients with septic shock, in addition to hypovolemia, severe systemic vasodilation is associated with a variable degree of depressed myocardial contractility.[51] Accordingly, dopamine at median or high doses has been recommended as the catecholamine of choice when arterial pressure remains low despite adequate volume resuscitation, as it can exert both an alpha-mediated increase in arterial tone and a beta-mediated increase in myocardial contractility. In this regard, numerous studies in septic shock patients demonstrated that dopamine is able to increase both arterial pressure and cardiac output.[52-54] However, in these studies the restoration of an adequate MAP was mainly produced by the increase in cardiac output, through an increase in stroke volume and to a lesser extent an increase in heart rate, whereas minimal effects on systemic arterial resistance were observed despite relatively high doses of this agent. Dopamine was even demonstrated to increase cardiac output markedly while systemic resistance fell in septic patients without shock.[55] Conversely, in another study of

patients with severe septic shock, cardiac output did not increase significantly with dopamine at doses up to 25 μg/kg/min while systemic vascular resistance (SVR) either did not change or significantly increased.[56] This emphasizes the great heterogeneity in the catecholamine response among septic patients and hence the difficulty in predicting clinical hemodynamic effects from pharmacologic properties because of interindividual differences in terms of severity of the insult, underlying diseases, comorbidities, integrity of the neurovegetative status, drugs concomitantly prescribed, and other factors.

Dobutamine is generally considered as the inotropic drug of choice when myocardial contractility is severely depressed in septic shock patients.[57] Comparison of dopamine and dobutamine has shown a similar increase in stroke volume (by 25%), heart rate (by less than 10%), and thus in cardiac output (by 33%) with the two agents but blood pressure increased only with dopamine, suggesting a vasodilatory (direct or indirect) effect of dobutamine.[52] Other authors reported decreased SVR with dobutamine in septic patients.[58,59] This emphasizes the absolute need to give a potent vasopressive agent to septic shock patients when dobutamine is chosen to support cardiac function in the presence of depressed myocardial contractility. One potential advantage of dobutamine is the decrease in cardiac filling pressures[60] that could allow an additional volume infusion to improve further cardiac output when necessary. A change from dopamine to dobutamine was shown to result in lower right and left ventricular filling pressures and an increase in right ventricular ejection fraction for the same pulmonary artery pressure and right ventricular end-diastolic volume, suggesting that dobutamine can exert a more favorable effect on cardiac contractility than dopamine.[61] This has justified the recommendation that dobutamine should be given rather than dopamine when the use of an inotropic drug is judged necessary in patients with severe sepsis or septic shock.[62] The detection of a marked decrease in left ventricular ejection fraction using bidimensional echocardiography[63] can help to diagnose a severe decrease in cardiac contractility and thus suggest the use of dobutamine when signs of peripheral hypoperfusion persist despite volume resuscitation and restoration of perfusion pressure with vasopressors. However, bedside bidimensional echocardiography is still not available in all general ICUs, so the recommendation of using an inotrope such as dobutamine is still based on the persistence of a low cardiac index (<2.5 L/min/m²) after fluid resuscitation and an adequate MAP.[32] Because of the alteration of the beta-adrenergic pathway in the septic heart, the effect on stroke volume and cardiac output of a beta-agonist agent such as dobutamine may be attenuated in septic patients in comparison with nonseptic patients. In this regard, infusion of dobutamine at 5 μg/kg/min, a dose able to increase cardiac output substantially in healthy volunteers[64] or in patients with congestive heart failure,[65,66] has been reported to exert variable effects in the context of sepsis. For example, dobutamine at 5 μg/kg/min has been reported to induce a substantial increase in cardiac output in some studies in patients with severe sepsis[14,58,67] and to have no significant effect on cardiac output in studies investigating patients with a more severe septic shock.[68-70] It is likely that these differences in response to dobutamine were related to various individual factors, including differences in the vasopressive treatment coadministered, and in the degree of myocardial depression and/or beta receptor down-regulation. In this regard, Silverman and associates[42] showed that incremental doses of dobutamine (0, 5, 10 μg/kg/min) produced a dose-related increase in cardiac output in septic patients without shock but no positive effect on cardiac output in patients with septic shock, even for the highest dose. Interestingly, they also showed that post-beta-adrenergic receptor signal transmission was impaired only in patients of the septic shock group and that impairment of beta-adrenergic receptor responsiveness found in both groups was significantly more marked in the septic shock group.[42] These findings, which allow the divergent results of numerous studies to be reconciled,[58,59,67-72] emphasize the unpredictability of the effects of beta-agonist agents in patients with sepsis. As a consequence, and because such agents have also potentially harmful effects (e.g., myocardial ischemia, cardiac arrhythmias), monitoring their effects on cardiac output to check their efficacy is the minimum required. However, no high-level recommendation on which method of cardiac output monitoring (e.g., pulmonary artery catheter, transesophageal Doppler, pulse contour method) is the more appropriate in this setting is currently available.

Epinephrine and Norepinephrine

Although these agents have $beta_1$-adrenergic properties and thus are able to increase myocardial contractility, they are used as vasoconstrictive agents in cases of severe hypotension, since they also have potent alpha-adrenergic properties. Yet significant increases in cardiac output with these drugs, consistent with potent inotropic effects, have been reported in septic patients.[54,73] In this regard, norepinephrine was shown to increase cardiac output to the same extent as dopamine for the same increase in MAP.[54] However, analysis of the existing literature indicates that the effects of norepinephrine on cardiac output are highly variable among septic patients.[74,75] By contrast, epinephrine appeared as a potent inotropic agent in most studies in septic patients.[70,76-78] However, epinephrine may impair splanchnic perfusion[79,80] and induce lactic acidosis,[81] despite its positive effects on cardiac output. Thus, epinephrine cannot be recommended as the first-choice drug when treatment of impaired cardiac contractility is considered. In the condition of depressed vascular tone and reduced myocardial function, epinephrine was even shown to be inferior to the combination of dobutamine and norepinephrine in terms of splanchnic perfusion, despite similar effects on systemic blood flow and pressure.[70,79,82]

Dopexamine

The pharmacologic properties of dopexamine should result in a combination of inotropic, afterload-reducing, and renal vasodilating effects, which could be useful for the management of acute exacerbation of congestive heart failure. In this regard, dopexamine was reported to substantially increase cardiac output in patients with heart failure without altering blood pressure: at doses up to 4 μg/kg/min, the majority of the effects resulted from an increase in stroke volume. At higher doses, the increase in heart rate made a greater contribution.[83] Similar results were found for the dose of 3 μg/kg/min in patients with acute respiratory failure and previous cardiomyopathy. In cases of human sepsis, dopexamine produced dose-dependent increases in stroke volume and heart rate but a dose-dependent decrease in SVR.[84] This underlines the marked vasodilating effect of this drug, which should not be administered in patients with severe sepsis in the absence of a potent vasopressor.

Under these conditions, dopexamine at doses ranging from 1 to 4 μg/kg/min could still enhance cardiac output without altering blood pressure.[85]

Phosphodiesterase Inhibitors

In patients with heart failure, phosphodiesterase inhibitors significantly increased cardiac output and stroke volume, while blood pressure slightly decreased due to a decrease in SVR, confirming the combined inotropic and vasodilating effects of these agents.[86] Because of the ability of beta-agonist agents to increase cAMP levels, thereby providing increased substrate for phosphodiesterase inhibitors, the combination of these two types of drugs would be attractive. Synergic effects on cardiac output of dobutamine and enoximone have been observed in patients with heart failure.[87] However, because of the disappointing results of trials of long-term oral phosphodiesterase inhibitor therapy in patients with chronic heart failure and of the OPTIME-CHF study in acute decompensation of congestive heart failure, the use of these agents is limited to a few categories of patients[88]: (1) patients with advanced heart failure awaiting transplantation, in whom intravenous milrinone may be better tolerated than dobutamine and its use may allow the continuation of beta-blocker therapy controlling arrhythmias or myocardial ischemia[89]; (2) patients with acute decompensation of chronic heart failure unable to achieve stabilization with standard treatment; and (3) patients with long-term beta-blocker use, in whom short-term intravenous milrinone may even be preferred to dobutamine. In septic patients, there is no recommendation to use these pharmacologic agents.

EFFECTS ON ARTERIAL OXYGEN CONTENT

The aim of inotropic therapy in critically ill patients with reduced cardiac contractility is not only to increase cardiac output but ultimately to improve oxygen delivery to the tissues. Thus, attention should be paid to the effects of these drugs on arterial oxygen content. Inotropes may affect arterial oxygen tension through several mechanisms. First, the reduction of lung filtration pressure resulting from improvement in cardiac function may decrease intrapulmonary shunt fraction and thus improve arterial oxygenation. Second, the increase in cardiac output may result in an increased venous admixture.[90] On the other hand, the increased mixed venous blood oxygen tension resulting from increased cardiac output may improve arterial oxygenation in the presence of ventilation/perfusion mismatching and thus may compensate for the increased venous admixture. Accordingly, when looking at the published data, it appears that even if venous admixture increased after dopamine[52,91,92] or dobutamine[52] administration, no significant change in arterial oxygen tension was observed with the use of any drug. Therefore, when an inotropic agent increases cardiac output in critically ill patients, it generally increases oxygen delivery to the same extent.[14,54,58,93]

EFFECTS ON TISSUE OXYGEN UTILIZATION

Even though an inotropic agent produces a large increase in oxygen delivery, its effectiveness in reducing oxygen deficit depends on its capacity to provide oxygen in the most hypoxic tissues. This concern is particularly crucial because, first, redistribution of blood flow is a characteristic pattern of shock states, and, second, inotropic drugs may also have vasoactive properties that interact with blood flow distribution.

Cardiogenic Shock

In this setting, redistribution of flow is recognized as a potent compensatory mechanism that, in response to reduced global oxygen delivery, attempts to deviate blood flow from nonvital organs with low oxygen extraction ratios toward vital organs with high oxygen extraction ratios, such as the heart or the brain. It must be kept in mind that administration of drugs with vasoactive properties may interfere with vasoregulation of regional blood flow. The extent to which this interference is beneficial in increasing oxygen supply and oxygen consumption in hypoxic areas remains speculative. This emphasizes the need to monitor, as far as possible, perfusion and function of critical organs.

Septic Shock

The maldistribution of flow at the macrocirculatory level as well as the microcirculatory level mainly contributes to defective tissue utilization and eventually to tissue oxygen debt in sepsis, even when systemic oxygen transport is greater than normal. Besides sepsis-induced microthrombosis, sepsis-induced alteration in vascular reactivity is a major cause of the altered distribution of blood flow between and within organs. In addition, severe sepsis can modify the impact of adrenergic drugs on regional blood flows, since a depressed vascular responsiveness to a vasoactive agent is likely to occur in this setting. This hypothesis may account for the absence of reduction of renal or splanchnic blood flow observed during vasoconstrictor therapy in endotoxic shock.[94] In cases of human sepsis, interference of sepsis-modified vasoactive drug properties by sepsis-induced macrocirculatory disturbances have been mostly investigated at the level of the splanchnic and the renal circulation.

Numerous clinical studies have examined the effects of adrenergic agents on splanchnic perfusion during sepsis. Their findings have sometimes varied, either because of differences in the methods used for assessing this regional circulation (e.g., gastric tonometry, laser-Doppler flowmetry, indocyanine green dilution) or because of the heterogeneity of the studied populations (e.g., differences in the severity of the septic insult, in the underlying diseases, in the therapy coadministered). However, from findings of the majority of these studies, some reasonable conclusions can be drawn. First, dobutamine is likely to exert a beneficial effect on the gut mucosal perfusion,[69,70,79,93] probably via a beta$_2$-adrenergic effect.[95] Second, dopamine may have deleterious effects on gut mucosal perfusion, despite its potential vasodilating action through mesenteric dopaminergic receptors. Third, epinephrine is probably the adrenergic agent with the least desirable effects on the splanchnic vasculature, as most studies showed a lower splanchnic blood flow with epinephrine than norepinephrine alone[80] or in combination with dobutamine,[69,70,79] even for global hemodynamic effects. Fourth, dopexamine can exert a favorable effect on splanchnic perfusion[19] comparable to that of dobutamine[69] and is likely to be related to a beta$_2$-adrenergic effect. Given all the available data, it is recommended that the combination of norepinephrine and dobutamine rather than epinephrine be used when an inotropic therapy is given to reverse cardiac dysfunction in severe sepsis.[32]

Regarding the effects of inotropic agents on the renal circulation in septic patients, two major points must be kept

in mind. First, an alpha-adrenergic agent, such as norepinephrine, is able to increase renal blood flow and urine output,[56,87,96] despite its potential vasoconstricting effect on the afferent glomerular arteries. This is probably due to the beneficial effect of increasing MAP when the renal blood flow is dependent on arterial pressure, as occurs in cases of profound systemic hypotension. Otherwise, a sepsis-induced depressed responsiveness of afferent glomerular arteries to the action of norepinephrine cannot be excluded. Accordingly, there is no evidence in the available literature that norepinephrine is capable of decreasing renal blood flow and urine output when given to septic patients to increase MAP toward normal values. Moreover, it has been demonstrated in patients with septic shock that elevating arterial pressure up to 85 mm Hg with incremental doses of norepinephrine was not associated with a decrease in urine output.[97] Second, although dopamine at low doses (<5 μg/kg/min) is pharmacologically able to vasodilate renal arteries through its action on dopaminergic receptors, the systematic administration of low doses of dopamine in critically ill patients, including patients with sepsis, does not result in improved outcome[98] and must no longer be recommended.

Finally, inotropic drugs may also exert nonhemodynamic effects that could affect cellular metabolism and/or organ function.[7,99] For example, catecholamines may modulate cytokine response to sepsis, trauma, or major surgery through beta-adrenergic receptor activation.[7] Whether this effect (inhibition of proinflammatory cytokines and enhancement of proinflammatory cytokine production) plays a beneficial role in the reversal of tissue hypoxia and organ dysfunction remains to be evaluated.

ANNOTATED REFERENCES

Bellomo R, Chapman M, Finfer S, et al: Low-dose dopamine in patients with early renal dysfunction: A placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet 2000;356:2139-2143.

Despite the effect of dopamine at low doses on renal dopaminergic receptors, the administration of low-dose dopamine in critically ill patients at risk of renal failure does not result in any benefit in terms of renal dysfunction or outcome. This result underlines the difficulty of extrapolating pharmacologic properties of therapeutic agents to clinical effects, in particular in critically ill patients.

Boyd O, Grounds M, Bennett D: A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 1993;270:2699-2707.

This monocentric randomized study demonstrated that deliberate increase in oxygen delivery toward supranormal values with dopexamine during the perioperative period was able to decrease mortality and complication rates dramatically in high-risk surgical patients.

Duranteau J, Sitbon P, Teboul JL, et al: Effects of epinephrine, norepinephrine or the combination of norepinephrine and dobutamine on gastric mucosa in septic shock. Crit Care Med 1999;27:893-900.

In this cross-over study in patients with septic shock, the addition of low-dose dobutamine to norepinephrine significantly increased gastric mucosal blood flow assessed with laser Doppler flowmetry while cardiac output and mean arterial pressure remained constant, suggesting a proper vasodilatory effect of dobutamine in this regional area. On the other hand, epinephrine at doses maintaining the same mean arterial pressure as norepinephrine did not produce any significant increase in gastric mucosal blood flow despite a large increase in cardiac output. This study confirms that catecholamines are not all equal in terms of regional blood flow.

Hayes MA, Timmins AC, Yau E, et al: Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994;330:1717-1722.

This randomized study showed that attempting to achieve supranormal values of oxygen delivery in patients with an established critical illness may worsen rather than improve outcome.

Silverman HJ, Penaranda R, Orens JB, et al: Impaired beta-adrenergic receptor stimulation of cyclic adenosine monophosphate in human septic shock: Association with myocardial hyporesponsiveness to catecholamines. Crit Care Med 1993;21:31-39.

This clinical study demonstrated that patients with septic shock exhibit a decreased hemodynamic response to dobutamine when compared with septic patients without shock. Moreover, the stimulation of circulating lymphocytes of the studied population showed that in patients with septic shock, the degree of impairment of beta-adrenergic receptor responsiveness as well as that of post-beta-adrenergic receptor signal transmission was higher than in septic patients without shock. This study provides strong evidence of a septic shock-related myocardial hyporesponsiveness to catecholamines that may contribute to the reduced myocardial performance observed in this critical illness.

Chapter 110
MECHANICAL SUPPORT IN CARDIOGENIC SHOCK

Thomas G. Gleason • Mariell Jessup

KEY POINTS

1. The **leading cause of death among hospitalized patients** with acute myocardial infarction (AMI) continues to be cardiogenic shock.
2. **Intra-aortic counterpulsation for patients in shock after AMI** is used in only 22% of eligible patients.
3. Pioneering surgeons recognized by the 1960s that **left ventricular decompression and myocardial rest** could afford enhanced cardiac recovery after the insult of open-heart surgery.
4. The **physiologic rationale for the efficacy of the intra-aortic balloon pump (IABP)** includes (a) left ventricular systolic unloading directly reduces stroke work, which in turn reduces myocardial oxygen consumption during the cardiac cycle, and (b) diastolic augmentation raises arterial blood pressure and provides better coronary arterial perfusion during diastole, yielding increased oxygen delivery to the myocardium.
5. The **absolute indications for IABP placement** include cardiogenic shock, uncontrolled angina pectoris, acute postinfarction ventricular septal defect or mitral regurgitation, and postcardiotomy left-sided heart failure with low cardiac output.
6. In the aforementioned settings in the previous point, **IABP should be considered a primary therapy** that should not be delayed until noncardiac injury is clinically evident.
7. **Cardiogenic shock and high-risk angioplasty** are the most common indications for use of the IABP.
8. The SHOCK trial showed that **early revascularization of patients with coronary artery disease and shock after AMI,** often facilitated by IABP use (86%), yielded a lower 6-month mortality rate (50%) than with medical therapy alone (63%).
9. **Timing of IABP** can be synchronized in one of three ways: using an arterial (preferably aortic) pressure tracing in synchrony with the dicrotic notch, using the descent of the R wave on a rhythm tracing, or timed after a ventricular pacing spike when a pacemaker is in use.
10. The effectiveness of IABP is significantly improved by **proper timing of inflation and deflation.**
11. **Relative contraindications to IABP use** include severe atheromatous and atherosclerotic descending thoracic aorta, descending aortic aneurysm, recent descending thoracic aortic surgery, and mild to moderate aortic insufficiency.
12. The **incidence of major vascular complications** according to the STS National Database (1996-1997) and the Benchmark Registry (1997-1999) is 5.4% and 1.4%, respectively.
13. It is clear that the **mortality rate of cardiogenic shock after AMI remains high** at 39%.
14. **IABP support, combined with revascularization,** portends a better prognosis than adjunctive IABP use with medical therapy alone.
15. **Short-term cardiopulmonary support for cardiogenic shock has emerged as an important adjunctive therapy.** It is a relatively simple means of establishing immediate and complete circulatory support, requiring no additional equipment other than that needed for standard cardiopulmonary bypass support during cardiac surgery.
16. **VADs that utilize direct cardiac outflow cannulation** (VAD inflow) provide better ventricular decompression and rest than peripheral bypass support systems.
17. **Two advantages to the Thoratec system** are the ability of secure ventricular inflow (VAD) cannulation and the applicability of long-term utilization.
18. The **hallmarks of cardiogenic shock** are low cardiac output, hypotension, peripheral vasoconstriction, cold extremities, poor urine output, and altered mental status.
19. **Intrinsic causes of cardiogenic shock** can be divided into four pathophysiologic classifications: (a) acute valvular insufficiency, (b) acute myocardial infarction, (c) acute myocarditis, and (d) postcardiotomy cardiac failure.
20. **Insertion of a pulmonary arterial balloon catheter and echocardiography** should be done to help formulate a differential diagnosis.

21. **Cardiogenic shock after AMI requires immediate IABP placement,** often with additional pharmacologic support.
22. **Initial placement of implantable VADs** (e.g., HeartMate or Novacor) for mechanical support in patients with cardiogenic shock is generally not indicated.

An estimated 61.8 million people in the United States have heart disease, among whom 950,000 die annually.[1] Of these, 540,000 people suffer myocardial infarctions each year; 193,000 succumb to complications directly related to the infarction. The leading cause of death among hospitalized patients with acute myocardial infarction (AMI) continues to be cardiogenic shock.[2] The incidence of cardiogenic shock complicating AMI (approximately 7%) has remained constant over the past 25 years. Accurate statistics on the worldwide utilization of all mechanical support for cardiogenic shock are not known. However, estimates on the use of intra-aortic counterpulsation for patients in shock after AMI suggest a rate of use in only 22% of eligible patients.[3] The reasons for the apparent underutilization of this readily available modality are not clear. Accordingly, the indications, benefits, and limitations of mechanical cardiac support are outlined in this chapter.

HISTORICAL BACKGROUND

The evolution of mechanical cardiac support dates to the early 1950s when Gibbon developed the prototype cardiopulmonary bypass (CPB) apparatus.[4] In the years following, Lillehei, Kirklin, and others applied the heart-lung machine to facilitate open-heart surgery; their pioneering work and early observations led directly to the development of modern mechanical cardiac support systems.[5-7] These surgeons recognized that some patients had improved outcomes after surgery if they were weaned slowly rather than abruptly from CPB support. Their initial publications introduced the concept that left ventricular (LV) decompression and myocardial rest could afford enhanced cardiac recovery after the insult of open-heart surgery. Clinical use of extracorporeal CPB for heart surgery became widespread in the early 1960s. Simultaneously, several groups of investigators were testing means of mechanical cardiac assistance for use outside the operating room for support of patients in cardiogenic shock. The current modes of mechanical support are derivations of those originally developed and include aortic counterpulsation, continuous flow pumps with or without an oxygenator, and pulsatile pumps.

HISTORY OF AORTIC COUNTERPULSATION

The concept of arterial counterpulsation was introduced in 1961 by Clauss and coworkers and involved use of an external "ventricular" chamber that filled with blood from a catheter in the iliac artery[8] and was subsequently compressed by a piston. Compression of the "ventricle" was synchronized to either the QRS complex of an electrocardiogram (ECG) or the impulse of a pacemaker, so that a counter pulse of blood was delivered into the arterial system during diastole. It was demonstrated in dogs that cardiac stroke work and LV end-systolic pressures could be substantially reduced with the use of a counterpulsation into the aorta. The following year Moulopaulus and associates adapted the model to create an intra-aortic balloon pump (IABP) that could provide a similar counterpulsation without the need for blood reservoirs.[9] The investigators used a balloon that was rapidly inflated and deflated with carbon dioxide during native diastole. The IABP was subsequently adapted and described for clinical use by Kantrowitz and colleagues in 1968.[10]

The original polyurethane balloon measured 1.8 cm in diameter by 14.8 cm in length when inflated (helium was used because its low density allows rapid delivery to and from the balloon) and displaced 32 mL of blood. There is little difference in the modern IABP and that originally described, other than the availability of different-sized balloons (30- to 50-mL balloons) and subtle differences in the materials used to make the catheters. The extracorporeal components of the IABP now include an electronically controlled pump with a solenoid valve in continuity with a pressurized helium source. The valve controls the flow of helium into and out of the balloon at intervals timed to either pressure changes on an arterial transducer, ECG signals (i.e., the QRS complex), or a ventricular pacer signal. This timing of balloon inflation and deflation is critical to attain optimal physiologic benefit of the cardiac support.

The physiologic rationale for the efficacy of the IABP is that balloon deflation provides a rapid, synchronized reduction in impedance (afterload) during isovolemic LV contraction. This is followed by a rapid, synchronized increase in aortic pressure during isovolemic LV relaxation (diastolic augmentation) caused by balloon inflation. In combination these events achieve two important goals. First, LV systolic unloading directly reduces stroke work, which in turn reduces myocardial oxygen consumption during the cardiac cycle. Second, diastolic augmentation raises arterial blood pressure and provides better coronary arterial perfusion during diastole, yielding increased oxygen delivery to the myocardium. The IABP does not directly move or redistribute blood flow; however, peak diastolic coronary flow velocity can be increased as much as 87% with IABP augmentation and peak diastolic flow velocity by as much as 117%.[11] Since introduction into clinical use in 1968, the IABP has remained an important adjunct to supporting patients in cardiogenic shock. Myocardial recovery is promoted by the reduction of cardiac work and the simultaneous increase in myocardial oxygen supply. However, therapeutic success is dependent on the patient having a minimum degree of left ventricular function that, in combination with IABP support, facilitates an adequate cardiac output to sustain end-organ function. When this minimal cardiac output is not met, alternative mechanical cardiac assistance must be considered.

HISTORY OF MECHANICAL ASSIST DEVICES

The need for effective mechanical cardiac assist devices became apparent in the 1950s during the development of CPB for open-heart surgery. Initial attempts with prolonged postoperative CPB demonstrated that the bypass circuit was damaging to both end-organ function and blood constituents after several hours of use.[12] The first attempt at isolated extracorporeal LV support was with a simple roller pump in 1962.[13] Subsequently, femoral venous-to-femoral arterial CPB was

successfully used by Spencer and colleagues in four patients with postcardiotomy cardiac failure.[14]

Simultaneous to Spencer and colleagues' work with extracorporeal systems, DeBakey designed the first intracorporeal LV assist device (LVAD), the DeBakey blood pump.[15] This device consisted of a Dacron-reinforced silicone rubber tube with an inner chamber of blood from the left atrium that was connected to the descending thoracic aorta. Pressurized air was instilled into the outer chamber by an external pneumatic controller to compress the inner blood chamber, timed to the R wave of the QRS complex. Blood flow was directed from the left atrium to the descending aorta with the use of ball valves at both the inflow and outflow ends of the device. The DeBakey blood pump was first used in a patient who died 4 days postoperatively of neurologic complications. A remodeled extracorporeal version was subsequently used for postcardiotomy failure in a 37-year-old woman after aortic and mitral valve replacements. The device was needed for 10 days, but the patient survived.[16]

By 1972, investigators at the Texas Heart Institute had developed a pneumatically driven LVAD designed to be implanted in the abdomen.[17] This device had a blood chamber compressed by pulses of air delivered into the pump by a percutaneous driveline. Modern devices have chamber compression that is electrically powered via percutaneous drivelines. Paracorporeal, pneumatically driven devices were a parallel development. Paramount to the evolution of these devices was the sponsorship of the Artificial Heart Program of the National Heart, Lung, and Blood Institute, which was chartered in 1964.

By the 1960s, continuous flow, as compared to pulsatile, pumps were under development.[18,19] Over the subsequent 15 years, centrifugal pumps were perfected and introduced into clinical use. These pumps work on the principle of a forced, constrained vortex devised from three magnetic cones.[20-22] They have been shown to be useful in a variety of clinical settings where short-term mechanical support is needed and an IABP is inadequate. Several types of small, axial-flow or rotary pumps have also been developed.[23-36] These are generally constructed of a magnetically suspended impeller that rotates at extremely fast rates (25,000 to 35,000 rpm). The axial rotary pump technology has some potential advantages over pulsatile devices; they are quite small with few moving parts and do not require a compliance chamber.

CURRENT MECHANICAL SUPPORT DEVICES

COUNTERPULSATION/INTRA-AORTIC BALLOON PUMP

Indications

The absolute indications for IABP placement include cardiogenic shock, uncontrolled angina pectoris, acute postinfarction ventricular septal defect or mitral regurgitation, and postcardiotomy left-sided heart failure with low cardiac output. In these settings, IABP should be considered a primary therapy that should not be delayed until noncardiac injury is clinically evident. It is important to recognize that blood pressure alone is not an adequate indication of hemodynamic or cardiac stability. Limb perfusion, renal function, mental status, and even gastrointestinal function need to be considered in the assessment of adequate resuscitation and homeostasis. Additional measurable indices include arterial (SaO_2) and mixed venous oxygen saturation ($S\bar{v}O_2$), acid-base status, urine output, and body temperature. A multivariate analysis of data accrued from 391 postcardiotomy patients requiring IABP demonstrated that epinephrine requirements greater than 0.5 μg/kg/min, a left atrial pressure greater than 15 mm Hg, urine output less than 100 mL/h, and $S\bar{v}O_2$ less than 60% correlated with mortality.[37] These criteria were used to help predict mortality and the need for subsequent mechanical support.

Other relative indications for IABP use include (1) high-risk, catheter-based interventional procedures such as left main coronary artery angioplasty, (2) after unsuccessful attempts at catheter-based intervention in patients with poorly controlled ventricular arrhythmias, and (3) concomitant poor LV function, and (4) in settings of persistent stunned, ischemic myocardium. These are all circumstances in which reduction of LV systolic wall tension and oxygen consumption by the IABP might enhance myocardial recovery after intervention. Conversely, the use of an IABP had no impact on mortality in a population of patients without hemodynamic instability undergoing high-risk angioplasty randomized in a prospective trial reported in 1997.[38] More recently, the Benchmark Counterpulsation Outcomes Registry of IABP use in 22,663 patients from 250 hospitals worldwide demonstrated that cardiogenic shock and high-risk angioplasty were the most common indications for utilization of the device.[39] Table 110-1 depicts a further characterization of the Benchmark report with respect to indications for use of the IABP and subsequent interventions.[40] Nevertheless, despite the widespread use of the IABP in over 150,000 patients worldwide each year,[41] no prospective, randomized trial has ever demonstrated a survival benefit with IABP use in the patient population undergoing high-risk catheter intervention. In contrast, the SHOCK trial showed that early revascularization of patients with coronary artery disease and shock after an AMI, often facilitated by IABP use (86%), yielded a lower 6-month mortality rate (50%) than with medical therapy alone (63%).[2] Additional studies have shown that in patients undergoing urgent or emergent revascularization after an AMI, those supported preoperatively with an IABP had a lower operative mortality than those in whom an IABP was not used (5.3% to 8.8% vs. 11.8% to 28.2%).[42,43] These data seem to justify a strategy of aggressive IABP use to facilitate early revascularization in the postinfarction patient.

Technical Considerations

The optimal site of insertion of an IABP is a common femoral artery that can be accessed either percutaneously with the use of a guidewire or by surgical cutdown. Modern intra-aortic balloon catheters are available for adults and children, according to the appropriate size and length for a given height and weight of the patient. Adult intra-aortic balloons have a range in volume filled between 25 and 50 mL, with a standard balloon size holding 40 mL of helium. IABP catheters placed through the femoral artery are positioned so that the tip is just distal to the takeoff of the left subclavian artery in the proximal descending thoracic aorta. Optimally, the tip of the catheter should be positioned with transesophageal echocardiographic (TEE) or fluoroscopic guidance.[44] To reduce the diameter of femoral cannulation, a sheathless IABP technique can be utilized and is our preferred method.[45]

Inflation of the balloon should be timed with closure of the aortic valve (at the dicrotic notch of the aortic pressure tracing) and should be inflated to nearly occlude the descending

TABLE 110–1. INDICATIONS FOR USE

	Total Population (n = 16,909)	Diagnostic Catheterization Only (n = 1,576)	Catheterization & PCI Only (n = 3,882)	Surgery		No Intervention (n = 1,186)
				CABG (n = 9,179)	*Non-CABG (n = 1,086)*	
Support and stabilization (%)	20.6	21.4	54.4	9.7	5.0	7.8
Cardiogenic shock (%)	18.8	33.1	23.7	12.3	23.8	29.4
Weaning from cardiopulmonary bypass (%)	16.1	0.4	0.1	24.9	31.4	7.1
Preop: high risk CABG (%)	13.0	4.6	0.2	22.1	6.4	1.9
Refractory unstable angina (%)	12.3	15.3	8.3	15.8	2.2	3.0
Refractory ventricular failure (%)	6.5	9.1	2.5	5.9	15.7	12.7
Mechanical complication due to AMI (%)	5.5	9.8	7.0	4.2	5.2	5.1
Ischemia related to intractable VA (%)	1.7	1.6	1.5	1.9	1.7	1.6
Cardiac support for high-risk general surgery (%)	0.9	2.1	0.2	0.5	4.3	1.1
Other (%)	0.8	0.7	0.2	0.8	2.5	2.0
Intraoperative pulsatile flow (%)	0.4	0.1	0.1	0.7	0.5	0.2
Missing indication (%)	3.3	1.8	1.9	1.2	1.5	28.1

AMI, Acute myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; VA, ventricular arrhythmias.
Modified from Ferguson JJ 3rd, Cohen M, Freedman RJ Jr, et al: The current practice of intra-aortic balloon counterpulsation: Results from the Benchmark Registry. J Am Coll Cardiol 2001;38:1456-1462.

thoracic aorta. Timing can be synchronized in one of three ways: (1) using an arterial (preferably aortic) pressure tracing in synchrony with the dicrotic notch, (2) using the descent of the R wave on a rhythm tracing, or (3) timed after a ventricular pacing spike when a pacemaker is in use.[46-50] The effectiveness of IABP is significantly improved by proper timing of inflation and deflation, which can be difficult when there is an accelerated heart rate, cardiac rhythm disturbances, atrioventricular dyssynchrony, or low mean arterial pressure. IABP timing should be adjusted to maximize diastolic augmentation; hence, deflation should be as late as possible but just before opening of the aortic valve. If this cannot be gauged by the pressure tracing, it can be timed to the onset of the R wave on the ECG tracing or with the use of M-mode echocardiography.[51]

IABP catheters should not be left in place after weaning because of the risk of thrombus formation and embolization. An IABP should be weaned stepwise from a rate that is equivalent to heart rate (1:1) down to a ratio of 1:3 just before removal. Balloon catheters placed via an open surgical technique should also be removed surgically. Percutaneous removal of catheters placed in the iliac artery above the inguinal ligament (often done in obese individuals) can result in significant retroperitoneal bleeding. Consideration of operative removal is warranted.

When femoral arterial cannulation is not desirable due to aortoiliac occlusive disease or extensive peripheral vascular disease, the subclavian artery or the ascending aorta can be utilized.[52-56] With either technique, the IABP catheters are advanced antegrade down the descending thoracic aorta so that the balloon tip sits above the level of the diaphragmatic hiatus, and the most proximal end of the balloon is distal to the takeoff of the left subclavian. These antegrade balloons should always be placed with either fluoroscopic or echocardiographic guidance. They should be removed with open arterial repair in all cases.

Relative contraindications to IABP use include severe atheromatous and atherosclerotic descending thoracic aorta, descending aortic dissection or aneurysm, recent descending thoracic aortic surgery, and mild to moderate aortic insufficiency. Severe aortic insufficiency is an absolute contraindication to use because diastolic augmentation cannot be accomplished, and LV end-diastolic volume and pressure are actually increased rather than decreased.

Complications

The overall complication rate of IABP utilization is 6.5% to 8.1%. Major complications occur at a rate of 2.7% and include severe bleeding, major limb ischemia or amputation, infection, visceral or spinal cord ischemia, and attributable IABP mortality.[39,43] A summary of IABP complications as they occur in relation to subsequent percutaneous or operative coronary revascularization from the Benchmark Registry are listed in Table 110-2.[40] In this registry, rates of complications were quite low, the most common being access-site bleeding (4.3%) and limb ischemia (2.3%).[39] The rates of amputation, stroke, visceral or spinal cord ischemia and IABP-related mortality are all 0.1% or less.[39] Intra-aortic balloon entrapment is a rare complication.[57-59] The incidence of major vascular complications according to the STS National Database (1996-1997) and the Benchmark Registry (1997-1999) is 5.4% and 1.4%, respectively.[40,43] Ipsilateral limb ischemia should be immediately addressed after its recognition. This usually requires removal of the IABP with replacement at another location if it is still indicated. The ischemic limb may require thrombectomy with or without revascularization and fasciotomy.[60-66]

Outcomes

In the absence of prospective, randomized data it is difficult to ascribe outcome secondary to IABP placement. The Second Angioplasty in Myocardial Infarction (PAMI-II) Trial data examined high-risk patients with acute myocardial infarction revascularized by percutaneous intervention only and demonstrated a modest survival advantage at 6 months with the use of periprocedural IABP support.[38] When evaluating hospital mortality rates among patients undergoing coronary artery bypass graft (CABG) and/or valve surgery who received

TABLE 110–2. IABP OUTCOMES AND COMPLICATIONS

	Total Population (n = 16,909)	Diagnostic Catheterization Only (n = 1,576)	Catheterization & PCI Only (n = 3,882)	Surgery		No Intervention (n = 1,186)
				CABG (n = 9,179)	*Non-CABG (n = 1,086)*	
In-hospital mortality (%)	21.2	32.2	18.4	16.8	37.8	34.1
Mortality: balloon in place (%)	11.6	17.6	10.1	9.2	19.8	20.2
IABP-related mortality* (%)	0.05	0.1	0.1	0.0	0.0	0.1
Amputation†	0.1	0.0	0.1	0.1	0.1	0.0
Major limb ischemia‡ (%)	0.9	0.6	0.5	1.2	1.0	0.5
Any limb ischemia (%)	2.9	3.2	1.9	3.5	2.5	1.7
Severe access site bleeding (%)	0.8	0.8	1.2	0.7	0.7	0.3
Any access site bleeding (%)	2.4	2.7	4.4	1.7	1.3	1.4
Balloon leak (%)	1.0	0.9	0.8	1.1	0.5	1.6
Composite Outcomes						
Major IABP complication§ (%)	2.8	2.8	2.2	3.0	2.9	2.4
Any IABP complication‖ (%)	7.0	7.6	7.5	7.1	6.0	5.2
Any unsuccessful IABP¶ (%)	2.3	2.5	1.7	2.5	2.4	2.7

CABG, coronary artery bypass graft; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention.
*Death as direct consequence of IABP therapy.
†All major limb ischemia.
‡Loss of pulse or sensation, abnormal limb temperature, or pallor, requiring surgical intervention.
§Balloon leak, severe bleeding, major limb ischemia, or death as a direct consequence of IABP therapy.
‖Any access site bleeding, any limb ischemia, balloon leak, poor inflation, poor augmentation, insertion difficulty, or death as direct result of IABP therapy.
¶Balloon leak, poor inflation, poor augmentation, or insertion difficulty.
From Ferguson JJ 3rd, Cohen M, Freedman RJ Jr, et al: The current practice of intra-aortic balloon counterpulsation: Results from the Benchmark Registry. J Am Coll Cardiol 2001;38:1456-1462.

preoperative IABP or required intraoperative/postoperative IABP support, it is evident that mortality was significantly lower among patients supported preoperatively, as depicted in Table 110-3.[40,43] Hence, there appears to be a survival advantage to earlier IABP support for patients with AMI and cardiogenic shock who need revascularization. In the setting of an acute ventricular septal defect (VSD) or acute mitral regurgitation after an AMI, IABP support can offer a dramatic improvement in the hemodynamic response of the patient.[67-71] Figures 110-1 and 110-2 stratify hospital mortality rates associated with IABP use in patients with AMI by principal usage indication or by performance of percutaneous or surgical coronary revascularization. It is clear that the mortality rate of cardiogenic shock after AMI remains high at 39%. However, IABP support, combined with revascularization, portends a better prognosis than adjunctive IABP use with medical therapy alone.[39]

CONTINUOUS FLOW PUMPS

Both roller pumps and centrifugal pumps deliver continuous flow, but have other, distinct limitations. Roller pumps remain in widespread use for cardiopulmonary support during cardiac surgery; applications outside the operating room have been virtually abandoned for several reasons. Roller pumps are insensitive to changes in arterial line resistance that may cause disruption of the apparatus. They require unobstructed venous flow. The rollers eventually cause spallation of tubing, leading to particle emboli and weakening of the tubing.[72] Roller compression causes hemolysis after prolonged use.[73]

Alternatively, centrifugal pumps are sensitive to both outflow resistance and filling pressure, offering a safer applicability outside the operating room. Centrifugal pumps like the Bio-Medicus Biopump (Medtronic, Corp., Minneapolis, MN) generate a constrained vortex within an acrylic shell

TABLE 110–3. HOSPITAL MORTALITY (OUTCOME PARAMETER) FOR PATIENTS UNDERGOING CARDIAC SURGERY WHO EITHER RECEIVED PREOPERATIVE IABP OR INTRA-/POSTOPERATIVE IABP SUPPORT

Type of Therapy	Benchmark Registry 1997-1999 Mortality/Total Operations with IABP, n (%)	STS National Database 1996-1997 Mortality/Total Operations with IABP, n (%)	STS National Database 1996-1997 Mortality/Total Operations without IABP, n (%)
Preoperative IABP	8.8 (329/3,721)	9.5 (2,487/26,077)	2.9 (10,919/378,810)
Intraoperative/ postoperative IABP	28.2 (954/3,380)	23.6 (3,528/14,933)	2.5 (9,878/389,954)

Based on data from the Benchmark Counterpulsation Registry 1997-1999 and the STS National Database 1996-97 compared with hospital mortality for patients who had neither preoperative nor intraoperative/postoperative IABP support.
From Christenson JT, Cohen M, Ferguson JJ 3rd, et al: Trends in intraaortic balloon counterpulsation: Complications and outcomes in cardiac surgery. Ann Thorac Surg 2002;74:1086-1090.

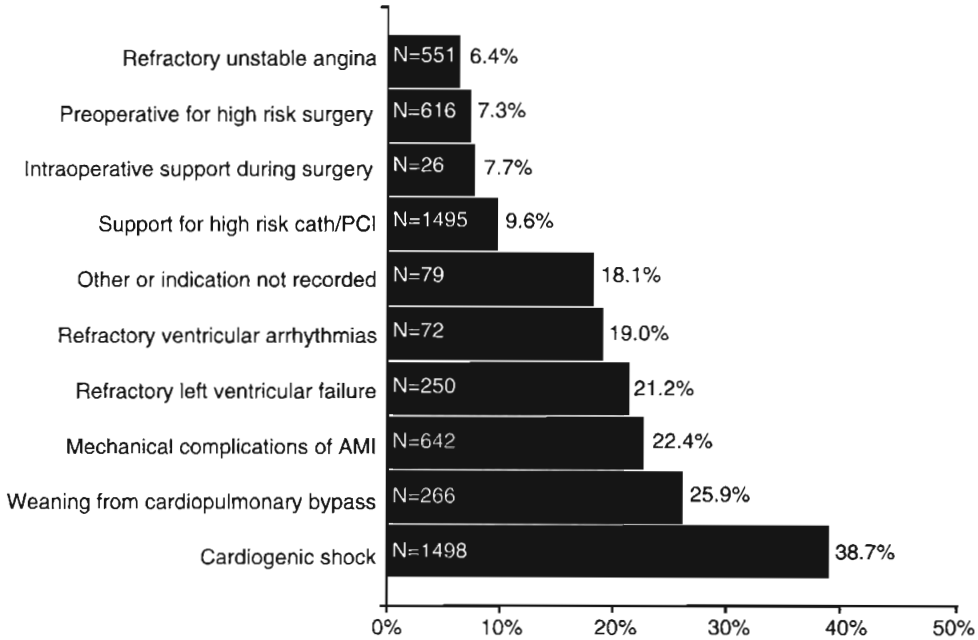

FIGURE 110–1. In-hospital mortality of 5,495 patients with acute myocardial infarction (AMI) requiring intra-aortic balloon pump counterpulsation, stratified by principal usage indication. PCI, percutaneous coronary intervention. (From Stone GW, Ohman EM, Miller MF, et al: Contemporary utilization and outcomes of intra-aortic balloon counterpulsation in acute myocardial infarction: The benchmark registry. J Am Coll Cardiol 2003;41:1940-1945.)

that houses concentric magnetic cones. The cones rotate as a magnetic rotary motor spins adjacent to the base of the cones[20-22] and can generate very high flows with less trauma to blood cells than roller pumps.[73-75]

The technology of centrifugal pumps, axial flow pumps, and membrane oxygenators has remarkably improved. Pump durability and reduced blood cell trauma have been demonstrated.[19,26,73-76] As a result, considerable experience has accumulated with the use of centrifugal pumps (cardiopulmonary support) for postcardiotomy LV failure, fulminant myocarditis, or cardiogenic shock after AMI.[32,77-93]

Indications

Short-term cardiopulmonary support for cardiogenic shock has emerged as an important adjunctive therapy. It is a relatively simple means of establishing immediate and complete circulatory support, requiring no additional equipment other than that needed for standard CPB support during cardiac surgery. Cardiopulmonary support can be initiated percutaneously via the common femoral artery and vein. Alternatively, when faced with postcardiotomy LV failure, cardiopulmonary support can facilitate patient stabilization for subsequent transport to a tertiary medical center for VAD placement. Cardiopulmonary support circuits can be converted to longer-term support (beyond 6 to 8 hours) by upgrading the oxygenator.[94,95] A standard microporous hollow-fiber oxygenator (the type used in most CPB circuits) has a life span of 6 to 12 hours.[96] Changing to a solid-silicone membrane oxygenator (not microporous) will lengthen the life span of the cardiopulmonary support circuit up to 21 days; this conversion constitutes extracorporeal membrane oxygenation (ECMO) support. ECMO is generally used in the adult population for periods of 1 to 10 days when there is marked concomitant pulmonary insufficiency and cardiac failure.

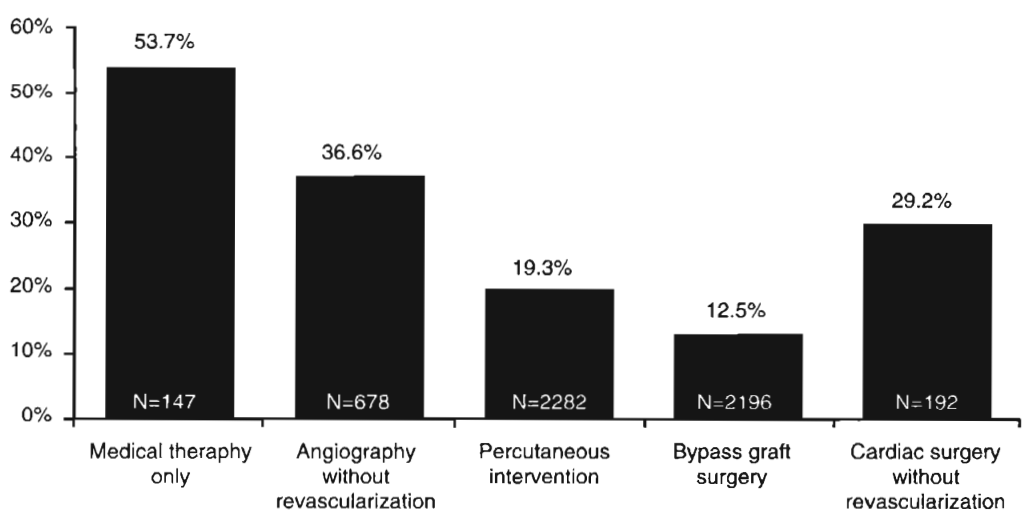

FIGURE 110–2. In-hospital mortality stratified by the performance of angiography and percutaneous or surgical coronary revascularization. (From Stone GW, Ohman EM, Miller MF, et al: Contemporary utilization and outcomes of intra-aortic balloon counterpulsation in acute myocardial infarction: The benchmark registry. J Am Coll Cardiol 2003;41:1940-1945.)

ECMO is also used for short-term (1 to 3 days) support when the neurologic status of a patient is unclear and longer-term support (i.e., VAD support) may not be appropriate until this status is clarified. Thus, ECMO can be used as a bridge to a longer-term, pulsatile flow assist device once the suitability of the patient is determined.

Technical Considerations and Complications

Disadvantages to the use of peripheral cardiopulmonary support or ECMO include the greater potential for ipsilateral limb complications, higher rates of hemolysis, the requirement for anticoagulation to prevent thrombosis of the oxygenator and circuit, and failure to adequately decompress the left ventricle.[97-103] Inadequate LV decompression with peripheral cardiopulmonary support/ECMO systems may be the mechanism responsible for some treatment failures. Regardless of the etiology of cardiogenic shock, a rested ventricle (i.e., decompressed) has a better chance of recovery than a distended ventricle.

Outcomes

The use of ECMO in the adult population for reasons other than primary cardiac failure with secondary pulmonary insufficiency has limited advantages over conventional therapies.[104,105] However, a substantial subset of patients who present with cardiogenic shock and are initially resuscitated with cardiopulmonary support/ECMO survive to revascularization, transplantation, or recovery, with survival rates as high as 75%.[77,78,81,82,106-112] ECMO used as a bridge to VAD placement for profound cardiogenic shock ("double bridge" mechanical assistance) can yield survival rates greater than 40%.[80] This strategy is pragmatic and offers immediate end-organ support while a subsequent definitive treatment plan can be designed.

VENTRICULAR ASSIST DEVICES

Pulsatile Pumps

There is a growing body of evidence suggesting that pulsatile assisted circulation, in the setting of acute cardiogenic shock, offers improved end-organ perfusion and lymphatic flow and is thus beneficial.[113-115] VADs that utilize direct cardiac outflow cannulation (VAD inflow) provide better ventricular decompression and rest than peripheral bypass support systems. There are now several mechanical assist devices that achieve these goals, including the extracorporeal ABIOMED BVS 5000 (ABIOMED, Inc., Danvers, MA) and the paracorporeal Thoratec VAD system (Thoratec Corp., Pleasanton, CA). Two other implantable, intracorporeal, pulsatile VADs that were designed for patients with chronic heart failure may have roles in certain subsets of patients with acute cardiogenic shock. These are the HeartMate LVAS XVE (Thoratec Corp., Pleasanton, CA) and the Novacor LVAS (World Heart Corp., Ottawa, Ontario).

Extracorporeal Short-term Support (ABIOMED)

The ABIOMED BVS 5000 was developed in the 1980s and was granted approval for use for postcardiotomy heart failure by the U.S. Food and Drug Administration in 1992.[116] Since that time, indications for the device have been broadened to include most patients with either postcardiotomy shock or precardiotomy shock who do not adequately respond to inotropes and an IABP. The ABIOMED system is a pneumatically driven, dual-chamber blood pump that delivers

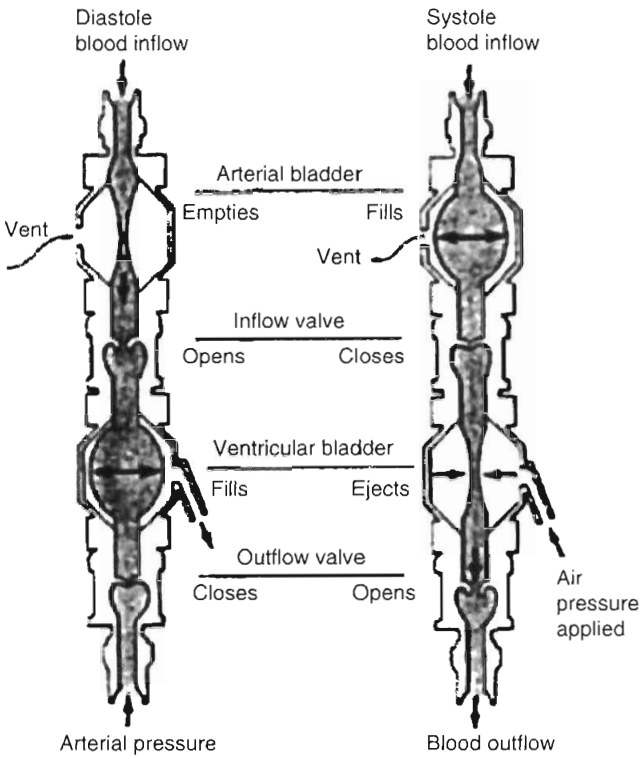

FIGURE 110–3. The ABIOMED BVS 5000. **Left,** The atrial chamber empties through a one-way valve into the ventricular chamber (diastole). **Right,** The pneumatically driven pump compresses the ventricular chamber and blood flows through a one-way valve into the patient (systole). The atrial chamber fills by gravity during pump systole. (From Moazami N, McCarthy PM: Temporary circulatory support. In Cohn LH, Edmunds LH Jr [eds]: Cardiac Surgery in the Adult. New York, McGraw-Hill, 2003.)

pulsatile flow. ABIOMED inflow cannulas are placed in the left and/or right atrium for univentricular or biventricular support. Outflow cannulas are housed with a Hemashield graft (Meadox Medicals Inc., Oakland CA) and are sewn to the aorta and/or pulmonary artery for left-sided and/or right-sided heart support. The pumps, as depicted in Figure 110-3, are extracorporeal. The upper (first) chamber fills passively by gravity, and the lower chamber serves as the pumping chamber. The two chambers are separated by a polyurethane trileaflet inflow valve; the lower chamber is separated from the arterial circulation by an outflow valve that prevents retrograde flow. As the pumping chamber is filled with blood, the surrounding air within the polycarbonate housing is displaced back into the drive console. This is sensed by the console; the console delivers compressed air back into the pumping chamber, which compresses the bladder and forces a pulse of blood into the arterial circulation.[116] The stroke volume that results is 70 to 80 mL with VAD output dependent on the rate of upper chamber filling. Flows of 5 L/min are typical for the ABIOMED system. This VAD requires anticoagulation, particularly for LV assistance. The device is generally useful for short-term (< 7 to 10 days) support because of the increased risk of thromboembolic complications or device malfunction beyond this period. If longer support is necessary, the ABIOMED pump can be exchanged with a new device or converted to a longer-term VAD system such as the Thoratec, HeartMate, or Novacor.

ABIOMED cannulation can be achieved either on or off CPB and with or without aortic cross-clamping. However, the condition of the patient is typically unstable, and cannulation,

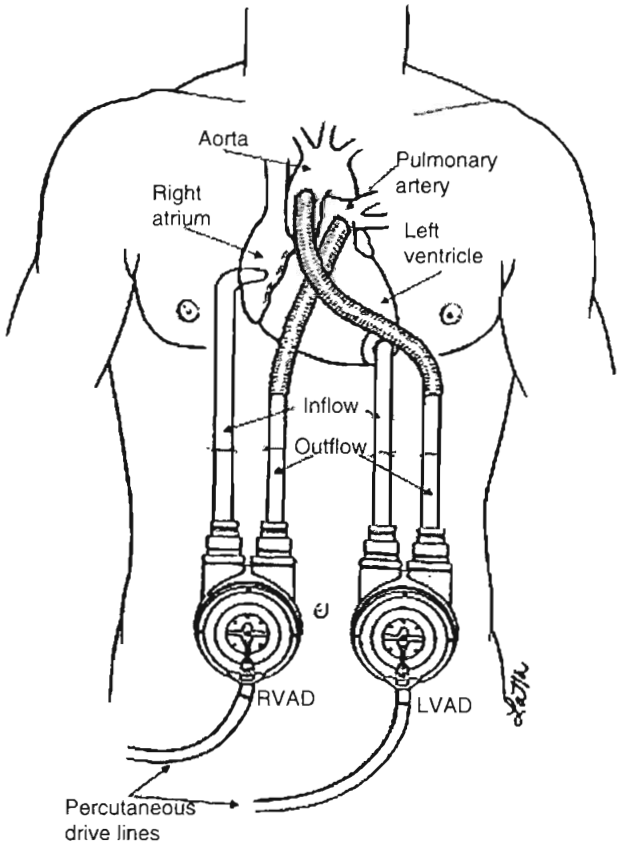

FIGURE 110–4. Thoratec ventricular assist system: a paracorporeal, pneumatically powered system configured for uni- or biventricular support. (From Hunt SA, Frazier OH: Mechanical circulatory support and cardiac transplantation. Circulation 1998;97:2079-2090. Copyright 1998, American Heart Association.)

particularly of the pulmonary artery and aorta, may be safer on bypass with a decompressed, supported heart. Access is obtained via median sternotomy, with all cuffed cannulas brought out of the chest through separate subcostal incisions. The cuffs allow soft tissue in growth and adherence to reduce the incidence of infection of the cannulas and endocardium.

Approximately 6000 ABIOMED VADs have been placed worldwide for precardiotomy or postcardiotomy cardiac failure.[114,116-119] Survival and hospital discharge rates have ranged from 20% to 45%, depending on the indication for the ABIOMED and the hemodynamic condition of the patient before surgery.[114,116-118] The most common complications directly attributed to this VAD include bleeding, stroke, and infection, with rates of 20% to 40%.[114,116,118] Hemolysis is not a common problem.

Paracorporeal Longer-term Support (Thoratec)

The Thoratec VAD system is composed of a single chamber with a polyurethane, seamless bladder housed in a rigid casing (Fig. 110-4).[120] VAD inflow cannulas are either atrial or ventricular. Outflow cannulas have a polyester graft attached for direct connection to the aorta or pulmonary artery, similar to the ABIOMED cannulas. There are Bjork-Shiley tilting disc valves at both the inflow and outflow connections to the bladder to ensure unidirectional flow; they require anticoagulation. A pneumatic driveline is connected to the rigid casing and supplies alternating vacuum and pressure to facilitate bladder filling and emptying, respectively. The blood pump can be adjusted to accommodate changing preload and afterload. The pneumatically driven pulses (systole) can be controlled in three different modes: asynchronous, synchronous, and volume. The asynchronous mode maintains a fixed rate, but stroke volume may vary. The synchronous mode provides counterpulsation by timing ejection to the patient's R wave—this provides both a variable rate and variable stroke volume. The volume mode delivers a fixed stroke volume triggered by bladder filling, but the rate will vary. The volume mode is usually the most practical because the VAD output changes with the patient's physiologic condition.

The Thoratec system is paracorporeal, similar to the ABIOMED, but is more portable and has the potential for outpatient use in patients who are bridging to recovery or transplantation.[120-123] Two advantages to the Thoratec system are the ability of secure ventricular inflow (VAD) cannulation and the applicability of long-term utilization. LV cannulation provides better ventricular decompression than atrial cannulation.[124-128] This is important because LV distention or inadequate decompression will limit ventricular recovery in some patients. Ventricular cannulation also provides better VAD performance and reduces the risk of thrombotic complications, particularly in the setting of AMI.[108,124,126,128] Right ventricular cannulation provides similar advantages over right atrial cannulation. However, these advantages may not be manifest if the tricuspid valve is left intact, because the tricuspid leaflets are often in close proximity to the cannulation tip and can obstruct VAD inflow.[129] In this situation, the advantages and disadvantages of right atrial versus right ventricular cannulation must be weighed to direct the best approach.

Over 3700 Thoratec VADs have been placed worldwide in over 2400 patients[130]; more then half of these patients received biventricular support. Survival and hospital discharge rates vary widely between 20% and 80%, depending on the etiology of shock and the medical center.[77,80,120,127,131-133] Cases of acute

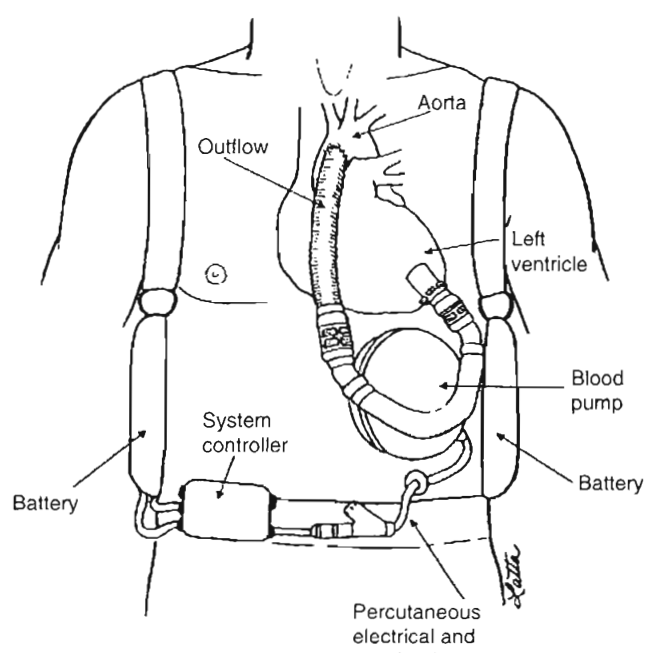

FIGURE 110–5. The HeartMate vented electric left ventricular assist device (HeartMate XVE): an intracorporeal, electrically powered system. (From Hunt SA, Frazier OH: Mechanical circulatory support and cardiac transplantation. Circulation 1998;97:2079-2090. Copyright 1998, American Heart Association.)

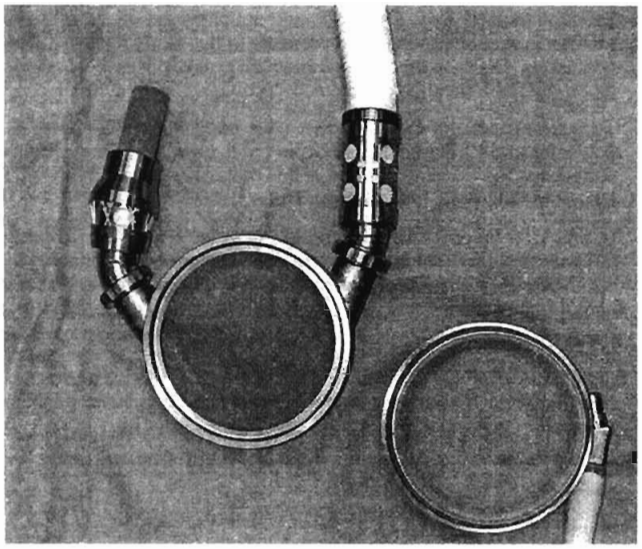

FIGURE 110–6. The HeartMate XVE left ventricular assist device in cross section depicting the pusher plate system responsible for displacement of blood within the chamber. (From Operating Manual for the HeartMate XVE LVAS, Thoratec Corporation, 2001.)

fulminant myocarditis with cardiogenic shock are among the best situations for VAD support with the Thoratec system, having an 88% recovery-with-discharge rate.[77] Complications of the Thoratec system are similar to other extracorporeal VAD systems when used for treatment of cardiogenic shock and include infection, stroke, bleeding, and acute renal failure. The rates of these complications vary among different series but range from 10% to 60%.[118,120,127,131,133-138]

Intracorporeal Long-term Support

The HeartMate LVAS XVE and Novacor LVAS have fully implanted pusher-plate blood pumps with externalized drivelines and are similar in their construction (Fig. 110-5). Each uses bioprosthetic valves to ensure unidirectional flow. The Novacor has bovine pericardial valves, and the HeartMate has porcine aortic valves. The Novacor has a seamless polyurethane pump sac between two pusher plates that generates a stroke volume of 70 mL. This surface requires anticoagulation. The HeartMate has a flexible polyurethane diaphragm that pushes against a titanium alloy housing generating a maximum stroke volume of 83 mL (Figs. 110-6 and 110-7). The blood contact surface is textured with polyurethane fibrils on one side and sintered titanium spheres on the housing. Fibrin and cellular components react and bond to the surface creating a pseudointima, precluding the need for anticoagulation. Antiplatelet therapy is recommended for both systems.

Both systems have variable modes that can generate fixed rates or demand-sensitive rates. Both are approved for use for the treatment of end-stage heart failure, but they may have a selective role for cardiogenic shock. These devices are practical alternatives for use in a "double-bridge" setting with initial resuscitation using a temporary device (i.e., ECMO/cardiopulmonary support or ABIOMED) for stabilization and pulmonary recovery.[80,109,110,139,140] Results with the HeartMate and Novacor devices have been favorable and, in certain subsets of patients, better than longer-term support with other systems.[77,138,141-145] Complications have been similar to other VADs and include bleeding, infection, stroke, thrombotic complications, and renal insufficiency.

There are several miniaturized rotary axial flow pumps that have been designed for long-term (potentially permanent) mechanical assistance, including the MicroMed-DeBakey pump, the Jarvik 2000, and the HeartMate II.[146-155] These devices are being studied in clinical trials for use as a bridge to transplantation, recovery, or permanent replacement therapy.[147,156] They have not yet received widespread use for acute cardiogenic shock.

TREATMENT OF CARDIOGENIC SHOCK: AN ALGORITHM FOR MECHANICAL SUPPORT

The hallmarks of cardiogenic shock are low cardiac output, hypotension, peripheral vasoconstriction, cold extremities, poor urine output, and altered mental status. As the pathophysiologic state progresses, pulmonary insufficiency and pulmonary edema ensue. Extrinsic causes of cardiogenic shock most commonly manifest as circulatory collapse secondary to pericardial tamponade. Acute tamponade is easily diagnosed by echocardiography and requires surgical or percutaneous evacuation and subsequent treatment of that which caused the tamponade (e.g., traumatic injury, aortic dissection, ruptured aneurysm). Extrinsic causes of cardiogenic shock usually require immediate surgical intervention but rarely necessitate mechanical assistance. However, intrinsic causes of acute cardiogenic shock can be refractory to both medical and surgical therapies and may require mechanical assistance. Intrinsic causes of cardiogenic shock can be divided into four pathophysiologic classifications: (1) acute valvular insufficiency, (2) AMI, (3) acute myocarditis, and (4) post-cardiotomy cardiac failure.

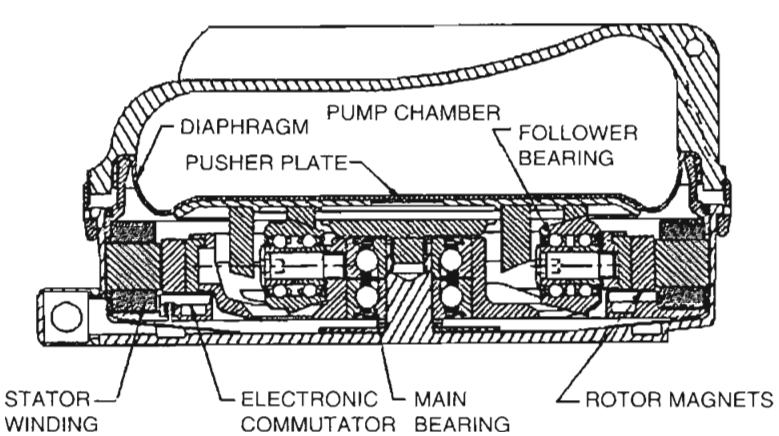

FIGURE 110–7. The HeartMate XVE blood pump compartment with the flexible polyurethane diaphragm within the housing pictured on the right. (From Operating Manual for the HeartMate XVE LVAS, Thoratec Corporation, 2001.)

Irrespective of the etiology of cardiogenic shock, the approach toward the initial management of patients should be fairly uniform, and a suggested management algorithm is outlined in Figure 110-8.

First, insertion of a pulmonary arterial balloon catheter and echocardiography should be done to help formulate a differential diagnosis. Severe valvular insufficiency can usually be effectively excluded at this juncture. If severe aortic insufficiency is present, chronotropic control (heart rate 80 to 100 beats/min) and afterload reduction with inotropic support should be the initial maneuvers. An IABP is contraindicated because aortic regurgitation will worsen, and the patient should be prepared for immediate aortic valve replacement. Likewise, acute, severe mitral regurgitation can be readily identified with an echocardiogram and hemodynamic assessment. An IABP should be placed immediately in conjunction with inotropes and/or afterload reduction. Surgical intervention should proceed emergently and cardiac catheterization pursued preoperatively only if the patient can be adequately stabilized.

Acute fulminant myocarditis usually presents in a previously healthy individual with no history of cardiac disease. Patients with presumed myocarditis who do not stabilize after the insertion of an IABP and concomitant inotropic infusion should be diverted to VAD support expeditiously. A remarkable percentage of these patients will recover if adequately supported during the acute phase of this disease. Short-term to intermediate-term VADs are optimal in these patients because of the ease of their insertion and removal and the anticipation for relatively short-term recovery. Giant cell myocarditis is one exception to this rule, because most patients with this diagnosis will require transplantation.[157-160]

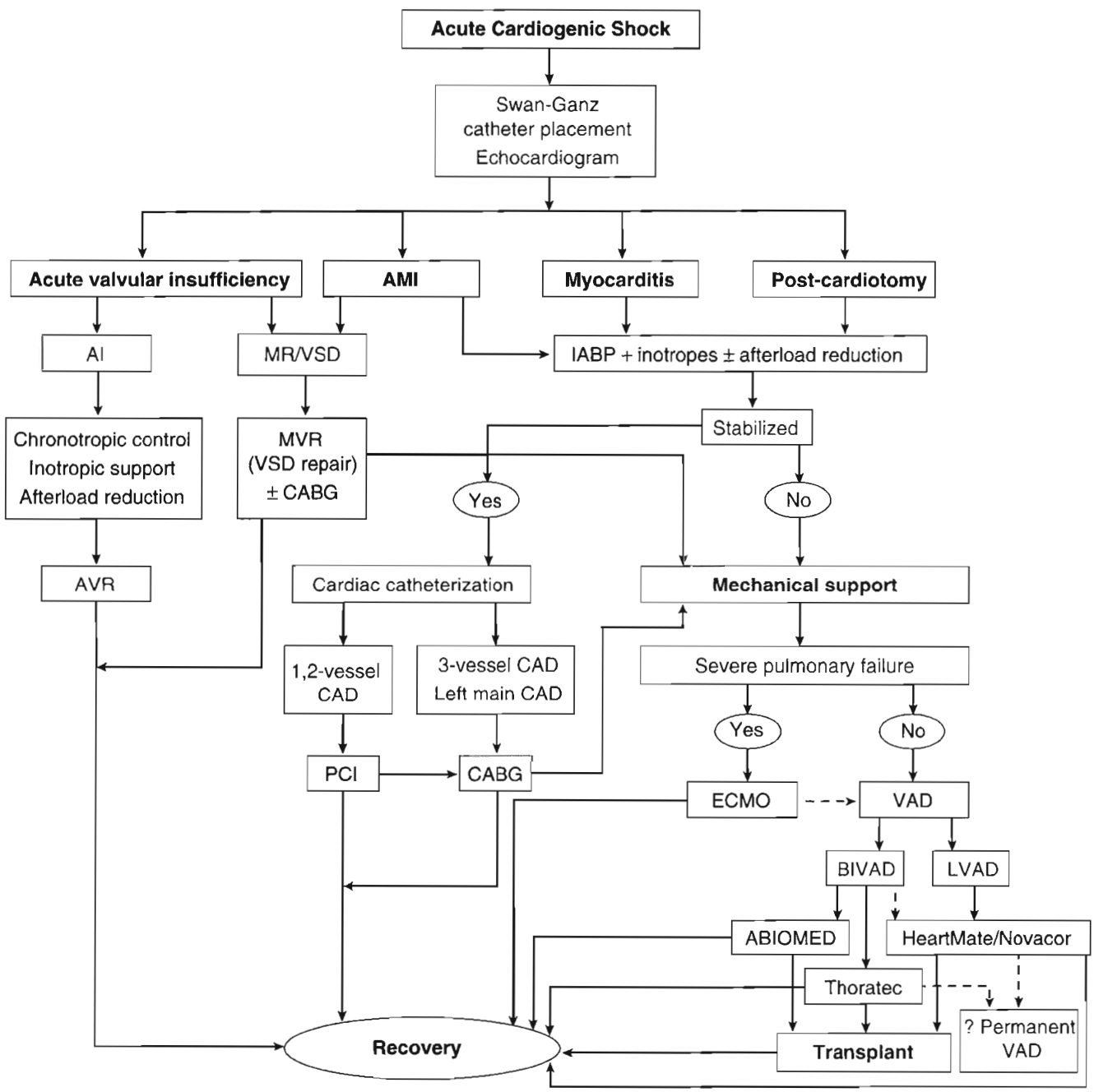

FIGURE 110–8. Algorithm for the management of acute cardiogenic shock.

Cardiogenic shock after AMI requires immediate IABP placement, often with additional pharmacologic support. If a mechanical complication (i.e., severe mitral regurgitation or VSD) has occurred, immediate surgical intervention is usually required. An expeditious cardiac catheterization is reasonable if the patient can be stabilized or placed on percutaneous bypass for the procedure. If no mechanical complication has occurred and the patient has been stabilized with IABP and medical therapy, cardiac catheterization may proceed. The number of diseased arteries usually determines subsequent allocation to percutaneous or surgical revascularization. Patients whose condition is unstable after an AMI, with continued cardiogenic shock despite IABP and inotropic support, should be considered for VAD support (see Fig. 110-6).

Postcardiotomy cardiogenic shock should be managed intraoperatively with an initial trial of IABP and inotropic support. If there is persistent shock or an inability to be weaned from CPB, VAD implantation is the next therapeutic step, provided a meaningful recovery is predictable or a plan for transplantation or permanent therapy can be clarified.

The mode of mechanical support used for cardiogenic shock is determined by a number of factors. The first is the degree of pulmonary insufficiency. If there is pulmonary failure with a very large alveolar-to-arterial oxygen gradient on maximal ventilatory support, ECMO support is indicated. A small percentage of ECMO patients in this setting will recover, some will require VAD placement as a bridge to transplantation, fewer still will bridge to VAD and then to recovery. If the degree of pulmonary insufficiency is limited to pulmonary edema that is likely to recover with adequate cardiac output, patients should undergo VAD placement directly. The choice of VAD in this situation is also dependent on several factors, including the predicted need for short-or longer-term support, the need for biventricular versus univentricular support, the chance of ventricular recovery, the institutional experience with different devices, and the relative risks of anticoagulation.

The ABIOMED system for postcardiotomy cardiac failure is preferred for those patients predicted to recover within days to a week of surgery, for cases when neurologic function is not known or is markedly compromised, and for patients who are not candidates for transplantation but may bridge to recovery or bridge to a longer-term and ambulatory device once stabilized with the ABIOMED. The ABIOMED system is the easiest to insert, so in cases of profound cardiogenic shock when operative brevity may be beneficial toward patient recovery, it may be the best choice. The system is also easy to convert to other longer-term VAD systems because the ABIOMED inflow cannulation is atrial and temporary.

The Thoratec system is the most versatile VAD and remains the support used most frequently at our institution for the treatment of refractory cardiogenic shock. The device is relatively easy to install, may be used for short-term or long-term univentricular or biventricular support, and allows the potential for ambulation. VAD inflow cannulation can be either via the atria or ventricles. Ventricular cannulation is preferable even in the case of AMI because of its hemodynamic efficiency, reliability, and better ventricular decompression. Despite the friability of freshly infarcted myocardium, the Thoratec ventricular cannulas are safe to insert through infarcted tissue. After review of our institutional data, we have observed no increase in VAD complications compared with those cannulas placed in uninfarcted tissue (Gleason and Acker, unpublished data). Once a patient is stabilized with the Thoratec system, a management strategy can be mapped out as bridge to recovery, transplantation, or permanent therapy with an intracorporeal device.

Initial placement of implantable VADs (e.g., HeartMate or Novacor) for mechanical support in patients with cardiogenic shock is generally not indicated. These devices may be used as a second bridge ("bridge-to-bridge") toward recovery, transplantation, or permanency. There may be a select group of patients in whom these intracorporeal VADs have a primary role in cardiogenic shock: (1) patients who require a larger cardiac output than other devices can generate (large individuals needing a cardiac output greater than 6 L/min to reverse the shock state); (2) patients who are more stable, can sustain longer operative times, and are unlikely to achieve myocardial recovery; and (3) patients in whom anticoagulation is contraindicated, making the HeartMate device potentially safer.

CONCLUSION

Cardiogenic shock remains a lethal problem with a mortality rate as high as 75%.[2,161,162] Patients who cannot be stabilized with inotropic support and an IABP should be considered for mechanical assistance with a VAD. The ideal assist device that can be easily placed, is versatile and portable, has minimal risk of complication, offers a normal cardiac output with physiologically equivalent characteristics such as pulsatile flow, and is easily removed does not yet exist. Currently, there are three modes of mechanical cardiac assistance that have received widespread use in the patient population with cardiogenic shock, including ECMO/cardiopulmonary support, the ABIOMED BVS 5000, and the Thoratec VAD system. Implantable devices such as the HeartMate LVAS XVE and Novacor LVAS have occasionally been used in this moribund population but have a more defined role in the subacute and chronic heart failure population.

The use of mechanical assistance for acute cardiogenic shock has facilitated impressive improvements in survival for certain disease cohorts such as those with acute myocarditis, with survival rates over 70%.[77] VADs have had less remarkable an impact on patients with postcardiotomy shock or AMI-induced shock,[108] but results in these patient populations are improving annually. Inherent to achieving better results is our understanding that patients who present with cardiogenic shock typically have significant underlying comorbidities with multiple-system organ dysfunction and marked derangements in both coagulation and inflammatory mediators that complicate management. They need to be approached by an integrated multidisciplinary team, including cardiologists, cardiac surgeons, anesthesiologists, critical care specialists, and experienced nursing staff, to implement efficient and decisive treatment plans. These integrated systems offer the greatest chance for success. Technologies expand and improve exponentially every year, and it is clear that mechanical assistance will continue to play a pivotal role in the management of these difficult patients.

ANNOTATED REFERENCES

Farrar DJ: The Thoratec ventricular assist device: A paracorporeal pump for treating acute and chronic heart failure. Semin Thorac Cardiovasc Surg 2000;12:243-250.

The experience with use of the Thoratec system through May 2000 is reviewed. The results of over 1300 implants are discussed. Survival rates

among patients transplanted and weaned from the Thoratec VAD support were 86% and 59%, respectively.

Hochman JS, Sleeper LA, Webb JG, et al: Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med 1999;341:625-634.

Results from the randomized SHOCK trial are reported. Emergency revascularization did not significantly reduce 30-day mortality, but it did reduce mortality at 6 months and IABP placement helped facilitate early revascularization.

Pagani FD, Lynch W, Swaniker F, et al: Extracorporeal life support to left ventricular assist device bridge to heart transplant: A strategy to optimize survival and resource utilization. Circulation 1999;100:II206-II210.

Experience using ECMO for the initial resuscitation and as a bridge to left ventricular assist device placement and subsequent heart transplantation in patients with severe hemodynamic instability is presented. ECMO can be used to salvage some survivors from this very high-risk cohort before the utilization of LVAD resources.

Samuels LE, Holmes EC, Thomas MP, et al: Management of acute cardiac failure with mechanical assist: Experience with the ABIOMED BVS 5000. Ann Thorac Surg 2001;71:S67-S72; discussion S82-S85.

Results of use of the ABIOMED ventricular assist device in pre- and post-cardiotomy shock from one of the initial testing centers are outlined. An algorithm and standardized protocol for management of refractory cardiogenic shock with VAD insertion is presented.

Stone GW, Ohman EM, Miller MF, et al: Contemporary utilization and outcomes of intra-aortic balloon counterpulsation in acute myocardial infarction: The benchmark registry. J Am Coll Cardiol 2003;41:1940-1945.

This study reviews the indications and outcomes for the usage of the intra-aortic balloon pump (IABP) from 1996-2001. Data were collected prospectively in 250 medical centers with over 22,000 IABPs placed worldwide.

Chapter 111

PERIPHERAL ARTERIOPATHIES INCLUDING EMBOLISM

David Laithwaite • Krishna Lingam • Richard Donnelly

KEY POINTS

1. **Peripheral arterial disease** is common, often asymptomatic, and associated with atherosclerotic vascular disease in other arterial territories. A relationship exists between ankle-brachial pressure index (ABPI, a marker of severity of occlusive arterial disease in the lower limb) and patient survival: a lower ABPI is generally associated with a much higher 5-year mortality.
2. **Most patients with intermittent claudication are managed medically,** but critical limb-threatening ischemia requires urgent endovascular or surgical intervention to prevent limb loss. Acute limb ischemia is caused by either primary thrombotic occlusion (thrombus superimposed on a ruptured atherosclerotic plaque) or embolism arising from the heart or proximal vessels. The mode of presentation and symptoms and signs of acute limb ischemia depend on the site and cause of the arterial occlusion and the extent to which preexisting peripheral arterial disease has led to collateral vessel formation. **Acute limb ischemia still carries a 15% mortality rate at 30 days.**
3. **Endovascular approaches** (e.g., angioplasty and stenting) are especially useful for discrete, proximal, and isolated stenoses (e.g., in the iliac arteries), but patients with diffuse, distal, and/or bilateral disease are less suitable for endovascular treatment.
4. **Outcomes after revascularization for critical limb ischemia** depend on the patency of distal (run-off) vessels and the presence of coexistent risk factors (e.g., diabetes and smoking).
5. **New approaches to treatment** include therapeutic angiogenesis, that is, administration of naked DNA or recombinant protein for vascular growth factors to stimulate new collateral vessel formation from existing vascular structures.

CLASSIFICATION OF PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease generally refers to the various manifestations of atherosclerosis in the major vessels of the lower limb, including thromboembolic complications associated with acute limb ischemia. Peripheral arterial disease is common, is often asymptomatic, and shows a steep age-related incidence in older people.[1] The clinical and biochemical risk factors for atherosclerosis (e.g., cigarette smoking, diabetes, and hypercholesterolemia) are associated with more severe and progressive disease in the lower limb. Diabetes, in particular, distorts the clinical presentation by causing more diffuse and distal arterial involvement. This, in turn, often hampers clinical management, including revascularization, and results in poorer clinical outcomes, such as higher amputation and graft failure rates.

Fontaine classified the severity of chronic arterial insufficiency of the lower limb in 1954 (Table 111-1),[2] but intensive care specialists are mainly concerned with the management of critical limb ischemia and patients with acute limb-threatening arterial occlusion.

EPIDEMIOLOGY AND CLINICAL PRESENTATION OF LOWER LIMB ISCHEMIA

Based on an objective measure of arterial insufficiency (e.g., an ABPI < 0.95), the incidence of peripheral arterial disease has been reported as 7% in the 49- to 74-year age group, but only 22% of patients with peripheral arterial disease had symptoms.[3] The ABPI is obtained by dividing the ankle systolic BP at the level of the malleolus by the higher of two brachial systolic BPs. Under normal circumstances the ABPI is 1.0 and an ABPI less than 0.8 is invariably abnormal, reflecting significant arterial stenosis. The ABPI in an affected limb often falls after a short period of exercise (e.g., a walk test). Occasionally, the ABPI is falsely elevated, such as in patients with diabetes, when arteries are calcified and resistant to compression.

The most common symptom of peripheral arterial disease, intermittent claudication (Fontaine stage II), occurs in only 0.6% of people age 45 to 54 years but affects 9% of the over 70-year age group.[1] Although intermittent claudication is troublesome and disabling, most patients remain symptomatically stable in the medium to long term. Each year, however, 15 to 20 patients per 100,000 population progress to rest pain and critical limb ischemia (Fontaine stages III and IV).[4] In the United Kingdom, about 50,000 patients each year are admitted urgently to hospital for the management of severely disabling peripheral arterial disease (ABPI typically < 0.5).

Critical limb ischemia secondary to acute thromboembolic occlusion of a peripheral artery accounts for at least 10% to 16% of a vascular surgeon's caseload and still carries a 15% 30-day mortality despite recent developments in immediate

TABLE 111–1. FONTAINE CLASSIFICATION OF CHRONIC LEG ISCHEMIA

Stage I	Asymptomatic
Stage II	Intermittent claudication
Stage III	Ischemic rest pain
Stage IV	Ulceration, gangrene, or both

management and revascularization techniques.[5] Patients with peripheral arterial disease have a considerably reduced survival (30% 5-year mortality) mainly due to atherosclerotic complications in other vascular territories.[6] Several studies have shown a clear relationship between ABPI and outcome (Fig. 111-1),[7] which highlights, not surprisingly, that more severe peripheral arterial disease tends to be associated with more severe coronary artery disease and shortened survival.

Cigarette smoking is the most powerful risk factor in the development of peripheral arterial disease. Smoking accounted for over 80% of cases of peripheral arterial disease in the Framingham study,[8,9] and most lower limb outcomes (e.g., amputation rates, patency of bypass grafts, and ischemic ulcer formation) are significantly worse in current or recent smokers. Similarly, diabetes and hypercholesterolemia are major risk factors associated with the development, progression, and complications of atherosclerosis in the legs. Amputation rates among diabetics are 15 to 70 times higher than in nondiabetics. Hypertension is also an important risk factor for peripheral arterial disease; high blood pressure increases the risk of intermittent claudication by a factor of three.

ATHEROSCLEROSIS OF LOWER LIMB ARTERIES

Atherogenesis is best described in three stages: initiation of the atherosclerotic lesion, progression, and plaque complications. During the initiation process, fatty streaks occur on the endothelial surface of the vessel and mononuclear leukocytes begin to invade the intima as part of a cytokine-mediated process of migration of inflammatory cells. These leukocytes (macrophages) steadily accumulate lipid and become foam cells. The fatty streak gradually progresses into an atherosclerotic plaque, which begins to encroach on the lumen of the vessel (Fig. 111-2). The iliac arteries and the superficial femoral artery in the lower limb are especially prone to

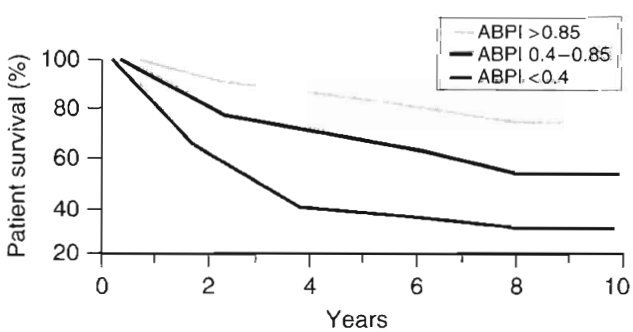

FIGURE 111–1. Relationship between ankle-brachial pressure index (ABPI) and survival in patients with symptomatic peripheral artery disease. This clearly illustrates how cardiovascular mortality increases in proportion to the severity of peripheral artery disease. (Modified with permission from McKenna M, Wolfson S, Kuller L: The ratio of ankle and arm arterial pressure as an independent predictor of mortality. Atherosclerosis 1991;87:119-128.)

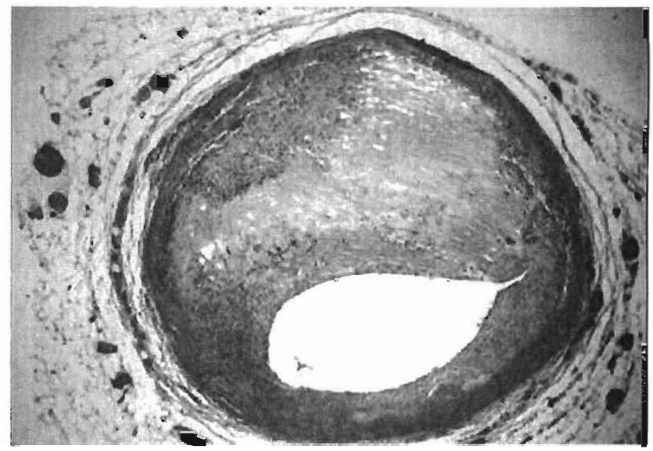

FIGURE 111–2. Histologic appearance of an atherosclerotic plaque illustrating infiltration with macrophages (which turn into foam cells) and acute inflammation, together with lipid accumulation and extracellular matrix expansion. A fibrous cap appears, which often ruptures, leading to platelet aggregation and acute thrombotic occlusion of the vessel.

plaque formation. Smooth muscle cells also migrate and accumulate within the atherosclerotic plaque, and a fibrous extracellular matrix develops.

The complications that occur in atherosclerotic plaques include intraplaque hemorrhage and cap rupture or ulceration, which in turn lead to superimposed thrombus formation and complete vessel occlusion (Fig. 111-3). Such events are often limb or life threatening. Rupture or fissuring of a plaque exposes the lipid core, which in turn activates platelets and the clotting cascade. Clumps of platelets may remain firmly attached to the plaque, resulting in more severe stenosis or complete occlusion of the lumen, or they may detach to form emboli that will lodge in smaller vessels downstream from the culprit lesion.

ACUTE LIMB ISCHEMIA

CLINICAL PRESENTATION AND ETIOLOGY

Acute lower limb ischemia is common (14 cases annually per 100,000 population)[10] and can present with a range of different signs and symptoms. The Society for Vascular Surgery and the International Society for Cardiovascular

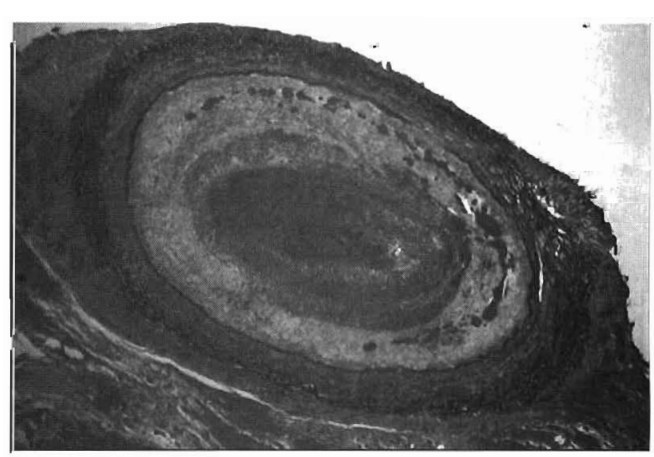

FIGURE 111–3. Acute thrombotic occlusion of a ruptured atherosclerotic plaque causing acute limb ischemia.

TABLE 111-2. CLINICAL CLASSIFICATION OF ACUTE LIMB ISCHEMIA

Category	Description/Prognosis	Findings		Doppler Signals	
		Sensory Loss	*Muscle Weakness*	*Arterial*	*Venous*
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	(Often) Inaudible	Audible
Immediately	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	(Usually) Inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

Surgery (SVS/ISCVS) have produced a classification system for acute limb ischemia that has been modified by Rutherford and colleagues[11] to improve its prognostic utility (Table 111-2).

The presentation of acute lower limb ischemia is strongly influenced by two factors: (1) the presence or absence of a preexisting collateral circulation and (2) the etiology of the occlusion (Table 111-3). In patients with previously normal arteries, the symptoms of acute lower limb ischemia are likely to be much more severe and abrupt in onset because there is unlikely to be any collateral circulation providing distal perfusion. Tissue ischemia downstream of the occlusion causes intense rest pain. In the absence of collateral flow, there is even greater urgency to restore perfusion to avoid irreversible tissue necrosis and/or permanent disability.

Inquiring in the history about the mode of onset of pain may allow some differentiation between primary thrombotic occlusion and those patients presenting with abrupt onset embolic occlusion. The presence or absence of any prior symptoms of peripheral arterial disease is important. Patients with moderate-to-severe intermittent claudication before the onset of acute lower limb ischemia are likely to have developed some degree of collateral circulation, and therefore the onset of acute lower limb ischemia may cause little more than a slight worsening of their usual lower limb symptoms.

Physical examination may reveal a classic acutely ischemic limb: it is pale, painful, cold, pulseless, paralyzed, and insensate. The presence of paralysis or paresthesia indicates a poor prognosis because of likely infarction of nerve and muscle tissue; at this stage primary amputation may be the most appropriate treatment option. Examination of the patient should also include the pulse rhythm and electrocardiogram to identify those patients in atrial fibrillation and a full assessment of the vascular supply to the contralateral limb.

The two most common causes of acute lower limb ischemia are primary thrombosis of a diseased native vessel or graft and embolic occlusion of an artery. Differentiation of these two causes is important because the approach to management is different. Embolectomy performed on a diseased artery may increase the risk of further thrombus formation and cause iatrogenic trauma to the vessel, in turn worsening limb ischemia. Primary thrombotic occlusion (e.g., following plaque rupture, see Fig. 111-3) is now the most common cause of acute lower limb ischemia because anticoagulants are used more widely in atrial fibrillation and the incidence of rheumatic heart disease is diminishing. Approximately 85% of acute peripheral arterial occlusions are now due to primary occlusion and 15% are secondary to embolism.[12,13]

TABLE 111-3. ETIOLOGY OF ACUTE LIMB ISCHEMIA

Causes of Acute Occlusions of Peripheral Arteries in Patients With Preexisting Atherosclerotic Disease

- Thrombosis of native artery with atherosclerotic stenosis
- Thrombosis of arterial bypass graft
- Embolism from heart, aneurysm, atherosclerotic plaque, or critical stenosis upstream (including cholesterol or atherothrombotic emboli during endovascular procedures)
- Thrombosed aneurysm (especially popliteal)

Causes of Acute Critical Limb Ischemia in Patients Without Preexisting Atherosclerotic Disease

- Arterial trauma (especially iatrogenic)
- Arterial dissection
- Arteritis with thrombosis (e.g., giant cell arteritis)
- Spontaneous thrombosis with hypercoagulable state
- Popliteal cyst with thrombosis
- Popliteal entrapment with thrombosis
- Vasospasm with thrombosis (e.g., ergotism)

UPPER LIMB ISCHEMIA

Acute limb ischemia is much more common in the leg compared with the upper limb. Upper limb ischemia accounts for 16.6% of all acute peripheral ischemic events.[14] Differentiation into acute and chronic ischemia in the upper limb is difficult owing to the rich collateral circulation present normally within the arm, allowing fairly severe disease to remain relatively asymptomatic. Embolic occlusion in the upper limb is much more common than primary thrombotic occlusion because the arm is seldom affected by atherosclerosis, but the principles of management are similar.

INVESTIGATIONS

Patients with a suspected embolic occlusion should ideally undergo radiologic investigation to confirm the level of occlusion, assuming time and expertise are available. Previously, this was routinely achieved by use of intra-arterial contrast angiography, but there have been concerns about delays to treatment and the risk of contrast nephrotoxicity. In addition, the technical limitations of angiography include poor resolution in low-flow states and the diagnosis of aneurysms is difficult (especially popliteal artery aneurysms). Thus, more recently, duplex ultrasound has been preferred for the diagnosis of acute arterial occlusion.

TABLE 111–4. CONTRAINDICATIONS TO USE OF THROMBOLYSIS IN ACUTE LIMB ISCHEMIA

Absolute Contraindications

- Active bleeding diathesis
- Acute gastroduodenal ulcers and/or recent gastrointestinal hemorrhage (within previous 10 days)
- History of stroke (excluding transient ischemic attack) in the previous 2 months
- Neurosurgery (intracranial, spinal) within the previous 3 months
- Intracranial trauma within the previous 3 months

Relative Contraindications

- Major nonvascular surgery or trauma within previous 10 days
- Cardiopulmonary resuscitation within previous 10 days
- Uncontrolled hypertension (systolic >180 mm Hg, diastolic >110 mm Hg)
- Puncture of uncompressible vessel
- Intracranial neoplasm
- Mitral valve disease
- Recent eye surgery
- Aneurysm, especially silent, intracerebral vascular malformations

Minor Contraindications

- Renal or hepatic insufficiency (especially if associated with coagulopathy)
- Bacterial endocarditis
- Pregnancy
- Diabetic hemorrhagic retinopathy
- Antiplatelet therapy

The use of duplex ultrasonography is well established in the diagnosis of chronic limb ischemia, but there is often difficulty in visualizing the aortoiliac segments owing to overlying bowel gas, obesity, and/or calcification and marked tortuosity of the iliac vessels. Nevertheless, a well-trained vascular technician acting in conjunction with a vascular surgeon can usually make an adequate assessment of the level of occlusion to plan management.

TREATMENT

Endovascular treatment of acute lower limb occlusion may involve suction embolectomy or local administration of thrombolytic therapy. A thrombolysis catheter is introduced into the thrombus, and a lytic agent such as urokinase or recombinant tissue plasminogen activator (rTPA) is delivered directly onto the occlusion.[27] Endovascular treatment of the underlying stenosis may also be attempted at this time (e.g., via balloon angioplasty or stent deployment).

Thrombolysis is indicated in patients who present early (<14 days' duration) with a primary thrombotic occlusion and those who are unsuitable or unfit for surgical embolectomy. The indications and contraindications for thrombolysis are shown in Table 111-4. Although direct thrombolysis avoids many of the risks of surgery, there are other potentially serious complications even though the thrombolytic is administered locally, such as stroke (1.2% to 2.3%), major hemorrhage (5.1%), distal embolization (5%), and compartment syndrome due to rapid reperfusion of the ischemic limb (2%).[10,15,16,28] In the case of an acute, severely ischemic limb, surgery is indicated to perform either embolectomy or primary amputation of an irreversibly infracted lower limb. Unless the history is clearly one of an embolic event, preoperative duplex or angiographic confirmation is required. Heparin (100 to 150 units/kg) is initiated immediately, and the patient is transferred to the operating room. For a femoral artery embolectomy, the procedure may be undertaken under local anesthesia, but close monitoring is mandatory given the high incidence of cardiovascular events in this population. In the case of primary thrombotic occlusion of a diseased vessel, arterial reconstruction is often required after angiography.

The outcome after peripheral artery embolism is often poor: mortality at 30 days is 15%, and amputation occurs in 10% to 30% of patients.[5] Identifying the source of the embolus is important by using echocardiography and ultrasound of the aorta.

CHRONIC CRITICAL LIMB ISCHEMIA

Critical limb ischemia is defined in nondiabetic patients as the presence of rest pain or tissue necrosis (ulceration or gangrene), with an ankle systolic pressure of less than 50 mm Hg or a toe pressure of less than 30 mm Hg[17] (ankle and toe pressures in diabetics may be artificially raised). These patients have a significant risk of limb loss, as well as a high cardiovascular and overall mortality rate. The management of chronic critical limb ischemia centers on restoring blood flow to the extremity by endovascular or surgical therapy.[29]

However, some patients present more urgently with an episode of "acute on chronic" limb ischemia. This requires prompt investigation and treatment to avoid long-term tissue loss and preserve the leg. These patients may, surprisingly, volunteer relatively few symptoms because their preexisting collateral vessels may be almost sufficient to nourish the limb. Patients without such well-developed collaterals will present more acutely with the classic findings of intense rest pain and signs of decreased perfusion. Some degree of tissue loss or necrosis may be present at diagnosis, and both lower limbs may be similarly affected.

TABLE 111–5. PATENCY RATES AFTER ENDOVASCULAR TREATMENT OF PERIPHERAL ARTERIAL DISEASE

Study	Segment	Patency		Time (yr)
		Primary	*Secondary*	
Henry, et al.[19]	Superficial femoral	65%		4
	Popliteal	50%		4
Capek, et al.[26]	Femoropopliteal	81%		1
		61%		3
		58%		5
Jamsen, et al.[24]	Femoropopliteal	46%	63%	1
		31%	50%	3
		25%	41%	5

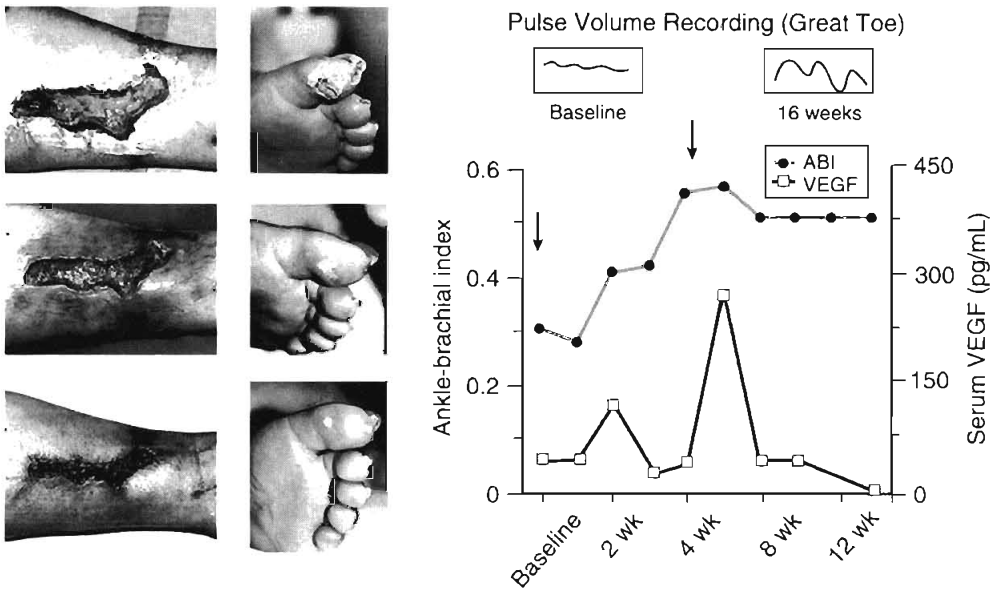

FIGURE 111–4. Therapeutic angiogenesis stimulates new vessel formation to develop collaterals. After intramuscular administration of naked DNA for VEGF in a patient with critical limb ischemia, there is evidence of VEGF formation and increased serum levels of VEGF associated with improved ABPI and resolution of ischemic tissue damage. (Reproduced with permission from Baumgartner I, Pieczek A, Manor O, et al: Constitutive expression of phVEGF165 after intramuscular gene transfer promotes collateral vessel development in patients with critical limb ischemia. Circulation 1998;97:1114-1123. Copyright 1998, American Heart Association.)

After angiographic assessment, the initial management should be endovascular. This is now accepted as first-line therapy and is usually successful (>85% restoration of perfusion). Patency rates for endovascular and surgical interventions depend on the site of intervention and the state of the distal vessels (degree of distal "run-off"). For example, iliac artery angioplasty has a 73% patency rate at 3 years if the run-off vessels are patent but only 30% patency if the distal vessels are also diseased.[18] Another study showed a 77% secondary patency rate at 6 years (secondary patency indicates that the vessel remains patent with the assistance of further interventions). Stenting in the iliac arteries is well established, increasing the patency of endovascular therapy to 86% at 4 years.[19] Results of angioplasty in the femoropopliteal vessels are less impressive, with a wide variety in the reported rates of primary and secondary patency. Some of these results are summarized in Table 111-5.

Analysis of pooled results from five separate studies[20-24] (n = 980) showed a 5-year patency rate after endovascular therapy of 41.9%, although the majority of these patients had intermittent claudication rather than critical limb ischemia. Surgery for similarly diseased segments, in those with critical ischemia, had a primary patency rate of 52% to 63% at 5 years, with corresponding limb salvage rates of 85% to 87%. Stenting in the infrainguinal arteries has not been shown to improve on the patency rates of bypass surgery and is therefore usually reserved for primary angioplasty failures.

NEW THERAPEUTIC APPROACHES

The management of peripheral arterial disease in general is steadily becoming more minimally invasive (e.g., with the wider application of endovascular approaches to abdominal aortic aneurysm repair and use of carotid artery angioplasty and stenting in place of endarterectomy). However, in the lower limbs, diffuse, distal, and/or bilateral disease is seldom amenable to a localized endovascular procedure. Angioplasty and stenting are mostly reserved for those patients with discrete, proximal, and unilateral stenoses (e.g., in the iliac vessels).

THERAPEUTIC ANGIOGENESIS

A novel development in this area includes therapeutic angiogenesis, which is the administration of naked DNA or recombinant proteins for vascular growth factors (e.g., vascular endothelial growth factor [VEGF] or basic fibroblast growth factor [bFGF]) to stimulate endothelial cell replication and migration to form new collateral vessels from existing vascular structures. Large placebo-controlled trials[25] have shown evidence that therapeutic angiogenesis may be effective in limb salvage in critical ischemia and in symptom relief for less acute forms of peripheral arterial disease, such as intermittent claudication (Fig. 111-4).

ANNOTATED REFERENCES

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