Joseph E. Parrillo
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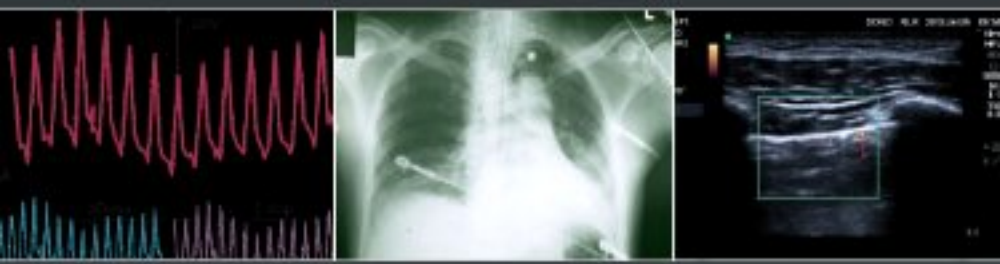
Critical Care Medicine

Principles of Diagnosis and Management in the Adult



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CRITICAL CARE MEDICINE

PRINCIPLES OF DIAGNOSIS
AND MANAGEMENT
IN THE ADULT

Fourth Edition

CRITICAL CARE MEDICINE

PRINCIPLES OF DIAGNOSIS AND MANAGEMENT IN THE ADULT

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21 Circulatory Shock

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CHAPTER OUTLINE

INTRODUCTION

The syndrome of shock in humans is often the final pathway through which a variety of pathologic processes lead to cardiovascular failure and death. As such, it is perhaps the most common and important problem with which critical care physicians contend. The importance of shock as a medical problem can be appreciated by the prominence of its three dominant forms. Cardiogenic shock related to pump failure is a major component of the mortality associated with cardiovascular disease, the leading cause of death in the United States with almost 800,000 deaths annually.[1] Similarly, hypovolemic shock remains a major contributor to early mortality from trauma, the most common cause of death in those between the ages of 1 and 45 (approximately 200,000 cases annually.[1,2] Finally, despite improving medical and surgical therapy, overall mortality coded as septicemia has increased from the 13th to the 11th most frequent cause of death in the United States.[1,3] Most current estimates suggest that there are more than 100,000 cases of septic shock annually in the United States alone.[4,5] In addition, all forms of shock increase the probability of other major comorbidities such as serious infection, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome (MODS).

This chapter provides an overview of circulatory shock with an emphasis on the common elements and important differences in the pathophysiology and pathogenesis of the various forms of the syndrome. This focus on common elements of different forms of shock will continue through sections on systemic shock hemodynamics, microvascular dysfunction, mechanisms of cellular injury, oxygen supply dependency, compensatory responses, diagnostic approach/evaluation, and management/therapy.

HISTORY

Despite recognition of a posttraumatic syndrome by Greek physicians such as Hippocrates and Galen, the origin of the term *shock* is generally credited to the French surgeon Henri Francois Le Dran who, in his 1737 "A Treatise of Reflections Drawn from Experience with Gunshot Wounds," coined the term *choc* to indicate a severe impact or jolt.[6] An inappropriate translation by the English physician Clarke, in 1743, led to the introduction of the word *shock* to the English language to indicate the sudden deterioration of a patient's condition with major trauma.[6] It was Edwin A. Moses,[7] however, who began to popularize the term, using it in his 1867 "A Practical Treatise on Shock after Operations and Injuries." He defined it as "a peculiar effect on the animal system, produced by violent injuries from any cause, or from violent mental emotions." Prior to this definition, the rarely used term *shock* referred in a nonspecific sense to the immediate and devastating effects of trauma, not a specific

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posttrauma syndrome. Although not entirely accurate by today's standards, his definition was one of the first to separate the syndrome involving the body's response to massive trauma from the immediate, direct manifestations of trauma itself.

By the late 1800s, two theories of traumatic shock physiology dominated. The first, based on observations by Bernard, Charcot, Goltz, and others, was proposed by Fischer in 1870.[8-10] He suggested that traumatic shock was caused by generalized "vasomotor paralysis" resulting in splanchnic blood pooling. The corollary was that total circulating blood volume is preserved in shock. The second dominant theory, articulated by Mapother in 1879, suggested that decreased cardiac output in traumatic shock is caused by intravascular volume loss due to extrusion of plasma through the vessel wall from the intravascular space to the interstitium.[11] He proposed that this was a consequence of the failure of "vasodilator nerves" in traumatic shock and subsequent generalized arteriolar vasoconstriction. With the 1899 publication of "An Experimental Research into Surgical Shock" (perhaps the first experimental studies of shock), George W. Crile provided scientific data supporting a variation of the vasomotor paralysis theory.[12] After documenting the importance of decreased central venous pressure and venous return in experimental shock due to hemorrhage and demonstrating the potential for intravascular volume replacement as therapy, he proposed that traumatic shock was caused by exhaustion of the overstimulated "vasomotor center" and subsequent generalized relaxation of large vessels (veins) leading to decreased ventricular filling and cardiac output.

Further advances in shock research were substantially driven by military concerns. During World War I, Walter B. Cannon and other physiologists/physicians studied the early clinical response to battlefield trauma. Their work eventually led to the publication of the classic monograph "Traumatic Shock" in 1923.[13] Cannon and his colleagues were the first to relate trauma-associated hypotension in a large group of patients to a fall in blood volume, loss of bicarbonate, and accumulation of organic acids. Others, using dye dilution techniques, demonstrated that severity of shock was directly related to the decrease in intravascular volume.[14] Clinical data from war casualties also suggested the importance of reduced blood flow (independent of blood pressure) in shock.[15] The observation that blood in the capillaries of victims of massive trauma was hemoconcentrated compared to venous blood would lead to the practice of resuscitating trauma patients with dried pooled plasma rather than whole blood in the early part of World War II.[16]

Although work originating from the battlefields of World War I clearly linked traumatic shock associated with substantial, obvious bleeding to a loss of circulating blood volume, the origin of traumatic shock in the absence of defined hemorrhage was unclear. The accepted explanation for this phenomenon remained a variation of the vasomotor paralysis theory of shock. It was postulated that nonhemorrhagic, posttraumatic shock ("wound shock") was caused by the liberation of "wound toxins" (histamine or other substances), which resulted in *neurogenic* vasodilation and peripheral blood pooling. However, after the war, Blalock and others demonstrated in animal models that nonhemorrhagic traumatic shock was due to the loss of blood and fluids into injured tissue rather than circulating toxins resulting in stasis of blood within the circulation.[17]

Additional advances occurred during World War II. Using injured subjects from the European front, Henry Beecher confirmed that hemorrhage and fluid loss leading to metabolic acidosis was a major cause of shock.[18] In the first use of indicator dye techniques in humans for studying blood flow, Cournand and Richard, in 1943, demonstrated that cardiac output was typically reduced in shock.[19] They also reinforced Blalock's findings regarding nonhemorrhagic "wound shock" in trauma patients by demonstrating that circulating blood volume was reduced in such patients through loss of fluid into damaged tissues. The importance of maintaining intravascular volume in traumatic and hemorrhagic shock was supported by the well-known cardiovascular physiologist, Carl J. Wiggers, who published a landmark series of studies[20] in the 1940s using a standardized animal model, which showed that prolonged hypovolemic shock resulted in a resuscitation-resistant state that he termed *irreversible shock*. He defined it as a condition resulting from "a depression of many functions but in which reduction of the effective circulating blood volume is of basic importance and in which impairment of the circulation steadily progresses until it eventuates in a state of irreversible circulatory failure." Aggressive fluid support became the standard of resuscitation for trauma and shock.

Subsequently, the Korean War fueled the research that demonstrated the relationship of acute tubular necrosis (ATN) and acute renal failure (ARF) to circulatory shock.[21] In addition, studies of battlefield casualties clearly demonstrated the relationship between early resuscitation and survival.[21] During the Vietnamese conflict, with the widespread use of ventilator technology, the dominant research concern became postshock infection and "shock lung" (ARDS), a concern that has evolved to the present interest in shock-related MODS.

DEFINITIONS AND CATEGORIZATION OF SHOCK

The definition of shock has evolved in parallel with our understanding of the phenomenon. As noted, until the late 1800s, the term *shock* was used to indicate the immediate response to massive trauma, without regard to a specific posttrauma syndrome. The definition consisted of descriptions of its obvious clinical signs. In 1895, John Collins Warren[22] referred to shock as "a momentary pause in the act of death," which was characterized by an "imperceptible" or "weak, threadlike" peripheral pulse and a "cold, clammy sweat."

Subsequently, with the introduction of noninvasive blood pressure monitoring devices, most clinical definitions of shock added the requirement for arterial hypotension. In 1930, Blalock[8] included arterial hypotension as one of the required manifestations of shock when he defined it as "peripheral circulatory failure resulting from a discrepancy in the size of the vascular bed and the volume of the intravascular fluid." Simeone,[23] as recently as 1964, suggested that shock exists when "the cardiac output is insufficient to fill the arterial tree with blood under sufficient pressure to provide organs and tissues with adequate blood flow."

Current technology, which allows for the assessment of perfusion independent of arterial pressure, has shown that hypotension does not define shock. The emphasis in defining shock is now on tissue perfusion in relation to cellular function. According to Fink,[24] shock is "a syndrome precipitated by a systemic derangement of perfusion leading to widespread cellular hypoxia and vital organ dysfunction." Cerra[25] has emphasized supply/demand mismatch in his definition: "a disordered response of organisms to an inappropriate balance of substrate supply and demand at a cellular level."

The appropriate definition of shock varies with the context of its use. For paramedical personnel, a definition that incorporates the typical clinical signs of shock (arterial hypotension, tachypnea, tachycardia, altered mental status, and decreased urine output) may suffice. For the physiologist, shock may be defined by specific hemodynamic criteria involving alterations of ventricular filling pressures, venous pressures, arterial pressures, cardiac output, and systemic vascular resistance. Similarly, in the appropriate context, shock could also be defined by alterations of biochemical/bioenergetic pathways or intracellular gene expression. For the physician, however, we find the most appropriate definition to be "the state in which profound and widespread reduction of effective tissue perfusion leads first to reversible, and then, if prolonged, to irreversible cellular injury."

Effective tissue perfusion, as opposed to tissue perfusion per se, is an important issue. Effective tissue perfusion may be reduced by either a global reduction of systemic perfusion (cardiac output) or by increased ineffective tissue perfusion due to a maldistribution of blood flow or a defect of substrate utilization at the subcellular level (Box 21.1).

Box 21.1 Determinants of Effective Tissue Perfusion in Shock

Cardiovascular Performance (Total Systemic Perfusion/Cardiac Output)

Cardiac Function

Preload
Afterload
Contractility
Heart rate

Venous Return

Right atrial pressure (dependent on cardiac function)
Mean circulatory pressure
  Stressed vascular volume
  Mean vascular compliance
Venous vascular resistance
  Distribution of blood flow

Distribution of Cardiac Output

Intrinsic regulatory systems (local tissue factors)
Extrinsic regulatory systems (sympathetic/adrenal activity)
Anatomic vascular disease
Exogenous vasoactive agents (inotropes, vasopressors, vasodilators)

Microvascular Function

Pre- and postcapillary sphincter function
Capillary endothelial integrity
Microvascular obstruction (fibrin, platelets, white blood cells, red blood cells)

Local Oxygen Unloading and Diffusion

Oxyhemoglobin affinity
  RBC 2,3 DPG
  Blood pH
  Temperature

Cellular Energy Generation/Utilization Capability

Citric acid (Krebs) cycle
Oxidative phosphorylation pathway
Other energy metabolism pathways (e.g., ATP utilization)

CLASSIFICATION

Although hypovolemic shock associated with trauma was the first form of shock to be recognized and studied, by the early 1900s it became broadly recognized that other clinical conditions could result in a similar constellation of signs and symptoms. Sepsis as a distinct cause of shock was initially proposed by Laennec (1831) and subsequently supported by Boise (1897).[26,27] In 1934, Fishberg and colleagues introduced the concept of primary cardiogenic shock due to myocardial infarction.[28] Later the same year, Blalock developed the precursor of the most commonly used classification systems of the present.[29] He subdivided shock into four etiologic categories: hematogenic or oligemic (hypovolemic), cardiogenic, neurogenic (e.g., shock after spinal injury), and vasogenic (primarily septic shock). Shubin and Weil, in 1967, proposed the additional etiologic categories of hypersensitivity (i.e., anaphylactic), bacteremic (i.e., septic), obstructive, and endocrinologic shock.[30] However, as the hemodynamic profiles of the different forms of shock were uncovered, a classification based on cardiovascular characteristics, initially proposed in 1972 by Hinshaw and Cox,[31] came to be accepted by most clinicians. The categories include (1) hypovolemic shock, due to a decreased circulating blood volume in relation to the total vascular capacity and characterized by a reduction of diastolic filling pressures and volumes; (2) cardiogenic shock related to cardiac pump failure due to loss of myocardial contractility/functional myocardium or structural/mechanical failure of the cardiac anatomy and characterized by elevations of diastolic filling pressures and volumes; (3) extracardiac obstructive shock involving obstruction to flow in the cardiovascular circuit and characterized by either impairment of diastolic filling or excessive afterload; and (4) distributive shock caused by loss of vasomotor control resulting in arteriolar and venular dilation and (after resuscitation with fluids) characterized by increased cardiac output with decreased systemic vascular resistance. We have adapted these categories into an etiologic/physiologic classification of shock that is summarized in Figure 21.1 and Box 21.2. This figure and box represent our current understanding of the causes and typical hemodynamic features of different forms of shock.

Despite this hemodynamic-based categorization system, it is important to note the mixed nature of most forms of clinical shock. Septic shock is nominally considered a form of distributive shock. However, prior to resuscitation with

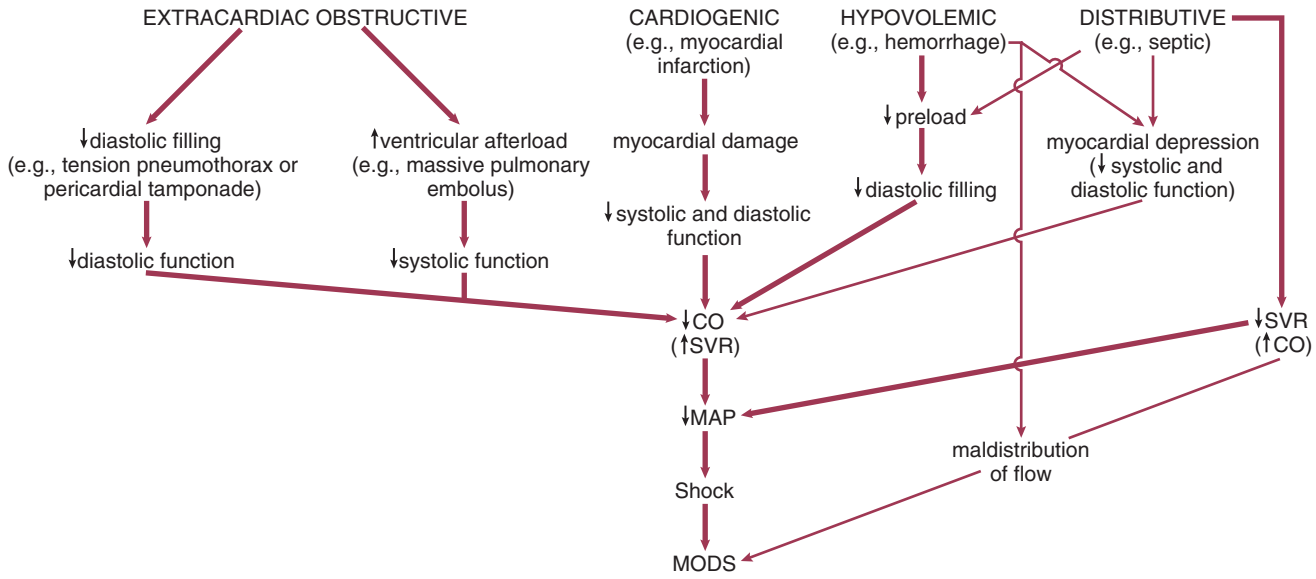

Figure 21.1 The interrelationships among different forms of shock. For cardiogenic, hypovolemic, and obstructive shock, hypotension is primarily due to decreased cardiac output with systemic vascular resistance rising secondarily. With distributive (particularly septic shock), hypotension is primarily due to a decrease in systemic vascular resistance with a secondary increase of cardiac output. In many forms of shock, the hemodynamic characteristics are influenced by elements of hypovolemia, myocardial depression (ischemic or otherwise), and vascular dysfunction (which may affect afterload). Dominant pathophysiologic pathways are denoted by heavier lines. CO, cardiac output; SVR, systemic vascular resistance; MAP, mean arterial blood pressure; MODS, multiple organ dysfunction syndrome.

fluids, a substantial hypovolemic component may exist due to venodilatation and third-spacing. In addition, depression of the myocardium in human septic shock is well documented (see Fig. 21.1).[32-34] Similarly, hemorrhagic shock in experimental models has been linked to both myocardial depression[35,36] and vascular dysfunction (see Fig. 21.1).[37,38] Cardiogenic shock typically presents with increased ventricular filling pressures. However, many patients have been aggressively diuresed prior to the onset of shock and may have a relative hypovolemic component. In addition, systemic vascular resistance (SVR) is only inconsistently increased in cardiogenic shock, suggesting that an inflammatory element may exist under some circumstances. Finally, shock from any cause may cause a deterioration of the coronary perfusion pressure, the difference between mean arterial pressure (MAP) and the higher of left ventricular diastolic pressure or the right atrial pressure, resulting in some degree of myocardial ischemia and myocardial dysfunction.[39] Thus, although four categories of shock exist based on hemodynamic profile, clinical shock states tend to combine components of each.

HYPOVOLEMIC SHOCK

Hypovolemic shock may be related to dehydration, internal or external hemorrhage, gastrointestinal fluid losses (diarrhea or vomiting), urinary losses due to either diuretics or kidney dysfunction, or loss of intravascular volume to the interstitium due to decrease of vascular permeability (in response to sepsis or trauma). In addition, venodilatation due to a number of causes (sepsis, spinal injury, various drugs and toxins) may result in a relative hypovolemic state (see Box. 21.2, Fig. 21.1). Hemodynamically, hypovolemic shock is characterized by a fall in ventricular preload resulting in decreased ventricular diastolic pressures and volumes (Table 21.1). Cardiac index (CI) and stroke volume index (SVI) are typically reduced. In addition to hypotension, a decreased pulse pressure may be noted. Due to a decreased output and unchanged or increased metabolic demand, mixed venous oxygen saturation (MVo_2) may be decreased and the arteriovenous oxygen content difference widened. Clinical characteristics include pale, cool, clammy skin (often mottled); tachycardia (or if severe shock, bradycardia)[7,40]; tachypnea; flat, nondistended peripheral veins; decreased jugular venous pulse; decreased urine output; and altered mental status.

A number of factors may influence the development and hemodynamic characteristics of hypovolemic shock in humans. Studies in animals and humans have demonstrated a clear relationship between the degree of circulating blood volume loss and clinical response.[41-44] Acute loss of 10% of the circulating blood volume is well tolerated, with tachycardia the only obvious sign. CI may be minimally decreased despite a compensatory increase in myocardial contractility. SVR typically increases slightly, particularly if sympathetic stimulation augments mean arterial pressure (MAP). Compensatory mechanisms begin to fail with a 20% to 25% volume loss. Mild to moderate hypotension and decreased CI may be present. Orthostasis (with a blood pressure decrease of 10 mm Hg and increased heart rate of 20 to 30 beats/minute) may become apparent. There is a marked increase in SVR and serum lactate may begin to rise. With decreases of the circulating volume of 40% or more, marked hypotension with clinical signs of shock is noted. CI and tissue perfusion may fall to less than half normal. Lactic acidosis is usually present at this stage and predicts a poor outcome.[45,46] The case fatality rate can exceed 50% in hemorrhagic shock associated with trauma.[47]

The rate of loss of intravascular volume and the preexisting cardiac reserve is of substantial importance in the

Box 21.2 Classification of Shock

Hypovolemic (Oligemic)

Hemorrhagic
Trauma
Gastrointestinal
Retroperitoneal
Fluid depletion (nonhemorrhagic)
External fluid loss
Dehydration
Vomiting
Diarrhea
Polyuria

Interstitial Fluid Redistribution

Thermal injury
Trauma
Anaphylaxis

Increased Vascular Capacitance (Venodilatation)

Sepsis
Anaphylaxis
Toxins/drugs

Cardiogenic

Myopathic

Myocardial infarction
Left ventricle
Right ventricle
Myocardial contusion (trauma)
Myocarditis
Cardiomyopathy
Postischemic myocardial stunning
Septic myocardial depression
Pharmacologic
Anthracycline cardiotoxicity
Calcium channel blockers

Mechanical

Valvular failure (stenotic or regurgitant)
Hypertropic cardiomyopathy
Ventricular septal defect

Arrhythmic

Bradycardia
Sinus (e.g., vagal syncope)
Atrioventricular blocks
Tachycardia
Supraventricular
Ventricular

Extracardiac Obstructive

Impaired diastolic filling (decreased ventricular preload)
Direct venous obstruction (vena cava)
Intrathoracic obstructive tumors
Increased intrathoracic pressure (decreased transmural pressure gradient)
Tension pneumothorax
Mechanical ventilation (with positive end-expiratory pressure [PEEP] or volume depletion)
Decreased cardiac compliance
Constrictive pericarditis
Cardiac tamponade
Acute
Post MI free wall rupture
Traumatic
Hemorrhagic (anticoagulation)
Chronic
Malignant
Uremic
Idiopathic

Impaired Systolic Contraction (Increased Ventricular Afterload)

Right Ventricle

Pulmonary embolus (massive)
Acute pulmonary hypertension

Left Ventricle

Saddle embolus
Aortic dissection

Distributive

Septic (bacterial, fungal, viral, rickettsial)
Toxic shock syndrome
Anaphylactic, anaphylactoid
Neurogenic (spinal shock)
Endocrinologic
Adrenal crisis
Thyroid storm
Toxic (e.g., nitroprusside, bretylium)

development of hypovolemic shock. As an example, whereas an acute blood loss of 1 L in a healthy adult may result in mild to moderate hypotension with a reduced pulmonary artery occlusion pressure (PAOP) and central venous pressure (CVP),[42] the same loss over a longer period of time may be well tolerated due to compensatory responses such as tachycardia, increased myocardial contractility, increased red blood cell 2,3-diphosphoglycerate (2,3 DPG), and increased fluid retention. On the other hand, a similar slow loss may lead to substantial hemodynamic compromise in a person with a limited cardiac reserve, even while the person's PAOP and CVP remain elevated.

Hypovolemic shock represents more than a simple mechanical response to loss of circulating volume. It is a dynamic process involving competing adaptive (compensatory) and maladaptive responses at each stage of development. Thus, although intravascular volume replacement is always a necessary component of resuscitation from hypovolemia or hypovolemic shock, the biologic responses to the insult may progress to the point where such resuscitation is insufficient to reverse the progression of the shock syndrome. Patients who have sustained a greater than 40% loss of blood volume for 2 hours or more may be unable to be effectively resuscitated.[37,41,44] A series of inflammatory mediator, cardiovascular, and organ responses to shock are initiated, which supersede the importance of the initial insult in driving further injury.

CARDIOGENIC SHOCK

Cardiogenic shock results from the failure of the heart as a pump (see Box 21.2, Fig. 21.1). It is the most common cause

Table 21.1 Hemodynamic Profiles of Shock*

Diagnosis	CO	SVR	PWP	CVP	$S\bar{V}O_2$	Comments
Cardiogenic shock						
Caused by myocardial dysfunction	↓↓	↑	↑↑	↑↑	↓	Usually occurs with evidence of extensive myocardial infarction (>40% of left ventricular myocardium nonfunctional), severe cardiomyopathy, or myocarditis
Caused by a mechanical defect						
Acute ventricular septal defect	LVCO ↓↓ RVCO > LVCO	↑	nl or ↑	↑↑	↑ or ↑↑	If shunt is left to right, pulmonary blood flow is greater than systemic blood flow; oxygen saturation "step-up" (≥5%) occurs at right ventricular level; ↑ $S\bar{V}O_2$ is caused by left to right shunt
Acute mitral regurgitation	Forward CO ↓↓	↑	↑↑	↑ or ↑↑	↓	Large V waves (≥10 mm Hg) in pulmonary wedge pressure tracing
Right ventricular infarction	↓↓	↑	nl or ↑	↑↑	↓	Elevated right atrial and right ventricular filling pressures with low or normal pulmonary wedge pressures
Extracardiac obstructive shock						
Pericardial tamponade	↓ or ↓↓	↑	↑↑	↑↑	↓	Dip and plateau in right and left ventricular pressure tracings. The right atrial mean, right ventricular end-diastolic, pulmonary artery end-diastolic, and pulmonary wedge pressures are within 5 mm Hg of each other
Massive pulmonary emboli	↓↓	↑	nl or ↓	↑↑	↓	Usual finding is elevated right-sided heart pressures with low or normal pulmonary wedge pressure
Hypovolemic shock	↓↓	↑	↓↓	↓↓	↓	Filling pressures may appear normal if hypovolemia occurs in the setting of baseline myocardial compromise
Distributive shock						
Septic shock	↑↑ or nl, rarely ↓	↓ or ↓↓	↓ or nl	↓ or nl	↑ or ↑↑	The hyperdynamic circulatory state (↑ CO, ↓ SVR) associated with distributive forms of shock usually depends on resuscitation with fluids; before such resuscitation, a hypodynamic circulation is typical
Anaphylaxis	↑↑ or nl, rarely ↓	↓ or ↓↓	↓ or nl	↓ or nl	↑ or ↑↑	

*The hemodynamic profiles summarized in this table refer to patients with the diagnosis listed in the left column who are also in shock (mean arterial blood pressure < 60-65 mm Hg).

CO, cardiac output; CVP, central venous pressure; LV, left ventricular; nl, normal; PWP, pulmonary wedge pressure; SVR, systemic vascular resistance; $S\bar{V}O_2$, mixed venous oxygen saturation; ↑↑ or ↓, mild to moderate increase or decrease; ↑↑ or ↓↓, moderate to severe increase or decrease.

Modified from Parrillo JE: Septic shock: Clinical manifestations, pathogenesis, hemodynamics, and management in a critical care unit. In Parrillo JE, Ayers SM (eds): Major Issues in Critical Care Medicine. Baltimore, Williams & Wilkins, 1984.

of in-hospital mortality in patients with Q-wave myocardial infarction.[48,49] Hemodynamically, cardiogenic shock is characterized by increased ventricular preload (increased ventricular volumes, pulmonary wedge pressure [PWP] and CVP) (see Table 21.1). Otherwise hemodynamic characteristics are similar to those for hypovolemic shock (see Table 21.1). In particular, both involve reduced CI, SVI, and ventricular stroke work indices with increased SVR. Due to inadequate tissue perfusion, the MVO_2 is substantially reduced and the arteriovenous oxygen content difference increased. The degree of lactic acidosis may predict mortality.[50] Clinically, the specific signs of shock are similar. However, signs of congestive heart failure (volume overload) are typically present in cardiogenic shock. The jugular and peripheral veins may be distended. An S3 and evidence of pulmonary edema are usually found.

Cardiogenic shock is most commonly due to ischemic myocardial injury with a total of 40% of the myocardium nonfunctional.[49,51-53] Such damage may involve a single large myocardial infarction or may involve accumulation of damage from multiple infarctions. In addition, viable but dysfunctional "stunned" myocardium may temporarily contribute to cardiogenic shock postinfarction. Cardiogenic shock usually involves an anterior myocardial infarction with left main or proximal left anterior descending artery occlusion. Historically, the incidence of cardiogenic shock

due to Q-wave infarction has ranged from 8% to 20%.[48,54-56] Although several large studies demonstrate lower incidence rates (4% to 7%) when patients receive thrombolytic interventions,[55,57-60] retrospective community studies suggest no overall decrease in the incidence of postinfarction cardiogenic shock or cardiogenic shock mortality (70% to 90%) in the first decades following the introduction of this therapy.[48] Further, no trials have demonstrated that thrombolytic therapy reduces mortality rates in patients with established cardiogenic shock.[60,61] In contrast, several major studies suggest that mortality of infarction-related cardiogenic shock may be improved by emergent angioplasty.[56,62-64] Accordingly, data suggest a reduction in the incidence of acute infarction-related cardiogenic shock to <2% in 2003 in association with widespread use of emergent percutaneous coronary intervention.[62] This intervention has also been associated with a reduction of cardiogenic shock mortality risk from 60% to 84% to 43% to 47% in two large analyses.[56,62]

Mortality is better for cardiogenic shock due to surgically remediable cardiac lesions. Mitral valve failure may be associated with rupture or dysfunction of chordae or papillary muscles due to myocardial ischemia or infarction, endocarditis, blunt chest trauma, or prosthetic valve deterioration and is characterized by "v" waves of greater than 10 mm Hg on a PAOP tracing. Ischemic papillary muscle rupture frequently occurs 3 to 7 days after an infarct in left anterior descending coronary artery territory and may be preceded by the onset of a mitral regurgitant murmur.[65] Mortality is high in the absence of surgical therapy.[65] Acute aortic valve failure is most commonly due to endocarditis but may involve mechanical failure of prosthetic valves, or aortic dissection. Ventricular septal defects caused by myocardial infarction may also result in the abrupt onset of cardiogenic shock and can be diagnosed by a 5% step up in hemoglobin oxygen saturation between the right atrium and the pulmonary artery (due to left-to-right shunting of blood through the septum).[66] As with ischemic papillary muscle rupture, rupture of the intraventricular septum is most frequently seen with occlusions of the left anterior descending artery, a few days after infarction.[66]

The pathophysiology of cardiogenic shock due to a right ventricular infarction and failure is different from other forms of cardiogenic shock. Although some degree of right ventricular involvement is seen in half of inferior myocardial infarctions, only the largest 10% to 20% result in right ventricular failure and cardiogenic shock.[67] These infarctions usually involve part of the left ventricular wall as well. Isolated infarctions of the right ventricle are rare.[67,68]

Because therapy of this form of shock requires fluid resuscitation and inotropes (rather than vasopressors), differentiation from other causes of cardiogenic shock is crucial. Conditions compromising right ventricular function such as cardiac tamponade, restrictive cardiomyopathy, constrictive pericarditis, and pulmonary embolus are also included in the differential diagnosis. Each of these conditions may present with some of the typical clinical and hemodynamic findings of right ventricular infarction including Kussmaul's sign, and pulsus paradoxus with elevation and equalization of CVP, right ventricular systolic pressure, pulmonary artery diastolic pressure, and PAOP. Prognosis in this form of cardiogenic shock is distinctly better than that of cardiogenic shock due to left ventricular infarction[69,70]; however, an inferior infarction with right ventricular injury has a substantially worse prognosis than such an infarction without significant right-sided involvement.[71]

As with hypovolemic shock, a number of interactions may complicate the development of cardiogenic shock. Optimal cardiac performance in patients with impaired myocardial contractility may occur at substantially higher than normal PAOP (i.e., 20 to 24 mm Hg). Yet patients who develop cardiogenic shock are frequently initially treated with diuretics and may have a degree of hypovolemia (relative to their optimal requirements). Thus, patients should not be diagnosed with cardiogenic shock unless hypotension (MAP < 65 mm Hg) and reduced cardiac output (CI < 2.2 L/min/m^2) coexist with an elevated ventricular filling pressure.[72] Cautious fluid challenge may be required (in the absence of overt pulmonary edema) to increase the filling pressures to an optimal range. Other interactions include increased right ventricular ischemia due to decreased right coronary perfusion pressure (MAP decreased while right ventricular end-diastolic pressure is increased) and increased right ventricular afterload due to pulmonary hypertension. Right ventricular ischemia may also lead to right ventricular dilatation, septal shift, and impairment of left ventricular function.

Other causes of cardiogenic shock include acute myocarditis, end-stage cardiomyopathy, brady- or tachyarrhythmias, hypertrophic cardiomyopathy with obstruction, and traumatic myocardial contusion (see Box 21.2).

OBSTRUCTIVE SHOCK

Extracardiac obstructive shock results from an obstruction to flow in the cardiovascular circuit (see Box 21.2, Fig. 21.1). Pericardial tamponade and constrictive pericarditis directly impair diastolic filling of the right ventricle. Tension pneumothorax and intrathoracic tumors indirectly impair right ventricular filling by obstructing venous return. Massive pulmonary emboli (two or more lobar arteries with >50% of the vascular bed occluded), nonembolic acute pulmonary hypertension, large systemic emboli (e.g., saddle embolus), and aortic dissection may result in shock due to increased ventricular afterload.

The characteristic hemodynamic/metabolic patterns are, in most ways, similar to other low output shock states (see Table 21.1). CI, SVI, and stroke work indices are usually decreased. Because tissue perfusion is decreased, the MVo_2 is low, the arteriovenous oxygen content difference increased, and serum lactate frequently elevated. Other hemodynamic parameters are dependent on the site of the obstruction. Tension pneumothorax and mediastinal tumors may obstruct the great thoracic veins, resulting in a hemodynamic pattern (decreased CI and elevated SVR) similar to hypovolemia (although distended jugular and peripheral veins may be seen). Cardiac tamponade typically causes increased and equalized right and left heart ventricular diastolic pressures, pulmonary artery diastolic pressure, CVP, and PAOP. In constrictive pericarditis, right and left ventricular diastolic pressures are elevated and within 5 mm Hg of each other. Mean right and left atrial pressures may or may not be equal as well. Massive pulmonary embolus will result in right ventricular failure with elevated pulmonary artery and right heart pressures whereas PAOP remains normal. A systemic saddle embolus or aortic occlusion

due to dissection causes peripheral hypotension and signs of left ventricular failure including an elevated PAOP. Clinical signs are similarly dependent on the site of the obstruction.

As with other forms of shock, the time course of development of the insult has a substantial impact on the clinical response. Ischemic rupture of the left ventricular free wall (usually 3 to 7 days after myocardial infarction) leads to immediate cardiac tamponade and shock with as little as 150 mL blood in the pericardium.[73-75] Survival requires emergency surgery.[74,75] Similar situations may develop with bleeding into the pericardium after blunt chest trauma or thrombolytic therapy. Pericardial tamponade due to malignant or inflammatory pericardial effusions usually develop much more slowly. Although shock may still develop, it usually requires substantially more pericardial fluid (1 to 2 L) to cause critical failure of right ventricular diastolic filling.[73] No large reliable studies examining mortality rates with and without therapy in these conditions are available due to the small numbers of cases.

A similar time course–dependent risk is seen with major pulmonary emboli. In those without preexisting cardiopulmonary disease, a massive embolus involving two or more lobar arteries and 50% to 60% of the vascular bed[76,77] may result in obstructive shock. However, if recurrent smaller pulmonary emboli result in right ventricular hypertrophy, a substantially larger total occlusion of the pulmonary vascular bed may be required to cause right ventricular decompensation. Analyses have suggested that the presence of shock due to pulmonary embolus (regardless of underlying chronic cardiopulmonary dysfunction) indicates a three- to sevenfold increase in mortality risk with the majority of deaths occurring within an hour of presentation.[78,79] An analysis of more than 70,000 unstable (hemodynamic instability or ventilator-requiring) patients with pulmonary embolus in the national inpatient sample shows that mortality in untreated patients is approximately 47%.[80] Systemic thrombolysis is associated with a substantial reduction in mortality to 15%. Where available, catheter-directed therapy may be even more efficacious with a lower risk of serious hemorrhage.[81] Shock due to pulmonary embolism is an indication for urgent thrombolytic or catheter-directed intervention.

DISTRIBUTIVE SHOCK

The defining feature of distributive shock is loss of peripheral resistance. Septic shock is the most common form and has the greatest impact on intensive care unit (ICU) morbidity and mortality.

Hemodynamically, distributive shock is characterized by an overall decrease in SVR (see Table 21.1). However, resistance in any specific organ bed or tissue may be decreased, increased, or unchanged. Initially, CI may be depressed and ventricular filling pressures decreased. After fluid resuscitation, when filling pressures are normalized or increased, CI is usually elevated. Due to hypotension, left and right ventricular stroke work indices are normally decreased. MVo_2 is increased above normal. Concomitantly, arteriovenous oxygen content difference is narrowed despite the fact that oxygen demand is usually increased (particularly in sepsis). The basis of this phenomenon may be that because total body perfusion (CI) is increased, perfusion is not effective in that either it does not reach the necessary tissues or the tissues cannot utilize the substrates presented. As a reflection of this inadequate "effective" tissue perfusion, lactic acidosis may ensue. Clinical characteristics of resuscitated distributive shock include, in contrast to the other forms of shock, warm, well-perfused extremities, a decreased diastolic blood pressure, and an increased pulse pressure. Nonspecific signs of shock include tachycardia, tachypnea, decreased urine output, and altered mentation. In addition, evidence of the primary insult may exist (urticaria for anaphylaxis, spinal injury for neurogenic shock, and evidence of infection in septic shock).

Septic shock (shock due to infection) and sepsis-associated multiple organ failure are the most common causes of death in ICUs of the industrialized world. As many as 800,000 cases of sepsis are admitted every year to American hospitals (comparable to the incidence of first myocardial infarctions) with half of those developing septic shock and about half of those (200,000) dying.[82] Since the 1970s there has been a progressive increase in the incidence of and total deaths from sepsis and septic shock.[5] The total toll of septic deaths is comparable to deaths from myocardial infarction and far exceeds the impact of illnesses such as AIDS or breast cancer.[82,83]

Septic shock is caused by the systemic activation of the inflammatory cascade. Numerous mediators including cytokines, kinins, complement, coagulation factors, and eicosanoids are activated or systemically released, resulting in profound disturbances of cardiovascular and organ system function[84] (Table 21.2). These mediators, particularly tumor necrosis factor α (TNFα), interleukin-1β (IL-1β), platelet activating factor (PAF), and prostaglandins are thought to mediate reduced peripheral vascular resistance seen in septic shock.

Loss of vascular autoregulatory control may explain some of the typical metabolic findings of sepsis and septic shock. An early theory postulated the existence of microanatomic shunts between the arterial and venous circulations. During sepsis, these shunts were said to result in decreased SVR and increased MVo_2.[85] However, although microanatomic shunting has been noted in localized areas of inflammation, systemic evidence of this phenomenon in sepsis and septic shock is lacking.[85-89] "Functional" shunting due to defects of microcirculatory regulation in sepsis has also been suggested.[90,91] Overperfusion of tissues with low metabolic requirements would increase MVo_2 and narrow the arteriovenous oxygen content difference. Relative vasoconstriction of vessels supplying more metabolically active tissues would result in tissue hypoxia and lactate production due to anaerobic metabolism. Observations that some capillary beds may be occluded by platelet microaggregates, leukocytes, fibrin deposits, and endothelial damage support this theory.[86,90,92] Additional support comes from studies that demonstrate evidence of oxygen supply–dependent oxygen consumption in sepsis.[93-97] A third theory suggests that circulating mediators cause an intracellular metabolic defect involving substrate utilization, which results in bioenergetic failure (decreased high-energy phosphate production) and lactate production.[98,99] Increased mixed venous oxygen saturation could then be explained by perfusion, which is increased in excess of tissue oxygen utilization capability. However,

Table 21.2 Inflammatory Mediators in Sepsis and Septic Shock

Mediator	Major Reported Effects
Pro-inflammatory Cytokines	
Tumor necrosis factor-α (TNFα)	Stimulates release of interleukin-1, interleukin-6, interleukin-8, platelet-activating factor, leukotrienes, thromboxane A_2, prostaglandins; may be able to stimulate macrophages directly to promote its own release Stimulates production of polymorphonuclear cells by bone marrow; enhances phagocytic activity of polymorphonuclear cells Promotes adhesion of endothelial cells, polymorphonuclear cells, eosinophils, basophils, monocytes, and, occasionally, lymphocytes by inducing increased expression of adhesion molecules Activates common pathway of coagulation and complement system Directly toxic to vascular endothelial cells; increases microvascular permeability Acts directly on hypothalamus to produce fever Reduces transmembrane potential of muscle cells and depresses myocardial contractility Decreases arterial pressure, systemic vascular resistance, and ventricular ejection fraction; increases cardiac output
Interleukin-1β (IL-1β)	Stimulates release of TNF, interleukin-6, interleukin-8, platelet-activating factor, leukotrienes, thromboxane A_2, prostaglandins; may also be capable of stimulating its own production Activates resting T cells to produce lymphocytes and other products; supports B-cell proliferation and antibody production; is cytotoxic for insulin-producing B cells Promotes adhesion of endothelial cells, polymorphonuclear cells, eosinophils, basophils, monocytes, and, occasionally, lymphocytes by inducing increased expression of adhesion molecules Promotes polymorphonuclear cell activation and accumulation Increases endothelial procoagulant activity Acts synergistically with TNF; enhances tissue cell sensitivity to TNF Depresses myocardial contractility Acts directly on hypothalamus to produce fever
Interleukin-2	May promote release of TNF and interferon-gamma Decreases arterial pressure, systemic vascular resistance, and ejection fraction; increases cardiac output
Interleukin-4	Enhances lymphocyte adhesion to endothelial cells Induces antigen expression on macrophages Synergistically increases TNF- or interleukin-1-induced antigen expression on endothelial cells, but inhibits the increased expression of adhesion molecules by TNF, interleukin-1, or interferon-gamma
Interleukin-6	Induction of hepatic acute phase protein response Induces myelomonocytic and terminal B lymphocyte differentiation; activates T cells/thymocytes May contribute to septic myocardial depression Inhibits TNF production
Interleukin-8	Chemotactic for both neutrophils and lymphocytes; induces tissue infiltration of both Inhibits endothelial-leukocyte adhesion; decreases the hyperadhesion induced by those molecules
Interleukin-17	Induces synthesis of TNF-α, IL-1β, IL-6, G-CSF, GM-CSF, TGF-β, and other chemokines
Interleukin-18	Initiates cell-mediated immune response Increases secretion of interferon-γ
Interferon-γ	Promotes release of TNF, interleukin-1, interleukin-6 (possibly due to its ability to augment effects of endotoxin on macrophages); augments production of adhesion molecules May act synergistically with TNF to produce cytotoxic and cytostatic activity; interacts with other cytokines in variable ways Encourages polymorphonuclear cell activation and accumulation; enhances the phagocytic activity of polymorphonuclear cells Promotes macrophage activation, macrophage microbicidal function, and expression of cellular receptors for TNF-α
Macrophage migration inhibitory factor (MIF)	Increases TNF-α and TLR4 expression Activates T-lymphocytes Increases mortality in experimental peritonitis
High-mobility group box protein-1 (HMGB1)	Possesses both cytokine and intracellular signaling activity May generate late organ failure of sepsis Impairs vascular endothelial integrity

Continued on following page

Table 21.2 Inflammatory Mediators in Sepsis and Septic Shock (Continued)

Mediator	Major Reported Effects
Anti-inflammatory Cytokines	
Interleukin-4	Induction of differentiation of naïve helper T cells to Th2 cells
Interleukin-10	Down-regulation of macrophage function, leading to decreased TNF-α release
Interleukin-1 receptor antagonist (IL-1RA)	Antagonistic blockade of IL-1β
Transforming growth factor β1 (TGFβ)	Broad immunomodulatory activity (protective in endotoxic shock) Inhibition of effect of proinflammatory cytokines on a variety of tissues Suppression of macrophage pro-inflammatory responses Interference with phagocytic activation
Endothelial Factors	
Endothelin 1	Strongly promotes vasoconstriction
Nitric oxide	Mediates vascular smooth muscle relaxation and arteriovenular dilatation in septic shock May be responsible for septic myocardial depression Involved in leukocyte/macrophage antimicrobial activity
Arachidonic Acid Pathway Factors and Metabolites	
Phospholipase A_2	Releases arachidonic acid (the precursor of eicosanoids such as leukotrienes, prostaglandins, and thromboxanes) Decreases arterial pressure, systemic vascular resistance, and ventricular ejection fraction; increases cardiac output
Leukotrienes	Promote neutrophil chemotaxis and adhesion of neutrophils to endothelium (neutrophils have specific receptors for leukotriene B_4) Increase vascular permeability, either directly or through interaction of neutrophils and endothelial cells Decrease coronary blood flow and myocardial contractility
Thromboxane A_2	Produces vasoconstriction of vascular beds; secondarily promotes release of endothelium-derived relaxing factor and may stimulate prostacyclin production Causes platelet aggregation and neutrophil accumulation Increases vascular permeability; enhances permeability of both single- and double-unit membranes Produces pulmonary bronchoconstriction
Prostaglandin E_2	Inhibits interleukin-1 production Low concentrations stimulate TNF release; higher concentrations suppress TNF production at a dose-dependent level Causes vasodilation and increased blood flow Has a beneficial effect on tissue perfusion and may thereby decrease the severity of tissue damage Acts synergistically with prostacyclin to increase the effects of serotonin and bradykinin on vascular permeability
Prostacyclin (prostaglandin I_2)	Inhibits platelet aggregation and adhesion Causes vasodilation and increased blood flow; in early sepsis, exerts a beneficial effect on tissue perfusion Produces smooth muscle relaxation
Others	
Platelet-activating factor	Stimulates release of TNF, leukotrienes, thromboxane A_2 Promotes leukocyte activation and subsequent free-radical formation Encourages platelet aggregation leading to thrombosis Markedly alters microvascular permeability, thereby promoting microvascular fluid loss Exerts a negative inotropic effect on the heart; lowers arterial blood pressure
Complement fragment C3a	Causes mast cell degranulation and vasodilatory mediator release
Fragment C5a	Causes smooth muscle contraction and mucous secretion Causes mast cells to degranulate and release vasodilatory mediators Promotes TNF release Enhances polymorphonuclear cell activation, migration, adherence, and aggregation Induces capillary leakage May decrease systemic vascular resistance and produce hypotension

Adapted from Bone RC: The pathogenesis of sepsis. Ann Intern Med 1991;115:457.

animal studies using nuclear magnetic resonance (NMR) spectroscopy demonstrate that high-energy phosphates are not depleted in septic animals as is expected in all of these theories.[100-102] According to these and other studies, cellular ischemia is not the dominant factor in metabolic dysfunction in sepsis.[100-106] Rather, circulating mediators may result in cellular dysfunction, aerobic glycolysis, and lactate production in the absence of global ischemia.[101] This position is weakened by data suggesting that increased lactate in septic shock is also associated with decreased pH (which would not be expected in aerobic glycolysis)[101] and, to some extent, by studies that support the existence of oxygen supply–dependent oxygen consumption in sepsis.[94-97]

The trigger for systemic activation of the inflammatory cascade is the presence of gram-negative bacilli in 50% to 75% of cases of septic shock. Gram-positive bacteria account for most of the remainder, but infection with fungi, protozoa, and viruses can also result in septic shock.[107-109] Investigations suggest a surprising commonality of signaling mechanisms in septic shock via Toll-like receptors from a broad range of etiologic agents.[110-114] Despite aggressive supportive care and antibiotic treatment, mortality is 50% overall and may exceed 70% for gram-negative septic shock.[107] Of those succumbing to septic shock, approximately 75% are early deaths (within 1 week of shock), primarily due to hyperdynamic circulatory failure.[115] Late mortality is usually due to MODS.[115]

More than any other form of shock, distributive and, particularly, septic shock involves substantial elements of the hemodynamic characteristics of other shock categories (see Fig. 21.1, Table 21.1). As noted, all forms of distributive shock involve decreased mean peripheral vascular resistance. Prior to fluid resuscitation, distributive shock also involves a relative hypovolemic component. The first element of this relative hypovolemia is an increase of the vascular capacitance due to venodilatation. This phenomenon has been directly supported in animal models of sepsis[116-120] and is reinforced by the fact that clinical hypodynamic septic shock (low cardiac output) can usually be converted to hyperdynamic shock (high cardiac output) with adequate fluid resuscitation.[115,121,122] Relaxation of vascular smooth muscle is attributed to a number of the mediators known to circulate during sepsis. These same mediators also contribute to the second cause of hypovolemia in sepsis, third-spacing of fluid to the interstitium due to a loss of endothelial integrity. In addition, a number of studies have demonstrated that human septic shock is characterized by myocardial depression (biventricular dilatation and decreased ejection fraction).[32-34] Circulating substances such as TNFα, IL-1β, platelet activating factor (PAF), leukotrienes, and, most recently, interleukin-6 (IL-6) have been implicated in this process.[123-130]

Anaphylactic shock is a form of distributive shock caused by the release of mediators from tissue mast cells and circulating basophils. Anaphylaxis, an immediate hypersensitivity reaction, is mediated by the interaction of IgE antibodies on the surface of mast cells and basophils with the appropriate antigen. Antigen binding results in the release of the primary mediators of anaphylaxis contained in the basophilic granules of mast cells and basophils. These include histamine, serotonin, eosinophil chemotactic factor, and various proteolytic enzymes.[131] Subsequently, a number of secondary lipid mediators are synthesized and released including PAF, bradykinin prostaglandins, and leukotrienes (slow-reacting substance of anaphylaxis).[131] An anaphylactoid reaction (clinically indistinguishable from anaphylaxis) results from the direct, nonimmunologic release of mediators from mast cells and basophils and can also result in shock.

Anaphylaxis is triggered by insect envenomations (*Hymenoptera* bees, hornets, and wasps) and certain drugs, especially antibiotics (beta-lactams, cephalosporins, sulfonamides, vancomycin).[131] In addition, less frequently, heterologous serum (e.g., tetanus antitoxin, snake antitoxin, antilymphocyte antisera), blood transfusion, immunoglobulin (particularly in IgA-deficient patients), and egg-based vaccine products have been implicated.[131] Anaphylactoid reactions can be caused by a wide range of medical agents including ionic contrast media, protamine, opiates, polysaccharide volume expanders such as dextran and hydroxyethyl starch, muscle relaxants, and anesthetics.[131]

The hemodynamic features of anaphylactic shock are very similar to those for septic shock and include elements of hypovolemia (due to interstitial edema and venodilatation) and myocardial depression.[132-136] Cardiac output and ventricular filling pressures may be reduced until patients are fluid resuscitated.[136,137] In addition to typical findings of shock, patients may demonstrate urticaria, angioedema, laryngeal edema, and severe bronchospasm.

Neurogenic shock involves the loss of peripheral vasomotor control due to dysfunction or injury of the nervous system. The classic example is shock associated with spinal injury. A similar phenomenon is active in vasovagal syncope and spinal anesthesia, but such conditions are self-limited and transient. The major cause of shock in spinal injury appears to be loss of venous tone resulting in increased venous capacitance. Arteriolar tone may also be affected, resulting in increased cardiac output after fluid resuscitation.

Adrenal crisis (see also Chapter 59) is an uncommon cause of shock, which can be difficult to diagnose as it occurs in patients with other active disease processes and the clinical features may mimic infection. It is a life-threatening emergency that requires prompt diagnosis and management.

Adrenal crisis is caused by a deficiency of adrenal production of mineralocorticoids and glucocorticoids. It may occur de novo in patients with critical illness or may occur against a background of occult adrenal insufficiency. In the critical care setting, the most common cause of de novo acute adrenal insufficiency is bilateral adrenal hemorrhage in association with overwhelming infections (classically meningococcal, but frequently gram-negative bacteria), human immunodeficiency virus infection, or anticoagulation.[138,139] In addition, fungal infections such as histoplasmosis, blastomycosis, and coccidioidomycosis and malignant infiltration of the adrenals may cause acute adrenal insufficiency in ICU patients.[139] In some patients, steroid production remains adequate for the baseline state despite adrenal disease. Once stressed, however, the adrenal response is inadequate, leading to decompensation and adrenal crisis. Stressors may be relatively innocuous or may be severe. A febrile illness, infection, trauma, surgery, dehydration, or any other intercurrent illness may trigger the crisis. Abrupt cessation of

glucocorticoid therapy or replacement may also result in adrenal crisis.

Symptoms are generally nonspecific and may include anorexia, nausea, vomiting, diarrhea, abdominal pain, myalgia, joint pains, headache, weakness, confusion, and agitation or delirium.[139,140] Fever (often out of proportion to any minor infection) is almost always present, and hypotension, initially due to hypovolemia, is frequent.[139] The initial hemodynamic pattern may resemble hypovolemic shock (if shock is due only to adrenal crisis). With volume resuscitation, a high output, vasopressor-refractory shock may become apparent.[141,142]

Shock due to adrenal crisis may be masked by or contribute to shock due to other concomitant critical illnesses, particularly septic shock. Thus, if vasopressor-refractory shock occurs in patients potentially predisposed to adrenal insufficiency, a cortisol level and rapid adrenocorticotropic hormone (ACTH) stimulation test must be performed and the patient given glucocorticoids and other therapy.

An unrecognized "relative" adrenal insufficiency has been implicated in the pathogenesis of human septic shock.[143-147] In this circumstance, sepsis is associated with a suboptimal adrenal response with an improvement in cardiovascular parameters or outcome with "stress" dose corticosteroid administration.[143,145,146,148,149] One randomized controlled trial has suggested that prospective "stress dose" therapy with a combination of hydrocortisone (50 mg intravenous every 6 hours) and fludrocortisone (50 μg oral/nasogastric daily) for 7 days improved outcome in nonresponders to corticotropin challenge.[150] Unfortunately, confirmatory randomized trials have failed to reproduce this finding.[151,152]

COMPENSATORY RESPONSES TO SHOCK

Shock is usually not a discrete condition occurring abruptly after injury or infection. With the onset of hemodynamic stress, homeostatic compensatory mechanisms engage to maintain effective tissue perfusion. At this time, subtle clinical evidence of hemodynamic stress may be apparent (tachycardia, decreased urine output), but overt evidence of shock (hypotension, altered sensorium, metabolic acidosis) may not. Therapeutic interventions have a high probability of preventing ischemic tissue injury and initiation of systemic inflammatory cascades during this early compensated stage. Adaptive compensatory mechanisms fail and organ injury ensues if the injury that initiates shock is too extensive or progresses despite therapy. As the duration of established shock increases, therapy is less likely to be effective in preventing organ failure and death.

Various sensing mechanisms involved in physiologic compensatory responses exist to recognize hemodynamic and metabolic dyshomeostasis (Fig. 21.2). Low-pressure right atrial and pulmonary artery stretch receptors sense volume changes. A decrease in circulating volume (or an increase of venous capacitance) results in an increase in sympathetic discharge from the medullary vasomotor center.[153,279,280] Aortic arch, carotid, and splanchnic high pressure baroreceptors sense early blood pressure changes close to the physiologic range.[153,279,280] An increase of sympathetic discharge from the medullary vasomotor center results from a small to moderate decrease in blood pressure associated with early shock. However, once mean arterial pressure falls below about 80 to 90 mm Hg, aortic baroreceptor activity is absent. Subsequently, carotid baroreceptor response is eliminated as mean pressure falls below 60 mm Hg. As blood pressure falls further, carotid and aortic chemoreceptors, sensitive to decreased Po_2, increased Pco_2, and increased hydrogen ion concentrations (decreased pH), dominate the response. These receptor complexes, active only when mean blood pressure is less than approximately 80 mm Hg, are of minimal relevance during physiologic states.[153] During shock, they make a substantial contribution to increases of sympathetic tone.

During severe shock, the most powerful stimulus to sympathetic tone is the central nervous system ischemic response.[153] The lower medullary chemoreceptors for this response (thought to be sensitive to increased CO_2 associated with decreased cerebral perfusion) become active when mean blood pressure falls below 60 mm Hg. Sympathetic stimulation provided by these receptors peaks at mean pressures of 15 to 20 mm Hg and results in maximal stimulation of the cardiovascular system.[153] The Cushing response to increased intracranial pressure is an example of activation of this reflex under different circumstances.

Other mechanisms also play a role in the compensatory response to shock. Vasopressin release is regulated by alterations of serum osmolality. During effective hypovolemia due to intravascular volume loss or increased vascular capacitance, low-pressure, right atrial stretch receptors can override osmolar control of vasopressin response to result in the retention of body water.[153,281] Similarly, during hypovolemia and shock, the juxtaglomerular apparatus in the kidneys responds to decreased perfusion pressure by renin release.[153]

All compensatory responses to shock, whether hemodynamic, metabolic, or biochemical, support oxygen delivery to vital organs. These responses are similar (to varying extents) for different classes of shock and can be broken down into four components: (1) preserving mean circulatory pressure (a measure of venous pressure) by either maintaining total intravascular volume or increasing stressed volume (i.e., increasing venous tone), (2) optimizing cardiac performance, (3) redistributing perfusion to vital organs, and (4) optimizing the unloading of oxygen at the tissues (Box 21.3, Fig. 21.E3).

Mean circulatory pressure and venous return are sustained in early shock by a number of mechanisms. Acutely, total intravascular volume is supported by alterations of capillary hydrostatic pressure as described by Starling.[282] Sympathetic activation results in precapillary vasoconstriction. In combination with initial hypotension, this results in decreased capillary hydrostatic pressure.[282] A decrease in capillary hydrostatic pressure enhances intravascular fluid shift due to maintained plasma oncotic pressures. Transcapillary fluid influx following the removal of 500- to 1000-mL blood volumes in humans can be as high as 2 mL/minute with full correction of intravascular volume by 24 to 48 hours.[283] The intravascular volume may also be supported by the osmotic activity of glucose generated by glycogenolysis. Increased extracellular osmolarity results in fluid redistribution from the intracellular to the extracellular space.

Intravascular volume is also conserved by decreasing renal fluid losses. Renal compensatory mechanisms are of limited value in acute shock but can have more impact in the subacute phase. Decreased renal perfusion associated with reduced cardiac output and afferent arteriolar

PATHOGENESIS AND PATHOPHYSIOLOGY OF SHOCK

The inability of cells to obtain or utilize oxygen in sufficient quantity to optimally meet their metabolic requirements has classically been considered to be the pathophysiologic basis of all forms of shock. In the first half of the twentieth century, the study of shock focused on the relatively distinct hemodynamic physiology, which characterizes the different forms of shock. Since then, evidence has accumulated that the various types of clinical shock have significant overlap in their hemodynamic characteristics. In parallel, shock of most etiologies has been shown to involve similar biochemical and metabolic pathways. In the following section, the pathophysiology and pathogenesis of shock will be reviewed from the hemodynamic to the molecular level.

HEMODYNAMIC BASIS OF SHOCK

From a hemodynamic perspective, shock is the failure of cardiovascular adaptation to systemic dyshomeostasis induced by trauma, infection, or other insult such that cardiac output or blood pressure are compromised. This failure is manifested by inadequate organ and tissue perfusion. Although effective perfusion also depends on microcirculatory and intracellular factors (see Box 21.1), the hemodynamic aspects of shock can be described, in part, by the contributions of cardiac and arterial vascular function to blood pressure and cardiac output.

ARTERIAL PRESSURE

Although cardiac output may be expressed as a function of MAP and vascular resistance (CO = [MAP − CVP]/SVR), cardiac output is not directly dependent on MAP in most physiologic states. Instead, blood pressure is typically dependent on cardiac output and vascular resistance. Blood pressure, however, does provide a mechanism to indirectly sense cardiac output and global perfusion perturbations for autoregulatory purposes.

The ability of all organ vascular beds to support normal blood flow depends on the maintenance of blood pressure within the defined range for that organ (Fig. 21.E1).[153] Vital organs such as the brain and heart, in particular, are able to autoregulate blood flow over a wide range of blood pressure. Failure to maintain the minimal MAP and perfusion pressure required for autoregulation during hypodynamic circulatory shock indicates a severe reduction in cardiac output. Pharmacologic support of blood pressure in such situations (with alpha-adrenergic agonists) usually results in decreased total systemic perfusion as sensitive vascular beds constrict and overall vascular resistance increases. However, due to their strong autoregulatory capacity, vital organs maintain increased perfusion under these conditions.

In addition to sufficient cardiac output, effective perfusion requires appropriate distribution of blood flow. Failure to maintain blood pressure within the autoregulatory range results in a distribution of blood flow that strictly depends on the passive mechanical properties of the vasculature.[154] This may result in inappropriate distribution of perfusion between and within tissues and organs. Late hemorrhagic shock has been shown to be characterized by abnormal microvascular flow with dilatation of precapillary sphincters.[37]

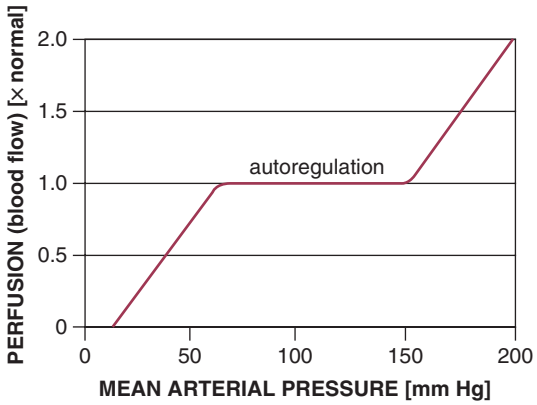

Figure 21.E1 Idealized representation of blood flow autoregulation. Within the autoregulatory range of blood pressure for a tissue or organ, perfusion can be held relatively constant. Outside this range, autoregulation fails and perfusion becomes a function of mean arterial pressure.

CARDIAC OUTPUT

The fact that total systemic perfusion is defined by cardiac output underlies its importance in shock. The product of heart rate and stroke volume determines cardiac output (CO = heart rate [HR] × stroke volume [SV]). Stroke volume (a measure of myocardial performance) is dependent on preload, afterload, and contractility.

Preload represents the extent of precontraction myocardial fiber (or sarcomere) stretch. In vivo, preload is the end-diastolic ventricular volume. Because measurement of such volumes in the clinical context is difficult, intracardiac pressures, which can be determined more easily, are frequently substituted. There are difficulties with this approach. The relationship of ventricular end-diastolic volume (preload) to end-diastolic pressure is nonlinear. Further, alterations of myocardial compliance render CVP and PAOP unreliable as estimates of preload in critically ill patients.[155]

Preload is dependent on circulating volume, venous tone, atrial contraction, and intrathoracic pressure among other factors.[153,156] Atrial contraction is particularly important in those with impaired ventricular function. Although it accounts for only 5% to 10% of cardiac output in healthy humans, synchronized atrial contraction contributes as much as 40% to 50% of the cardiac output in patients with severe left ventricular dysfunction.[156] Increased intrathoracic pressure or increased venous capacitance affects preload by reducing venous return.[153,157] Nitrovasodilators such as nitroglycerin may decrease cardiac output despite arteriolar vasodilation due to their venodilatory (decreased preload) effects. Conversely, the earliest increases in cardiac output seen with sympathetic stimulation and exogenous catecholamine infusion are related to venoconstriction-induced increases of venous return and preload.[158] Cardiogenic and some forms of obstructive shock are typically characterized by increased preload. Preresuscitation distributive shock and hypovolemic shock are uniformly associated with decreased preload.

Afterload refers to the total resistance to the ejection of blood from the ventricle during contraction. Increasing

afterload results in decreased extent and velocity of myocardial contraction. Excessive afterload (aortic dissection, pulmonary embolus) causes some forms of obstructive shock. Ex vivo, afterload can be easily defined as a resistive force applied to an isolated papillary muscle. Because the heart does not displace a fixed mass but rather rhythmically moves a viscous, non-newtonian fluid through branching viscoelastic conduits, the definition of afterload in vivo is difficult.

Afterload has been suggested to be equivalent to systolic myocardial wall stress. This definition suggests that afterload is substantially dependent on intrinsic cardiac mechanical and functional properties.[159] An alternative approach equates left ventricular afterload with the mechanical properties of the arterial side of the circulatory system. Aortic input impedance, which represents the total resistance to flow from outside the left ventricle, is determined by the inertial and viscous properties of blood and the resistive and viscoelastic properties of the arterial system. The term covers SVR, heart rate effects, and pulse wave reflections in the arterial tree.[159] Although it is an accurate measure of afterload in pulsatile systems, assessment of impedance is technically difficult, requiring continuous harmonic analysis of rhythmic variations of aortic pressure and flow. Systemic vascular resistance is a limited approximation of aortic input impedance based on a model that assumes nonpulsatile flow. At a heart rate of 0, SVR and aortic input impedance are equivalent. From a clinical point of view, SVR is the most practical way of assessing afterload.

Afterload is increased in pathologic conditions such as aortic stenosis, systemic embolism, and hypertension. Vasopressors including α-agonists (e.g., phenylephrine, norepinephrine) and vasopressin also increase afterload, whereas nitrates and other vasodilator agents decrease it. Increased intrathoracic pressure due to mechanical ventilation and positive end-expiratory pressure (PEEP) decrease left ventricular afterload while increasing right ventricular afterload. Hypodynamic and hyperdynamic shock are usually characterized by increased and decreased afterload, respectively.

Contractility refers to the intrinsic ability of myocardial fibers to shorten under given loading conditions. Under normal conditions, determinants of contractility include myocardial mass and sympathoadrenal activation state. In pathologic states (e.g., shock), hypoperfusion/ischemia, myocardial cell injury (e.g., reperfusion injury, myocarditis), acidosis, and circulating myocardial depressant substances (such as seen in sepsis) depress cardiac contractility (Fig. 21.E2).

As with preload and afterload, the ex vivo/in vitro assessment of contractility is straightforward. Assessment of in vivo contractility (even in experimental animals) is substantially more difficult due to the intrinsic lability of preload and afterload. Relatively load-independent variables such as peak systolic pressure/end-systolic volume ratio may be the most clinically useful measures of contractility.[160] Many of these variables can be obtained echocardiographically.

VENOUS FUNCTION IN SHOCK

Given that the cardiovascular circuit is a closed system and cardiac output cannot exceed the rate of return of blood to the right ventricle, venous return can be considered a fundamental determinant of cardiac performance. Although

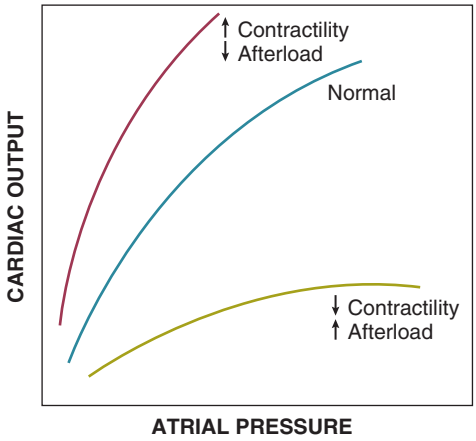

Figure 21.E2 Cardiac function curve demonstrating the effect of variations of preload (atrial pressure), contractility, and afterload on cardiac performance.

preload is a related variable, it primarily reflects ventricular properties related to compliance and heart rate, whereas venous return is substantially dependent on the extracardiac properties of the systemic venous circulation. Maximum venous return is described by the equation:

$$(Pmc - Pa)/Rv \quad [1]$$

where Pmc is the mean circulatory pressure (the upstream driving pressure of the systemic venous circulation, i.e., the intravascular pressure measured when the heart is stopped), Pa is the right atrial pressure (the downstream pressure that opposes flow to the right ventricle), and Rv is the venous resistance (resistance of the conduit to flow). Pmc equals the stressed volume or Vs portion of the vascular volume, which contributes to venous pressure, divided by the mean vascular compliance (C):

$$Pmc = Vs/C \quad [2]$$

Stressed volume is dependent on total vascular volume (Vt) and the state of venous tone (i.e., venoconstriction). It is defined as the difference between Vt and the unstressed vascular volume (Vo), the intravascular volume that remains when the vascular circuit is equalized to atmospheric pressure (i.e., the volume remaining after passive exsanguination). Stressed volume is approximately 30% of total blood volume in both humans and experimental animals.[161-163] Compliance refers to the total elastic properties of the entire cardiovascular circuit inclusive of the heart and vasculature.

As Equation 1 shows, the only direct role the heart plays on venous return is to alter right atrial pressure (Pa). Mean arterial pressure has no direct effect at all despite the fact that it is closely related to cardiac output in the systemic circulation (MAP − CVP = CO × SVR).

Rapid alterations of venous return are typically mediated by changes of Pmc or Rv. Pmc is acutely influenced by changes of Vs, either directly through alterations of venous capacitance, which primarily involves changes of small vein and venular tone (exogenous vasopressors or vasodilators, sympathetic stimulation), or indirectly by changes of Vt (volume depletion or infusion). Compliance is substantially a passive mechanical property of the vasculature and does

not cause acute alterations of Pmc or venous return. Venous resistance (Rv) to flow is acutely altered by changes of the caliber of large diameter veins, particularly the vena cava and great veins of the thorax. However, although resistance resides primarily in large veins and the vena cava, and venous capacitance resides primarily in small veins and venules, all veins contribute to resistance and capacitance to some extent. Alterations of venous tone (either pharmacologic or physiologic), therefore, tend to induce opposing changes in Pmc and Rv with respect to venous return. Vasodilatation decreases Pmc by decreasing stressed volume but also decreases Rv. Vasoconstriction results in increases of both Pmc and Rv. Only alterations in Vt alter Pmc without affecting Rv.

The venous return relationship is shown in Figure 21.E3.[153,164,165] Because the systemic venous bed comprises the bulk of venous capacitance, the systemic venous vasculature dominates the physiology of venous return. Venous return is linearly related to Pa (right atrial pressure) down to 0 cm H_2O (= atmospheric pressure), at which point intermittent collapse of the great veins results in limitation of return producing the plateau.[153,166] The slope of the line representing venous return is the inverse of the resistance (1/Rv). The ordinate intercept denotes the right atrial pressure (Pa) at which venous return is zero. But according to Equation 1, venous return is zero only when right atrial pressure (Pa) equals the Pmc. Thus, the intercept of the atrial pressure axis represents Pmc. Changes of Pmc shift the curve to the left or right without changing the slope of the line (see Fig. 21.E3, line a to line b and c). Changes of Rv change the slope of the line without changing the Pmc (see Fig. 21.E3, line a to line d and e).

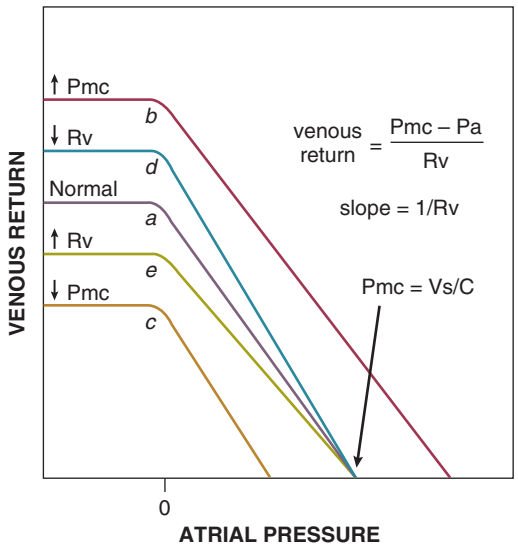

Figure 21.E3 Graphic representation of venous return with varying atrial pressures, mean circulatory pressures, and venous resistance. Altering mean circulatory pressure displaces the line representing venous return (line **a** to line **b** or **c**) without changing the slope (which represents venous resistance to flow). Altering venous resistance changes the slope of the venous return curve (line **a** to line **d** or **e**) without changing the intercept point of the venous return line with the ordinate (which defines mean circulatory pressure). See text for details.

GRAPHIC ANALYSIS OF VENOUS-CARDIAC INTERACTIONS DURING SHOCK

In a closed system, cardiac output as determined by heart rate, preload, afterload, and contractility must equal venous return as determined by mean circulatory pressure, right atrial pressure, and venous resistance. Cardiac output, therefore, is not strictly a product of cardiac or vascular function but is dependent on their interaction. Because venous return and cardiac output are equal and are dependent on atrial pressure, the right heart Starling function curves can be superimposed on the systemic venous return curves using the same graphic parameters. The intersection of the two curves defines cardiac output and venous return for any given set of conditions involving the right heart and the systemic venous circulation. The circulatory physiology of shock can be described by the interaction of cardiac function and venous return curves.

Cardiogenic shock and obstructive shock due to increased afterload of the right or left ventricle (e.g., massive pulmonary embolus) result in a common change of the right ventricular Starling function curves. In the case of primary left ventricular loading or damage, this occurs because increased left ventricular filling pressures are passively transmitted to the right ventricle. The Starling curves are shifted downward and to the right (flatter) (Fig. 21.E4, point A to B), resulting in decreased cardiac output at increased atrial pressures. Therapy can consist of fluid resuscitation (increased Vt and Pmc), which may result in only modest augmentation of cardiac output despite significant increases of atrial pressures and ventricular filling pressures (point C); dobutamine, a beta-1 and beta-2 agonist that increases cardiac output by increasing contractility (point D); and both fluids and dobutamine (point E). Other catecholamines such as dopamine and norepinephrine, which both increase myocardial contractility and reduce venous capacitance, also increase afterload and have variable effects on cardiac output and venous return depending on which effect is dominant. Resistance to therapy may be noted if myocardial damage is sufficiently severe to flatten the Starling function curve to the point that increasing Pmc has

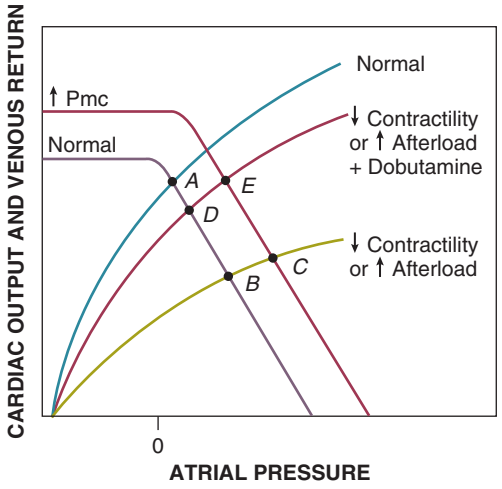

Figure 21.E4 Graphic representation of systemic venous return/right heart performance interactions during cardiogenic shock (point A to B) and therapy (see text for details).

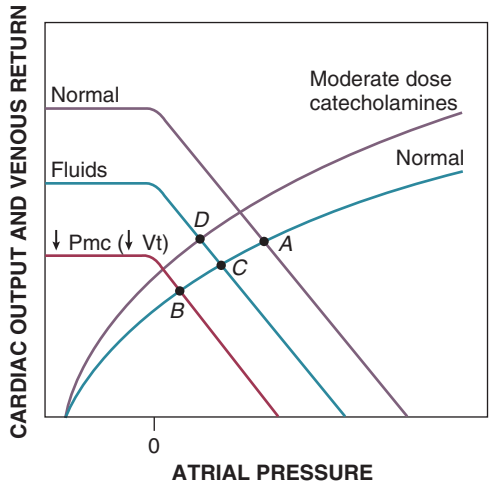

Figure 21.E5 Graphic representation of systemic venous return/right heart performance interactions during hypovolemic shock (point A to B) and therapy (see text for details).

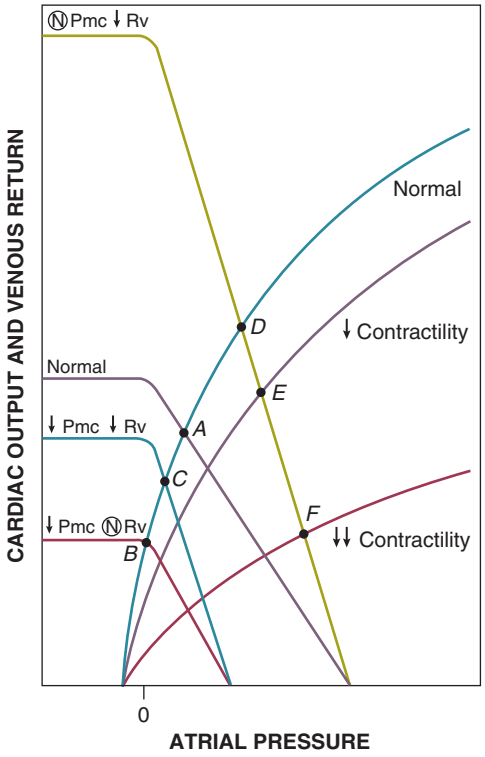

Figure 21.E6 Graphic representation of systemic venous return/right heart performance interactions during septic shock (point A to B) and therapy (see text for details).

little effect on increasing venous return/cardiac output and insufficient functional myocardium remains to respond to inotropes with increased contractility (a steeper Starling relationship).

Hypovolemic shock results from decreased Vt, Vs, and Pmc (Fig. 21.E5, point A to B). The venous return curve is shifted downward and to the left, resulting in a reduced venous return and cardiac output at lower right atrial pressures. Although late depression of myocardial contractility with shift of the Starling function curve downward and to the right (analogous to myocardial depression during cardiogenic shock) has been noted in experimental hemorrhagic shock,[35,36] this phenomenon is be considered here. Volume therapy, whether with crystalloid or colloid, tends to correct Pmc and venous return toward the original value (point C). Although optimal therapy of hypovolemic shock involves volume resuscitation, low-dose catecholamines exert similar hemodynamic effects; Pmc (and venous return) are augmented by an increase of the stressed volume (Vs), whereas the total (reduced from baseline) circulating volume (Vt) is unchanged (also point C).[165,167,168] These changes outweigh any deleterious effect on increasing venous resistance (Rv). Cardiac contractility and vascular resistance are minimally affected at these doses. At moderate infusion rates (and with sympathetic stimulation), cardiac contractility is also augmented (point D). With higher catecholamine infusion rates, venous resistance and afterload may increase to the point of decreasing cardiac output and venous return (not shown). For that reason, vasopressors may be used only with great caution in hypovolemic shock.

Septic shock is especially complicated. Sepsis may involve elements of hypovolemia, myocardial depression, and altered distribution of cardiac output. Total circulating volume (Vt) and stressed volume (Vs) are decreased due to loss of fluids to the interstitium (third-spacing) and due to insensible losses. Stressed circulating volume (Vs) is further decreased due to active dilation of small venules/veins resulting in increased venous capacitance. This increase in unstressed volume (Vt) and decrease in stressed volume (Vs) have been confirmed in experimental animal models of canine and porcine endotoxemia.[120,169] Thus, in unresuscitated septic shock, Pmc is almost universally decreased, resulting in reduced venous return and cardiac output (Fig. 21.E6, point A to B). Sepsis is also associated with dilatation of large veins and shunting of arterial blood flow to low-resistance (fast time constant) vascular beds, both of which decrease venous resistance and tend to augment venous return. Decreased venous resistance, however, does not fully compensate for decreased Pmc in unresuscitated septic shock. Cardiac output remains depressed (point B to C). With fluid resuscitation, Pmc may be corrected back toward normal, allowing the decreased Rv to be manifested by supernormal cardiac output and venous return (point D).[120] Patients with septic shock also develop myocardial depression, which is typically masked by the overall increase in cardiac output (point E). In about a fifth of patients, however, myocardial depression is sufficiently severe that venous return and, therefore, cardiac output remain depressed even after resuscitation (point F).

Human data suggest that sepsis is associated with a decrease of total vascular compliance.[170,171] However, it is unclear whether this represents a primary septic phenomenon or a neurohumorally mediated compensatory response.[170,172,173] Following fluid resuscitation, therapy of septic shock primarily involves catecholamines such as norepinephrine and dopamine. These affect the venous and cardiac function curves as specified earlier, although there are some data to suggest that both vascular and myocardial responsiveness to sympathomimetics may be reduced. In addition, they may also affect vascular compliance similar to

the potential compensatory neurohumoral effects described earlier.

Obstructive forms of shock such as those due to pericardial tamponade and tension pneumothorax can also be analyzed in the context of venous-cardiac interactions. For a detailed review of this subject matter, the reader is referred to several excellent reviews.[158,174]

Ventricular function of each distinct form of shock can also be examined by using end-systolic and end-diastolic pressure-volume analysis. This analysis can be demonstrated graphically using ventricular pressure-volume loops. Changes in stroke volume and ventricular contractility can be examined with respect to ventricular volume and pressure alterations in circulatory shock states. Although this represents a useful approach to the study of circulatory shock physiology, a review of the subject is beyond the scope of this chapter. The interested reader is referred to a number of cogent reviews.[175-177]

MICROVASCULAR FUNCTION IN SHOCK

Preserved microvascular (vessels less than 100 to 150 μM in diameter) function is a critical determinant of appropriate tissue perfusion during shock. Although adequate cardiac output at sufficient blood pressure is required for appropriate global perfusion and systemic hemodynamics, effective tissue perfusion also requires intact local and systemic microvascular function.

Distribution of cardiac output is a complicated process involving local intrinsic autoregulation and extrinsic regulation mediated by autonomic tone and humoral factors. Blood flow to individual organs may be affected by system-wide changes in microarteriolar tone or by local alterations in metabolic activity. Blood flow within organs also requires microvascular regulation to match blood flow to areas of highest metabolic activity.

Intrinsic control (autoregulation) of blood flow is thought to occur through two mechanisms. Rapid alterations of microvascular tone are mediated though endothelial stretch receptors so that sudden changes in perfusion pressure can be compensated by opposing changes in vascular resistance in order to maintain perfusion.[178] In addition, increases in metabolic activity within tissues and organs are thought to cause local elevation of various metabolites (CO_2, H+, etc.), resulting in vasodilation and increased perfusion to match substrate demand.[178]

Extrinsic control of vascular tone is primarily exerted through the autonomic nervous system. Parasympathetic release of acetylcholine to blood vessels results in nitric oxide and cyclic guanosine monophosphate (cGMP) generation in endothelial cells and vascular smooth muscle leading to vascular relaxation. Increases of sympathetic tone cause local norepinephrine release, activation of vascular alpha-adrenoreceptors, and increased vascular tone (Fig. 21.E7). Under stress, epinephrine and norepinephrine can be systemically released by sympathetic stimulation of the adrenal medulla. Basal control of blood pressure and flow resides in the activity of the renin-angiotensin system.

Alterations in microvascular function are effected through pre- and postcapillary sphincters that are sensitive to both intrinsic and extrinsic control mechanisms. Because the exchange of carbon dioxide, oxygen, and other substrates/metabolites as well as the compartmental regulation of fluids occurs at the capillary level, alteration of tone of either sphincter may have varying effects. Opening of either non-nutrient capillary sphincters (microanatomic shunts)[85] or increased flow to hypometabolic tissues (functional shunts)[86] will result in a suboptimal distribution of substrate supply with increased MVo_2. Failure to dilate sphincters supplying metabolically active tissues may result in ischemia and anaerobic metabolism with lactate production. Increased precapillary tone as seen with sympathetic stimulation results in increased blood pressure systemically and decreased hydrostatic pressure locally. This decreased hydrostatic pressure favors redistribution of volume from the interstitium to the circulation. Increased postcapillary

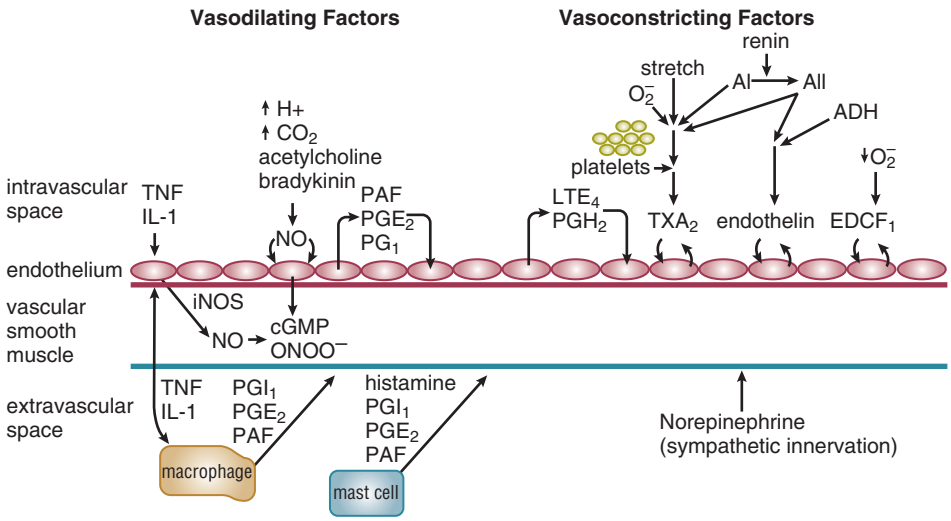

Figure 21.E7 Physiologic and pathophysiologic vasoactive factors. IL-1, interleukin-1β; TNF, tumor necrosis factor-α; NO, nitric oxide; iNOS, inducible nitric oxide synthetase; $ONOO^-$, peroxynitrite; PAF, platelet activating factor; PGE_2, prostaglandin E_2; PGI_2, prostacyclin; cGMP, cyclic GMP; TXA_2, thromboxane A_2; PGH_2, prostaglandin H_2; LTE_4, leukotriene E_4; $EDCF_1$, endothelium-derived contracting factor; O_2^-, superoxide anion; AI, angiotensin I; AII, angiotensin II; ADH, antidiuretic hormone (vasopressin).

tone (relative to precapillary) results in vascular pooling of blood and loss of fluid to the interstitium (due to increased hydrostatic pressure).

Organ blood flow changes are well characterized in shock states. Autoregulation of blood flow is dependent on maintenance of blood pressure within a defined range that varies among organs. The autoregulatory capacity of various organs can be determined by mechanically altering blood pressure in the organ vascular bed. With isolated local hypotension, the brain exhibits dominant autoregulatory capability with the ability to maintain blood flow over a wide range of pressures (30 to 200 mm Hg in dogs).[154] Coronary perfusion is also substantially autoregulated between 40 and 100 mm Hg. In contrast, mesenteric and renal blood flow becomes pressure dependent below about 60 mm Hg, whereas the vascular bed of skeletal muscle behaves in a passive manner at pressures outside 50 and 100 mm Hg. Human data suggest that overall, good autoregulation of blood flow exists in humans between pressures of 60 and 100 mm Hg.[154] In the context of normal physiology, blood flow is not effectively autoregulated outside this range. Without local adaptation, this would result in a mismatching of blood flow and metabolic demands producing organ failure and the metabolic correlates of shock. However, extrinsic adaptive mechanisms to protect the most vital organs come into play.

During hypovolemia and other hypodynamic forms of shock, extrinsic blood flow regulatory mechanisms overwhelm the autoregulatory response of most vascular beds. Blood flow to the heart and brain are well preserved due to dominant local autoregulation of flow. Blood flow to other organs is reduced relative to the decrease in total cardiac output as organ vascular resistance increases to maintain blood pressure.[179] This effect is mediated in part by both sympathetic neural activity and adrenal release of catecholamines.[154,179] This adaptive mechanism maintains perfusion to vital organs at mild to moderate levels of reduced cardiac output. If the insult is sufficiently severe or prolonged, organ ischemia and subsequent organ failure may develop. Even if resuscitation restores systemic circulatory hemodynamics, microvascular perfusion abnormalities persist for days.[180] Experimental data suggest that perfusion of brain, kidneys, liver, and other splanchnic organs remains impaired following resuscitation from hemorrhagic shock.[180] Persistence of inadequate matching of tissue substrate demand and delivery after resuscitation of shock can lead to continued ischemia/hypoxia of some tissues. This may explain why hemorrhagic shock–related tissue injury can be irreversible if its duration and severity are excessive. Animal models suggest this irreversible phase of severe hemorrhagic shock is characterized by vasodilatation of precapillary sphincters.[37]

During sepsis and septic shock, organ blood flow is disturbed at higher mean arterial pressures, suggesting a primary defect of microvascular function. Cerebral blood flow to the brain in humans has been shown to be depressed even before the onset of septic shock in patients with systemic inflammatory response syndrome.[181] This pathologic vasoconstriction (apparently a unique response of the cerebral circulation to sepsis) does not appear to be the cause of septic encephalopathy. Cerebral autoregulation remains intact during sepsis.[182] The greater decrease in coronary than systemic vascular resistance during human septic shock may suggest that myocardial autoregulation also remains intact despite the fact that, in contrast to the brain, myocardial perfusion is often increased during septic shock.[183,184]

Animal models demonstrate that all other vascular beds (splanchnic, renal, skeletal, cutaneous) exhibit decreased vascular resistance, with flow in these beds becoming increasingly dependent on cardiac output. This suggests both an active vasodilatory process and failure of extrinsic control of blood flow.[154] Inappropriate levels of splanchnic and skeletal muscle perfusion are also observed in humans during sepsis.[88] Other experimental data suggest that sepsis and septic shock are also associated with aberrant distribution of flow within organs.[86] In sepsis, vasodilatation and autoregulatory failure of the microvasculature may be responsible for mismatches of oxygen delivery and demand, resulting in anaerobic glycolysis with lactate production despite increased mixed venous oxygen saturation.

During both irreversible hemorrhagic shock and septic shock, peripheral vascular failure results in worsened matching of tissue demand and substrate supply, leading to failure of all organs and death. Among the potential responsible mechanisms are (1) tissue acidosis,[185] (2) catecholamine depletion and mediator-related vascular resistance to catecholamines,[186] (3) release of vasodilating and vasoconstricting arachidonic acid metabolites,[187] (4) decreased sympathetic tone due to altered central nervous system perfusion,[188] and (5) pathologic generation of nitric oxide by vascular smooth muscle cells.[38,189]

In addition to vasomotor dysfunction, shock is associated with other microvascular pathology. Prime among these is disruption of endothelial cell barrier integrity. The endothelial layer is responsible for maintaining oncotic proteins (mostly albumin) within the circulatory space. During shock, capillary permeability increases, resulting in a loss of plasma proteins into the interstitium. Endothelial injury, through the action of neutrophil-generated free radicals[190] and nitric oxide/peroxynitrite generation,[191,192] may account for this phenomenon. The release of vasoactive intermediaries such as histamine, bradykinin, PAF, leukotrienes, and TNFα appear to drive this pathologic process. Injury is initiated by leukocyte-endothelial cell interactions via adhesion molecules (integrins, selectins) that allow emigration of neutrophils to the tissues. Blockade of such activity or depletion of neutrophils attenuates tissue injury in animal models of shock.[193] With the loss of plasma proteins, the plasma oncotic pressure drops, interstitial edema develops, and circulating volume falls.

There is also evidence of intravascular hemagglutination of red cells, white cells, and platelets in almost all shock syndromes.[86,194] This may be due to primary microvascular clotting leading to microthrombi. Alternately, clotting may occur as a consequence of primary endothelial damage due to circulating cytokines, free radicals produced by reperfusion and neutrophils, or complement activation. In any case, the result may be further endothelial cell injury, microvascular abnormalities, and inadequate distribution of perfusion within tissues. Decreased deformability of erythrocytes due to membrane free radical injury may also play a role in microcirculatory alterations in hemorrhagic and septic shock.[195]

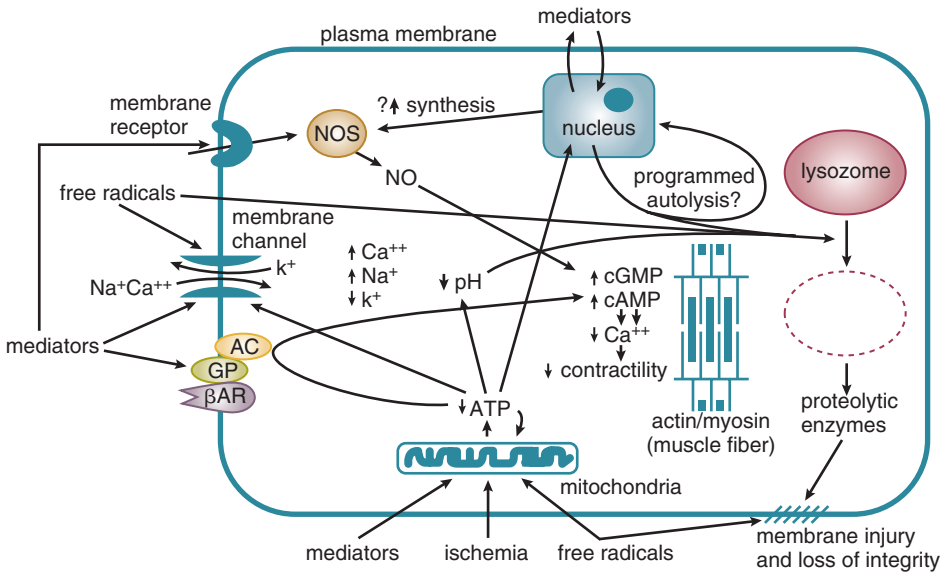

Figure 21.E8 Mechanisms of cellular dysfunction and injury in shock. Cell injury is mediated by multiple mechanisms during shock. Tissue ischemia may limit aerobic ATP generation. This results in further mitochondrial impairment due to deficits of mitochondrial membrane function, altered signal transduction including decreased muscle contractility (ATP is the precursor of cyclic AMP), impaired energy-dependent maintenance of transmembrane potential and ion gradients, increased intracellular pH due to anaerobic metabolism, and possible initiation of autolytic mechanisms. Free radicals may result in broad injury to cellular membranes resulting in impaired maintenance of transmembrane potential and ion gradients, mitochondrial generation of ATP, and activation of autolytic pathways involving DNA degradation and lysosomal rupture (apoptosis). Various circulating mediators (including cytokines, kinins, eicosanoids, and complement components) may result in mitochondrial dysfunction, signal transduction abnormalities, membrane protein channel alterations, and possibly alterations of gene expression. Any of these may lead to cell death through metabolic failure and lysosomal enzyme release. βAR, beta adrenergic receptor; GP, G proteins; NOS, nitric oxide synthetase; NO, nitric oxide; cGMP, cyclic GMP; cAMP, cyclic AMP.

MECHANISMS OF CELLULAR INJURY IN SHOCK

Although different forms of shock have their different precipitants, they do share common mechanisms of cellular dysfunction and injury. Eventually, events at the cellular level result in organ dysfunction and death. The pathogenesis of the cellular dysfunction is a combination of the interrelated precipitants and consequences of shock, including (1) ischemia, (2) inflammation, and (3) free radical injury (Fig. 21.E8). Genetic factors are also felt to play a role in an individual's susceptibility and response to shock.

The metabolic pathways involved in shock, like all cellular pathways, involve multiple levels of feedback. Some pathways will have positive feedback mechanisms, where an initial small signal will result in accelerating downstream effects, and negative feedback mechanisms, where downstream effects will result in down-regulation of upstream processes. Because cellular mechanisms from different signal transduction pathways often share common elements, different pathways will have positive and negative feedback effects on each other: this is termed *crosstalk*.

In all forms of shock, the hemodynamic changes involved eventually result in decreased oxygen delivery to target organs, with resultant cellular ischemia. The degree to which this is important in the development of organ damage and death in the different shock forms may vary, but it clearly is the major factor in hypodynamic forms of shock, and it also plays a large role in the ultimate mortality of hyperdynamic, hypermetabolic shock.

In the stressed preshock phase, physiologic adaptive mechanisms attempt to compensate, and perfusion to vital

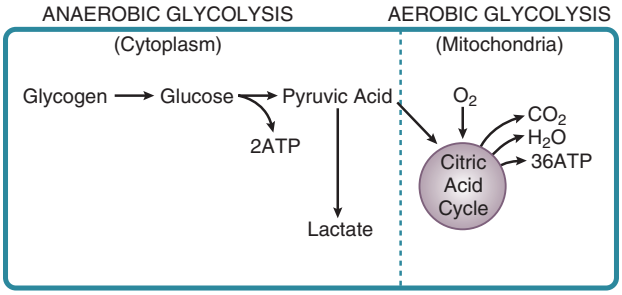

Figure 21.E9 Aerobic and anaerobic glucose metabolism. Under anaerobic conditions, pyruvic acid cannot enter the citric acid cycle in the mitochondria (in order to optimally produce ATP) and is shunted to lactate in the cytoplasm. This produces fewer high-energy phosphates per mole of glucose metabolized. Hydrolysis of ATP molecules in an anaerobic environment results in production of H^+ ions, which cannot be metabolized or cleared, resulting in intracellular acidosis. (Adapted with permission from Mizock BA, Falk JL: Lactic acidosis in critical illness. Crit Care Med 1992;20:80.)

organs is maintained. With the onset of shock, these mechanisms fail, and thus oxygen delivery to tissues is not maintained. At the cellular level, a lack of oxygen prevents the mitochondrial citric acid cycle from functioning, and pyruvate accumulates (Fig. 21.E9). The failure of aerobic respiration requires shunting of pyruvate into the lactic acid pathway in order to recycle NAD and allow glycolysis to continue. However, the loss of the aerobic citric acid cycle results in a large decrease in adenosine triphosphate (ATP) production (net 2 molecules of ATP per molecule of glucose,

versus a theoretical net of 38 molecules of ATP per glucose molecule in the entire aerobic pathway). In addition, shunting to the lactic acid pathway results in the accumulation of hydrogen ions. Thus, loss of perfusion results in a rapid decrease in cellular energy stores, with inadequate ATP regeneration rates. As ATP is the primary source of energy in the cell, energy-dependent cellular systems cease functioning. This includes energy-dependent enzymes, maintenance of transmembrane gradients including electrical potential,[196] mitochondrial function,[197] carbohydrate metabolism,[198] and even the glycolysis pathway itself, which requires two ATP molecules to prime each glucose molecule at the entry point into the pathway. Some cell types are more sensitive than others to the depletion of energy stores, such as in the liver and kidney, but eventually all organs are affected.[196,199-202] With the loss of energy-dependent cell maintenance functions, ultrastructural breakdown, including mitochondria, occurs.[203] Systemically, the combination of worsening acidosis and loss of energy stores results in a positive feedback loop of worsening shock, organ failure, and eventual death.

Ischemia is felt to play a minor role in early sepsis, with high cardiac outputs maintaining perfusion to more sensitive, higher energy-consuming tissues, and that ATP levels remain normal in these tissues, with mitochondrial function preserved. Instead, early septic organ dysfunction results from other causes.[101,102,105] However, localized areas of ischemia are not ruled out. Potentially, microthrombi may result in small areas of decreased microcirculatory flow, resulting in localized ischemia. Evidence to support a role for ischemia in cellular dysfunction in sepsis includes oxygen-supply–dependent oxygen consumption, washout of organic acids from ischemic areas in patients in septic shock on vasodilators, and elevated ATP degradation products. In any case, the role of ischemia in septic shock remains a question. For example, alterations of liver and skeletal muscle transmembrane potential occur early in shock prior to the decrease in levels of high-energy phosphates and onset of hypotension. Further, this membrane defect is not prevented by the administration of membrane-permeable forms of high-energy phosphates such as ATP-$MgCl_2$.[204]

Inflammation, on the other hand, is a major contributor to the development of septic shock and its effects on cellular and organ dysfunction.[205,206] Other forms of shock also activate the inflammatory cascade—for example, hemorrhagic shock with tissue trauma.[207] Indeed, shock is associated with systemic activation of the inflammatory cascade. The resulting cellular and tissue dysfunction, and thus hypermetabolic state, contributes to organ dysfunction and failure. The inflammatory cascade in sepsis can be roughly broken down into initiation, transduction, and release of inflammatory mediators.

Initiation of the inflammatory cascade in sepsis is thought to rely largely on the innate immune response.[206,208,209] This ancient immune pathway evolved to recognize non-self molecular signatures, produced by pathogens including bacteria, yeast, and viruses, which have remained invariant over time. These signatures are called pathogen-associated molecular patterns (PAMPs), and they are recognized by a series of receptors known as pattern recognition receptors (PRRs). In addition, signature host proteins can also be released extracellularly in response to cellular damage, and these proteins, also called alarmins, are known as damage-associated molecular patterns (DAMPs), and these too may be recognized by PRRs. Thus, both non-self PAMPs and self-expressed DAMPs may lead to initiation of the inflammatory cascade via the PRRs.

Known PRRs include (1) the Toll-like receptors (TLRs), (2) the C-type lectin receptors (CLRs), (3) the nucleotide oligomerization domain (NOD)-like receptors (NLRs), and (4) retinoic acid inducible gene I-like receptors (RLRs).

The TLRs and CLRs, being transmembrane, are presented on the cell surface or within the lumens of endosomes or lysosomes.[206,210,211] Ten families of TLRs have been identified in humans. Different TLR families on the cell surface recognize various bacterial lipoproteins, lipopolysaccharides, or flagellins, with sources that may be bacterial, viral, or protozoan. In contrast, TLR families located in endosomal lumens recognize ssRNA, dsRNA, and modified CpG-DNA, which may be of viral or bacterial origin. Interestingly, different individual families of TLRs can form both homodimers and heterodimers on the cell surface, increasing their range of ligand recognition. Meanwhile, the CLRs are presented on the cell surface, and being lectins, they recognize polysaccharides present in yeast and fungi, mycobacteria, and viruses.

In contrast, the NLRs and RLRs are intracellular and require that their ligands be present in the cytoplasm of the cell.[211] NLRs recognize bacterial peptidoglycans; the RLR ligands consist primarily of dsRNA, cytoplasmically produced either by dsRNA viruses or as an intermediate step in the replication of ssRNA viruses.

Once initiated by recognition of PAMPs or DAMPs, the inflammatory cascade involves a large number of protein, kinase, and second messenger cascades. These cascades can lead to the activation of transcription factors or to the post-transcriptional or posttranslational activation of inflammatory mediators.

The TLRs have been shown to use two primary pathways.[211] All the TLRs, with the exception of TLR3, use a pathway dependent on the adaptor protein MyD88, which binds to the intracellular sections of the TLRs; for some of the TLRs, another adaptor protein is required to bind MyD88. Upon activation of the TLR, MyD88 recruits a serine/threonine kinase, IRAK-4, in turn recruiting further kinases such as IRAK-1 and IRAK-2. Ultimately, the cytoplasmic cascade results in phosphorylation and degradation of IκB, an inhibitor of the transcription factor NF-κB. This allows NF-κB to enter the nucleus, resulting in the activation of transcription of a suite of inflammatory mediators and modulators. In contrast, TLR3 uses a pathway dependent on the TRIF adaptor protein, which also ultimately results in NF-κB activation. In both pathways, other adaptor proteins may be required for individual TLRs to activate these cascades; for example, TLR4 can also utilize the TRIF-dependent pathway but is dependent on the TRAM adaptor protein to do this. Different cell types may express different adaptor proteins, resulting in intertissue variation in the cascades. In addition, protein inhibitors of the cascades can be expressed variably in different cell types.

In contrast, the NLRs act via formation of a multiprotein complex, termed the *inflammasome*.[206,211,212] Central to this cascade are the caspases,[213] a family of cysteine proteases. Upon activation, the NLR will recruit a pro-caspase, along

with an adaptor protein ASC, which recruits a second pro-caspase. This complex allows the pro-caspase pair to auto-activate, resulting in active caspase. The best studied of these is caspase 1, although other caspases may be involved. Once activated, caspase 1 in turn activates the inflammatory cytokine IL-1β, allowing its release from the cell. Similarly, caspase1 is also responsible for the activation and release of other cytokines, including IL-18. In this way, the NLR's prime function is to regulate inflammatory mediator release through a posttranslation system. Crosstalk from the TLR cascades may also activate some NLRs and result in inflammasome formation.

At the center of these cascades is transcriptional regulation of inflammatory cytokines and mediators. The transcription factor NF-κB sits at the end of many of these cascades and plays a crucial role in the regulation of expression of many of these factors.[206,211,214] NF-κB is present in an inactive form in the cytoplasm, in complex with repressor proteins.[215] When the repressors, known as IκB proteins, are phosphorylated and subsequently degraded, NF-κB is released and transported into the nucleus where it can act on its target sequences. By being stored in inactive form in the cytoplasm, no new NF-κB need be expressed, allowing for rapid response to the signals received by the PRRs. Inflammatory mediators under the control of NF-κB include cytokines such as TNFα, IL-1β and IL-6, enzymes involved in inflammation such as iNOS, and others.[206]

Inflammatory mediator effects on cellular metabolism are of prime importance in organ dysfunction due to sepsis and septic shock. Circulating inflammatory mediators may also play a substantial role in other forms of shock, including hemorrhagic shock associated with extensive tissue trauma.[216,217] Both sepsis and trauma are associated with generalized, systemic activation of the inflammatory response. Resulting cell injury and hypermetabolism may culminate in organ failure. A number of triggers can result in activation of the inflammatory cascade. The best studied is endotoxin from gram-negative bacteria, but other bacterial antigens and cell injury itself can also initiate the cascade. Macrophage production of cytokines such as TNFα, IL-1β, and IL-6 appears to be central.

Tumor necrosis factor-alpha (TNFα) is a 51-kD trimeric peptide produced by macrophages in response to a variety of inflammatory stimuli including bacterial antigens and other cytokines. Circulating levels of TNFα are transiently elevated soon after the onset of shock (particularly septic shock).[218] Administration of TNFα to animals or humans results in a hyperdynamic circulatory state (± dose-dependent hypotension) similar to untreated sepsis and septic shock.[126] Although clinical trials to date have yielded disappointing results, anti-TNFα strategies protect animals from experimental endotoxic and septic shock.[219] Among the many effects of TNFα are the release of IL-1β, IL-6, IL-8, PAF, leukotrienes, thromboxanes, and prostaglandins; stimulation of production and activity of polymorphonuclear leukocytes; promotion of immune cell adhesion to endothelium; activation of coagulation and complement systems; direct endothelial cell cytotoxicity; depression of myocardial contractility; and fever production by the hypothalamus.[126,220] Notably, TNFα causes alterations of skeletal transmembrane electrical potential similar to those described in hemorrhagic and septic shock.[221] These membrane effects precede hemodynamic alterations, suggesting that TNFα exerts a primary effect on cell metabolism independent of perfusion alterations. Although TNFα appears to be of central importance in the pathogenesis of septic shock, it is also known to be elevated in congestive heart failure[222] and hemorrhagic shock.[216]

Other substances involved in the inflammatory process include IL-1β, which can potentiate the in vivo effects of TNFα; IL-2, which can cause hemodynamic abnormalities in humans; IL-6, which is involved in the acute phase response and has been implicated in septic myocardial depression; interferon-gamma, which promotes the release of other cytokines, enhances adhesion of immune cells, and promotes macrophage activation; IL-10, which is an anti-inflammatory cytokine that limits macrophage generation of pro-inflammatory cytokines; TGFβ, which is another anti-inflammatory cytokine that, in addition to limiting macrophage pro-inflammatory responses, also blocks the effects of proinflammatory cytokines on target cells; endothelin-1, a cytokine that strongly promotes vasoconstriction, particularly in the renal vascular bed, possibly resulting in renal hypoperfusion and decreased glomerular filtration rate; PAF, which stimulates TNFα, thromboxane, and leukotriene release, stimulates free radical formation, and alters microvascular permeability; leukotrienes, which release other arachidonic acid metabolites, alter vascular endothelial permeability, and may mediate vascular and myocardial depression in shock; thromboxanes, which may contribute to altered microvascular vasomotor and permeability function; prostaglandins, which produce fever, induce vasodilatation, and inhibit thrombus formation; and complement fragments C3a and C5a, which constrict vascular smooth muscle, release histamine, and promote chemotaxis.[130,220,223]

Several newly recognized mediators/mediator groups have been shown to have important roles in shock, particularly septic shock. These include high-mobility group 1 protein (HMG-1), myocardial depressant substances and nitric oxide/peroxynitrites. HMG-1 appears to have a key role in the late pathogenesis of sepsis[224,225] and may also have a role in traumatic/hemorrhagic shock.[226-228] HMG-1 is a late mediator of inflammation. Mice show increased levels of HMG-1 in serum 8 to 32 hours after endotoxin administration. Patients succumbing to septic shock also demonstrate increased serum HMG-1 levels.[224] Administration of HMG-1 to normal and endotoxin-resistant mice induces dose-dependent mortality with signs consistent with endotoxic shock.[224,225] Several anti-HMG-1 therapies are in development.[228]

A circulating myocardial depressant substance is present in the blood of patients with septic shock who exhibit myocardial depression with biventricular dilatation and reduced ventricular ejection fractions.[229] Similar substances have been shown to be present in animal models of hemorrhagic shock.[230] Other data suggest canine myocardial infarction[231] and human cardiogenic shock[232] may also be associated with circulating myocardial depressant substances. Serum from appropriate septic patients or animal models depresses myocardial tissue in vitro.[32,229] Myocardial depressant substances from both septic and hemorrhagic shock appear to be dependent on calcium.[233] The substance implicated in human sepsis may represent a synergistic combination of TNFα and IL-1β that produces depression by inducing

myocardial nitric oxide production.[229,234,235] TNFα and IL-1β are both elevated in shock and cause similar depression of myocardial tissue.[234,236] Other data suggest that IL-6 may have a central role.[130,223,237]

Another important mediator, nitric oxide (NO), has a vital role in normal intracellular signal transduction.[238] Of particular importance to shock, NO is the mediator through which endothelial cells normally cause relaxation of adjacent smooth muscle.[238] Endothelial cells, through a constitutive nitric oxide synthetase, produce picomolar quantities of nitric oxide in response to a number of vasodilatory mediators such as acetylcholine and bradykinin. This NO diffuses to adjacent smooth muscle and activates guanylate cyclase to produce cyclic GMP, which affects vascular relaxation. Nitrovasodilators bypass nitric oxide synthetase to relax smooth muscle directly though the guanylate cyclase pathway. During septic shock, an inducible NO synthetase capable of producing nanomolar quantities of NO is generated in vascular smooth muscle.[189,238] Studies have also implicated NO in late vascular dysfunction seen in hemorrhagic shock.[38] Nitric oxide–mediated generation of cyclic GMP may explain the profound loss of arterial vascular tone and venodilatation seen in septic shock[189,239] and may, in part, explain the irreversible vascular collapse seen late in hemorrhagic shock.[38] A potential role for NO in inflammation-associated edema and third-spacing during shock has also been suggested.[191] The in vitro myocardial depressant effects of TNFα, IL-1β, and serum from septic humans may be mediated by a similar NO– and cyclic GMP–dependent pathway.[126,234]

An alternative pathway by which NO may play a role in the cardiovascular pathophysiology of shock and sepsis was described by Beckman and colleagues in 1990.[240] Peroxynitrite (ONOO-), a highly reactive oxidant, is produced from the interaction of superoxide (OH-) and nitric oxide (NO-). It is known to react rapidly with proteins, lipids, and DNA during sepsis and shock states.[241-244] Lipids may be peroxidized, and although proteins may be oxidized, nitrated, or nitrosated, the latter result in nitrotyrosine residues.[240,245,246] Peroxynitrite inactivates mitochondrial aconitase disrupting the Krebs cycle and otherwise interferes with ATP production and utilization,[247-252] an activity similar to that described for NO.[253-255] It also generates DNA strand breaks leading to poly-ADP ribose synthetase (PARS) activation that may itself have significant pathophysiologic effects.[256,257] Peroxynitrite, like NO, also activates guanylate cyclase in vascular tissues.[258,259] In the periphery, the result may be cellular energetic failure, vascular contractile dysfunction (vasodilation), and reperfusion injury.[256,260-262] Many other molecular targets of NO relevant to the cardiovascular system exist and are well reviewed elsewhere.[245,263]

It is of note that as part of the release of inflammatory mediators, immune cells including macrophages, polymorphonuclear leukocytes, and lymphocytes may also be activated in some forms of hypodynamic shock (e.g., hemorrhagic shock), resulting in a self-perpetuating, systemic inflammatory response (similar to that seen in sepsis). This response can contribute to vascular and parenchymal injury and culminate in MODS.

Free radical injury induced by reperfusion or neutrophil activity is another mechanism of organ injury during hemorrhagic and septic shock as well as burns and myocardial infarction.[264] During tissue ischemia, oxygen deficiency leads to accumulation of ATP degradation products including adenosine, inosine, and hypoxanthine (Fig. 21.E10).[265] With resuscitation and reperfusion of ischemic areas, oxygen drives the generation of superoxide (O_2^-), the most common precursor of reactive oxidants, by xanthine oxidase, in endothelial cells. Most of the superoxide is converted, either spontaneously or through superoxide dismutase, to hydrogen peroxide ($H_2O_2^-$). This further reacts to produce tissue-damaging hydroxyl radicals (or other highly reactive free radicals).[264] These radicals interact with critical cell targets such as the plasma membrane, lipid membranes of organelles, and various enzymes, resulting in cell lysis and tissue injury. Oxidant activity, directly and through endothelial damage, attracts and activates neutrophils, resulting in amplification of superoxide generation by a neutrophil NADPH-oxidase and in further tissue damage due to neutrophil protease release.[264] Injured tissue may release xanthine oxidase into the circulation, resulting in systemic microvascular injury.[266]

A parallel process is found during reperfusion of ischemic myocardium following myocardial infarction.[267] Thrombolytic therapy or balloon angioplasty results in sudden delivery of oxygen to ischemic myocardium. Although substantial salvage of myocardial function results, free oxygen radical–mediated reperfusion injury can contribute to myocardial "stunning."[268] Cardiogenic shock during this phase may resolve as the reperfusion injury settles. Free radical damage likely also plays a role in tissue damage during sepsis and septic shock. Following activation by inflammatory mediators and during phagocytosis, polymorphonuclear leukocytes undergo a respiratory burst during which they consume oxygen and generate both superoxide and hydrogen peroxide through a membrane-associated NADPH-oxidase.[264] Macrophages similarly produce oxygen radicals upon activation. Activation also enhances adhesion and tissue migration of leukocytes so that both vascular endothelial and parenchymal tissue damage may result. Free radical injury may play an important role in the development of organ failure following shock.[269]

Variations in stress response genes between individuals and alteration of gene expression in immune, endothelial, muscle, and organ parenchymal cells are other important aspects of cellular dysfunction/injury in circulatory shock. Although shock can be present immediately after injury (massive trauma, hemorrhage, or endotoxin infusion) prior to the onset of substantial alterations of gene expression, its evolution is dependent on a combination of the ongoing nature of the insult, the genetically passive compensatory physiologic/metabolic response, the underlying genotype with respect to stress response elements, and stress-related modulation of gene expression in a variety of cells.

The clinical presentation of shock, progression of the syndrome, and final outcome may be substantially controlled by genetic factors.[270] Genetic factors have been best studied in septic shock. Studies have demonstrated that the human TNFα promoter polymorphism, TNF2, imparts an increased susceptibility to and mortality from septic shock.[271] Other studies suggest increased TNFα generation, severity of sepsis, and mortality with another human TNFα gene polymorphism.[272] A specific locus on chromosome 12 in mice has been shown to be associated with resistance to

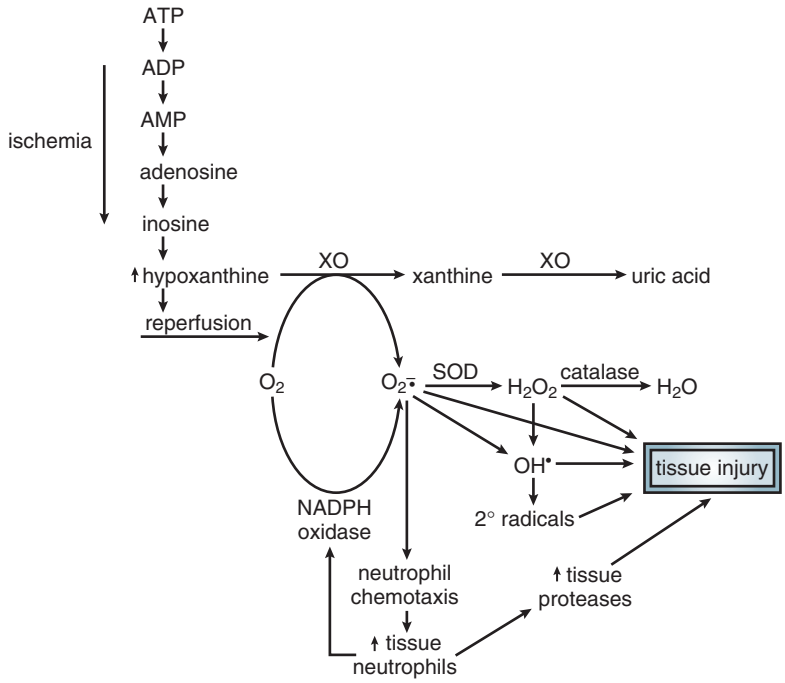

Figure 21.E10 Free radical-mediated tissue injury. Superoxide (O_2^-) is primarily produced in shock from hypoxanthine (a metabolite of ATP degradation) by xanthine oxidase (XO) during reperfusion post ischemia. Superoxide can be converted to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD) and then to H_2O or may be converted to the highly reactive hydroxyl (OH^-), which mediates tissue injury. Free radical tissue injury may be amplified by superoxide recruitment of neutrophils, which secondarily produce additional superoxide through NADPH oxidase. (Adapted with permission from Calandra T, Baumgartner J, Grau GE, et al: Prognostic values of tumor necrosis factor/cachectin, interleukin-1, and interferon-γ in the serum of patients with septic shock. J Infect Dis 1990;161:982-987.)

mortality due to TNFα-induced shock.[273] A human IL-1β receptor antagonist gene polymorphism has been linked to increased susceptibility to sepsis.[274] Several additional linked polymorphisms have been described.[275] It appears likely that gene polymorphisms may play similar roles in other forms of shock.

Beyond the role of gene alleles in the development and clinical response to shock, the progression of irreversible circulatory shock and MODS may have its basis in genetically driven vascular or parenchymal responses. Production of cytokines by macrophages during shock requires acute expression of the genes coding for TNFα, IL-1β, and other proinflammatory cytokines. The production of adhesion molecules by endothelial cells and inducible nitric oxide synthetase by vascular smooth muscle during shock requires active up-regulation of gene expression. Both events are thought to be key to the development of MODS following shock in humans. In addition, human and animal research indicates that apoptosis, a genetically programmed process of cell autolysis, occurs in a variety of organs during shock and subsequent organ failure.[276,277] Data suggest that a variety of transcription factors may be activated in models of sepsis in association with the process.[278] Further research should elucidate the important link between irreversible/refractory shock/shock-associated MODS and genetically programmed cell responses to inflammatory stimulation or injury.

Whatever the initiating event or events, progressive cell metabolic failure occurs. Mitochondrial activity continues to deteriorate, subcellular organelles are damaged, and the intracellular (and possibly, systemic) release of lysosome hydrolytic enzymes occurs, accelerating cell death and organ failure.

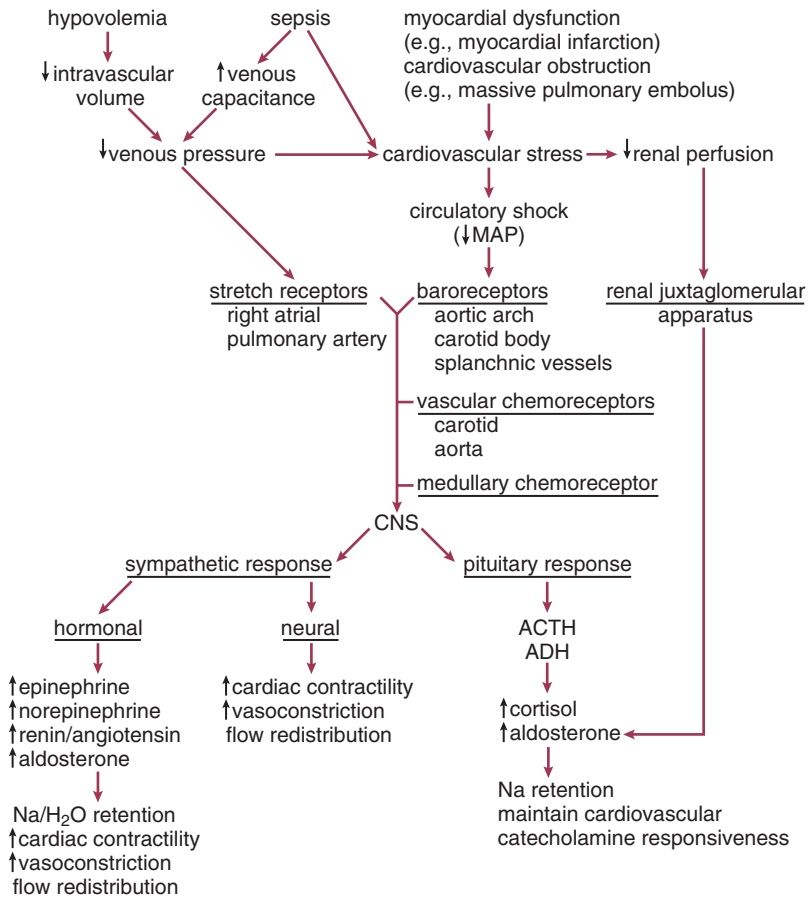

Figure 21.2 Neurohormonal response to shock. During early cardiovascular stress, the neurohormonal response may be limited to increased activity of the juxtaglomerular apparatus and stimulation of right atrial and pulmonary artery low-pressure mechanoreceptors. With further hypotension, high-pressure vascular baroreceptors, vascular chemoreceptors, and the medullary chemoreceptor are sequentially stimulated, resulting in augmented neurohormonal activity with increased pituitary hormone (ACTH and ADH) release and increased sympathetic outflow from the central nervous system. Volume retention, increased venous tone, increased cardiac contractility, and blood flow redistribution to vital organs results.

constriction results in a fall in glomerular filtration rate and urine output. In addition, decreased renal perfusion pressure, sympathetic stimulation, and compositional changes in tubular fluid[153] result in renin release from the juxtaglomerular apparatus. Renin release leads to the adrenal cortical release of aldosterone (via angiotensin II), which increases sodium reabsorption in the distal tubules of the kidney in exchange for potassium or hydrogen ion.[153] Angiotensin II also exerts a powerful direct vasoconstricting effect (particularly on mesenteric vessels) while increasing sympathetic outflow and adrenal epinephrine release. As noted, vasopressin (antidiuretic hormone) release occurs through activation of right atrial low pressure. Angiotensin II augments this release by increasing sympathetic outflow. The release of vasopressin from the posterior pituitary results in water retention at the expense of osmolarity. Hyponatremia can result. Vasopressin, like angiotensin II, also results in vasoconstriction, particularly of the splanchnic circulation.

Finally, increased sympathetic activity and release of adrenal epinephrine results in systemic venoconstriction, particularly of the venous capacitance vessels of the splanchnic circulation. This supports mean circulatory pressure and venous return by increasing stressed volume.

Increased sympathetic nervous system activity accounts for most of the enhancement of cardiac performance during shock. Local release of norepinephrine by sympathetic nerves and the systemic release of epinephrine result in the stimulation of cardiac alpha and beta-adrenergic receptors resulting in increases of heart rate and contractility that optimize cardiac output and support blood pressure. Angiotensin II may also exert direct as well as indirect (sympathetic stimulation) inotropic effects on myocardium. Improved cardiac function also results in decreased right atrial pressure, which tends to increase venous return.

Redistribution of blood flow during shock has already been discussed. Increased sympathetic vasoconstrictor tone, systemic release of epinephrine from the adrenals, vasopressin, endothelin, and angiotensin II cause vasoconstriction in all sensitive vascular beds including the skin, skeletal muscle, kidneys, and splanchnic organs.[154] Dominant autoregulatory control of blood flow spares brain and heart blood work from these effects. Redistribution of flow to these vital organs is the effective result.

The effects of decreased delivery of oxygen to the tissues during shock can be attenuated by local adaptive responses. Hypoperfusion and tissue ischemia will result in local acidosis due to decreased clearance of CO_2 and anaerobic metabolism. Local acidosis decreases the affinity between oxygen and hemoglobin at the capillary level.[153] The resultant rightward shift of the oxyhemoglobin dissociation curve allows

Box 21.3 Cardiovascular/Metabolic Compensatory Responses to Shock

Maintain Mean Circulatory Pressure (Venous Pressure)

Volume
Fluid redistribution to vascular space (increased total vascular volume)
- From interstitium (Starling effect)
- From intracellular space (osmotic)

Decreased renal fluid losses
- Decreased glomerular filtration rate (GFR)
- Increased aldosterone
- Increased vasopressin

Pressure
Decreased venous capacitance (increased stressed volume)
- Increased sympathetic activity
- Increased circulating (adrenal) epinephrine
- Increased angiotensin
- Increased vasopressin

Maximize Cardiac Performance

Increased contractility
Sympathetic stimulation
Adrenal stimulation

Redistribute Perfusion

Extrinsic regulation of systemic arterial tone
Dominant autoregulation of vital organs (heart, brain)

Optimize Oxygen Unloading

Increased RBC 2,3 DPG
Tissue acidosis
Pyrexia
Decreased tissue Po_2

Table 21.3 Organ System Dysfunction in Shock

Central Nervous System	Encephalopathy (ischemic or septic) Cortical necrosis
Heart	Tachycardia, bradycardia Supraventricular tachycardia Ventricular ectopy Myocardial ischemia Myocardial depression
Pulmonary System	Acute respiratory failure Acute respiratory distress syndrome
Kidney	Prerenal failure Acute tubular necrosis
Gastrointestinal System	Ileus Erosive gastritis Pancreatitis Acalculous cholecystitis Colonic submucosal hemorrhage Transluminal translocation of bacteria/antigens
Liver	Ischemic hepatitis "Shock" liver Intrahepatic cholestasis
Hematologic System	Disseminated intravascular coagulation Dilutional thrombocytopenia
Metabolic	Hyperglycemia Glycogenolysis Gluconeogenesis Hypoglycemia (late) Hypertriglyceridemia
Immune System	Gut barrier function depression Cellular immune depression Humoral immune depression

greater unloading of oxygen from hemoglobin for a given Po_2. Tissue ischemia is also accompanied by decreased tissue Po_2 (relative to normal), which further augments the unloading of oxygen. Pyrexia associated with sepsis may also contribute to a rightward shift of the oxyhemoglobin dissociation curve, whereas hypothermia is associated with a leftward shift. For that reason, maintenance of normothermia during resuscitation from shock helps to optimize oxygen unloading.

ORGAN SYSTEM DYSFUNCTION DUE TO SHOCK (TABLE 21.3)

CENTRAL NERVOUS SYSTEM

Central nervous system neurons are extremely sensitive to ischemia. Fortunately, the central nervous system vascular supply is highly resistant to extrinsic regulatory mechanisms. Although cerebral perfusion is clearly impaired in shock, flow remains relatively well preserved until the later stages.[284,285] Absent primary cerebrovascular impairment, cerebral function is well supported until mean arterial pressure falls below approximately 50 to 60 mm Hg.[286] Eventually, irreversible ischemic injury may occur to the most sensitive areas of the brain (cerebral cortex). Before this fixed injury, an altered level of consciousness, varying from confusion to unconsciousness, may be seen depending on the degree of perfusion deficit. Disturbances of acid/base/electrolytes may also contribute. Electroencephalographic (EEG) recordings demonstrate nonspecific changes compatible with encephalopathy. Sepsis-related encephalopathy may occur at higher blood pressures (due in part to the effects of circulating inflammatory mediators) and is associated with increased mortality.[287]

HEART

The major clinically apparent manifestations of shock on the heart are due to sympathoadrenal stimulation. Increased heart rate, in the absence of disturbances of cardiac conduction, is almost universally present. Vagally mediated paradoxical bradycardia may seen on occasion in severe hemorrhage.[40] In patients predisposed to myocardial ischemia or irritability, catecholamine-driven supraventricular tachycardias and ventricular ectopy with ischemic electrocardiogram (ECG) changes are not common. Like the brain, the blood supply to the heart is autoregulated. This, in combination with the resilient nature of myocardial tissue, renders it resistant to sympathetically driven

vasoconstriction and shock-related hypoperfusion injury. Overt necrosis does not typically occur, although evidence of cellular injury may be present.

Most forms of shock are associated with increased contractility of healthy myocardium. Regardless, shock can have a substantial impact on myocardial contractility and compliance. Hypotension during cardiogenic (and other forms of shock) is associated with decreased coronary artery perfusion pressure. In patients with coronary artery disease or increased filling pressures, decreased coronary artery perfusion pressure may lead to overt ischemia. Further, circulating myocardial depressant substances contribute to myocardial depression in septic[229] and hemorrhagic[230] shock. This has been linked to decreased beta adrenoreceptor affinity and density as well as potential defects of intracellular signal transduction involving nitric oxide, G proteins, cAMP, and cGMP.[126] Circulating depressant substances may also be present during cardiogenic shock.[232]

RESPIRATORY SYSTEM

Early alterations of pulmonary function seen during acute circulatory shock are primarily related to changes in central drive or muscle fatigue. Increased minute volume occurs as a result of augmented respiratory drive due to peripheral stimulation of pulmonary J receptors and carotid body chemoreceptors as well as hypoperfusion of the medullary respiratory center. This results in hypocapnia and primary respiratory alkalosis.[153,288] With increased minute volume and decreased cardiac output, the V/Q ratio increases. Unless arterial hypoxemia complicates shock, pulmonary resistance is initially unchanged or minimally increased. Coupled with an increased workload, respiratory and diaphragmatic muscle impairment due to hypoperfusion (manifested by decreased transmembrane electrical potential) may lead to early respiratory failure.[289] Adult respiratory distress syndrome (ARDS) due to inflammatory or free radical injury to the alveolar capillary cell layers following established shock may develop as a late cause of respiratory failure.

KIDNEY

Acute renal failure is a major complication of circulatory shock with associated mortality rates between 35% and 80%.[290] Although initial injury manifested by decreased urine output occurs, other clinical manifestations of renal dysfunction (increased creatinine, urea, and potassium) may not be noted for 1 to 3 days. Once hemodynamic stabilization has been achieved, it becomes apparent that urine output does not immediately improve and both serum creatinine and urea continue to rise. The single most common cause of acute renal failure is renal hypoperfusion resulting in acute tubular necrosis (ATN). The most frequent cause of renal hypoperfusion is hemodynamic compromise from septic shock, hemorrhage, hypovolemia, trauma, and major operative procedures. ATN that occurs in the setting of circulatory shock is associated with a higher mortality than in other situations.

Part of the reason for the kidney's sensitivity to hypoperfusion has to do with the nature of its vascular supply. The renal vascular bed is moderately autoregulated. Increases of efferent arteriolar tone can initially maintain glomerular perfusion despite compromise of renal flow.[291] Renal hypoperfusion does not become critical until relatively late in shock when maximal vasoconstriction of renal preglomerular arterioles[291] results in cortical, then medullary, ischemic injury.

Decreased urine output in shock can pose a diagnostic dilemma, as it can be associated with both oliguric ATN and hypoperfusion-related prerenal failure without ATN. Indices suggestive of the latter include a benign urine sediment, a urine sodium concentration <20 mEq/L, fractional urine sodium excretion <1%, urine osmolality >450 mOsm/L, and a urine/plasma creatinine ratio >40. Useful markers of acute renal failure due to ATN include hematuria and heme granular casts, a urine sodium concentration >40 mEq/mL, fractional excretion of urine sodium to >2%, urine osmolarity <350 mOsm/L, and a urine:plasma creatinine ratio <20.[292] Of note, ATN caused by circulatory shock may be associated with urine sodium <20 mEq/L and fractional excretion < 1% if the acute renal injury is superimposed upon chronic effective volume depletion as may be seen with cirrhosis and congestive heart failure.[293]

GASTROINTESTINAL SYSTEM

The gut is relatively sensitive to circulatory failure. The splanchnic vasculature is highly responsive to sympathetic vasoconstriction. Typical clinical gut manifestations of hypoperfusion, sympathetic stimulation, and inflammatory injury associated with shock include ileus, erosive gastritis, pancreatitis, acalculous cholecystitis, and colonic submucosal hemorrhage. Enteric ischemia produced by circulatory shock and free radical injury with resuscitation may breach gut barrier integrity with translocation of enteric bacteria and antigens (notably endotoxin) from the gut lumen to the systemic circulation, resulting in the propagation and amplification of shock and MODS.[294,295]

LIVER

Like the gut, the liver is highly sensitive to hypotension and hypoperfusion injury. "Shock liver," associated with massive ischemic necrosis and major elevations of transaminases, is atypical in the absence of extensive hepatocellular disease on very severe insult.[296] Centrilobular injury with mild increases of transaminases and lactate dehydrogenase is more typical. Transaminases usually peak within 1 to 3 days of the insult and resolve over 3 to 10 days. In either case, early increases in bilirubin and alkaline phosphatase are modest. Despite the production of acute phase reactants in early circulatory shock, synthetic functions may be impaired with decreased generation of prealbumin, albumin, and hepatic coagulation factors. After hemodynamic resolution of shock, evidence of biliary stasis with increased bilirubin and alkaline phosphatase can develop, even though the patient is otherwise improving. Postshock MODS involves similar hepatic pathology.

HEMATOLOGIC SYSTEM

Hematologic manifestations of circulatory shock tend to depend on the nature of shock. Disseminated intravascular coagulation (DIC), characterized by microangiopathic hemolysis, consumptive thrombocytopenia, consumptive coagulopathy, and microthrombi with tissue injury, is most commonly seen in association with septic shock. Because it is due to simultaneous systemic activation of coagulation

and fibrinolysis cascades, it can be differentiated from the coagulopathy of liver failure by determination of endothelial cell–produced factor 8 (normal or increased with hepatic dysfunction). In the absence of extensive tissue injury/trauma, hemorrhagic shock is rarely associated with DIC.[297] Dilutional thrombocytopenia is the most common cause of coagulation deficits after resuscitation for hemorrhage.[298]

METABOLIC ALTERATIONS

Metabolic alterations associated with shock occur in a predictable pattern. Early in shock, when hemodynamic instability triggers compensatory responses, sympathoadrenal activity is enhanced. Increased release of ACTH, glucocorticoids, and glucagon and a decreased release of insulin results in glycogenolysis, gluconeogenesis, and hyperglycemia.[281,299] An increased release of epinephrine results in skeletal muscle insulin resistance sparing glucose for use by glucose-dependent organs (heart and brain). Late in shock, hypoglycemia may develop, possibly due to glycogen depletion or failure of hepatic glucose synthesis. Fatty acids are increased early in shock but fall later as hypoperfusion of adipose containing peripheral tissue progresses. Hypertriglyceridemia is often seen during shock as a consequence of catecholamine stimulation and reduced lipoprotein lipase expression induced by circulating TNFα.[299] Increased catecholamines, glucocorticoids, and glucagon also increase protein catabolism, resulting in a negative nitrogen balance.[299]

IMMUNE SYSTEM

Immune dysfunction, frequent during and after circulatory shock and trauma, rarely has immediate adverse effects but likely contributes to late mortality. Underlying mechanisms of immune dysfunction include ischemic injury to barrier mucosa (particularly of the gut), leading to anatomic breaches (colonic ulceration) and potential mucosal translocation of bacteria and bacterial products; parenchymal tissue injury due to associated trauma, inflammation, ischemia or free radical injury; and direct ischemic or mediator (immunosuppressant cytokines, corticosteroids, prostaglandins, catecholamines, endorphins)-induced dysfunction of the cellular and humoral immune systems.[300,301] In particular, macrophage function is adversely affected during trauma and circulatory shock. A decrease in antigen presenting ability impairs the activation of T and B lymphocytes. Associated with this defect are a decrease in Ia antigen expression, a decrease in membrane IL-1β receptors, and the presence of suppressor T-lymphocytes. Phagocytic activity of the reticuloendothelial system is also compromised, partially due to an acute decrease in fibronectin levels. Suppression of T lymphocyte immune function is manifested by decreased responsiveness to antigenic stimulation and a decreased helper:suppressor ratio. Decreased production of IgG and IgM suggests B cell suppression. Nonspecific immune suppression is expressed as decreased neutrophil bactericidal function, chemotaxis, opsonization, and phagocytosis.

Resuscitation agents used in shock may also substantially depress immune function. For example, red blood cell transfusion used in traumatic hemorrhagic shock and in support of oxygen transport in septic shock[302] has been shown to suppress immune function and lead to increased infections (and improved allograft survival).[303,304] Similarly, dopamine, used for hemodynamic support in shock, has been shown to suppress pituitary production of prolactin (required for optimal immune function), thereby suppressing T-cell proliferative responses.[305] Thus, dopamine may contribute, along with stress-induced increases in immunosuppressive glucocorticoids, to T-cell anergy seen in critically ill patients.

All of these factors may contribute to the propensity of critically ill patients to develop ongoing organ system dysfunction as well as a variety of infections during the post-shock phase. It is notable that one third to one half of patients with shock die late in their course following resolution of the acute shock phase.

DIAGNOSTIC APPROACH AND EVALUATION

Shock is always a life-threatening emergency. Diagnosis, evaluation, and management must often occur virtually simultaneously. The diagnosis must be made as early as possible while shock is well compensated. Once marked hypotension and hypoperfusion are present, mortality increases. Because early recognition and treatment are key to survival, the diagnosis is primarily a clinical one. Laboratory and imaging studies are useful for confirming the diagnosis and determining the specific shock etiology. However, therapy of shock should never be delayed in order to accommodate these studies. The initial diagnosis of shock can and should be made strictly on clinical signs and symptoms.

Because shock is the common end point of a variety of insults, evaluation and management for all forms of shock involve a common approach (Box 21.4).

CLINICAL EVALUATION

Impending shock is characterized by the typical compensatory response to cardiovascular stress. Tachycardia, tachypnea, and oliguria (<0.5 mL/kg/h) are usually present. Cool extremities are seen in hypodynamic shock. The blood pressure may be elevated or normal with maximal sympathetic stimulation. With progression, however, blood pressure falls, whereas pulse pressure narrows (except in the case of distributive shock). Frank hypotension (mean arterial pressure <60 to 65 mm Hg in adults) may ensue. The chronic level of blood pressure must be considered. Normotension in a normally hypertensive patient may denote a critical degree of hypoperfusion. With further progression anuria may develop, extremities may become mottled and dusky (except in distributive shock), and the sensorium may become clouded. It is important to note that clinical parameters can underestimate initial resuscitative requirements in critically ill subjects including those with septic shock.[306-309]

Other clinical manifestations of shock are useful for attempting to differentiate the etiology. Hypovolemic shock is characterized by decreased jugular venous pressure. Cardiogenic shock may evidence elevated jugular venous pressure with hepatojugular reflux, an S3, an S4, and regurgitant heart murmurs. Obstructive shock signs usually depend on the nature of the obstruction. Pulmonary embolus may be characterized by dyspnea and right-sided evidence of heart

Box 21.4 General Approach to Shock: Initial Diagnosis and Evaluation

Clinical (Primary Diagnosis)

Tachycardia, tachypnea, cyanosis, oliguria, encephalopathy (confusion), peripheral hypoperfusion (mottled extremities), hypotension (systolic blood pressure < 90 mm Hg)

Laboratory (Confirmatory)

Hemoglobin, WBC, platelets
PT/PTT
Electrolytes, arterial blood gases
Ca, Mg
BUN, creatinine
Serum lactate
ECG

Monitoring

Continuous ECG and respiratory monitors
Arterial pressure catheter
Central venous pressure monitor (uncomplicated shock)
Venous oximetry*
Pulmonary artery flotation catheter*
- Cardiac output
- Pulmonary artery occlusion pressure
- Central or mixed venous oxygen saturation (intermittent or continuous)

Oximetry*
Echocardiogram (functional assessment)*

Imaging

Chest x-ray
X-ray views of abdomen*
Computerized axial tomogram (CT scan)—abdomen or chest*
Echocardiogram (anatomic and functional assessment)*
Pulmonary perfusion scan*

*Optional.

failure. Cardiac tamponade may demonstrate Kussmaul's sign, a pulsus paradoxus and distant heart sounds. Septic shock in the absence of neutropenia usually exhibits a focus of infection along with fever, chills, and warm extremities. Patients with septic shock and neutropenia often have no clinically apparent focus. Elderly patients may present with little more than unexplained hyperventilation and hypotension.

LABORATORY STUDIES

Laboratory data are used to confirm the diagnosis of shock and to help clarify the etiology. Leukocyte count is frequently elevated early in shock due to demargination of neutrophils. Leukopenia may be found in sepsis and late shock. Hemoglobin concentration is variably affected depending on the etiology of shock. For example, nonhemorrhagic hypovolemic shock and septic shock with extravasation of intravascular water to the interstitium may result in an apparent erythrocytosis. Platelet count increases acutely with the stress of circulatory shock, but with progression of sepsis or resuscitation of massive hemorrhage, thrombocytopenia may occur. Arterial blood gases and electrolytes may demonstrate a nonanion gap acidosis if hypovolemic shock is associated with excessive diarrhea and metabolic alkalosis if associated with vomiting. An anion gap acidosis, often due to elevated levels of lactic acid, usually reflects prolonged inadequate tissue perfusion. Serum creatinine and blood urea nitrogen (BUN) are rarely changed after the acute onset of shock, even if renal injury is present. With slower onset of shock—for example, in sepsis—increased creatinine is common and early resolution is an excellent marker of effective resuscitation and survival. Markers of renal function can also be helpful diagnostically. An isolated increased BUN with anemia and normal creatinine may suggest gastrointestinal bleeding. An arterial blood gas will help to determine the adequacy of oxygenation and give evidence of acid base disturbances. An electrocardiogram (ECG) is critical for the diagnosis of ischemic cardiac injury either as a primary cause of cardiogenic shock or secondary to hypotension associated with shock of another etiology.

Lactate levels (particularly serial determinations) are of use in assessment of prognosis. Substantial data suggest that lactate levels, as a marker of tissue oxygen debt, can predict outcome in shock.[45,46,310-314] The utility of lactate assessment is limited by the fact that it is a relatively late marker of tissue hypoperfusion.[315,316] Significant tissue ischemia and injury are present by the time it is elevated. In addition, the liver clears lactate. Liver failure may markedly increase elevated lactate levels during hypoperfusion. Conversely, normal hepatic clearance may obscure limited lactate production by ischemic tissues. Glycolysis and alkalosis will also nonspecifically increase lactate levels.[317,318] However, since in the appropriate setting, arterial lactate levels beyond 2 mEq/L are associated with increased mortality,[46,50,312,313,319] such levels should be considered to represent tissue ischemia in the absence of another clearly defined etiology. The adequacy of resuscitation of shock can also be assessed using serial changes of systemic lactate.[314,319,320] Resolution of elevated lactate, however, may lag following the implementation of effective resuscitation.[321]

Central venous oxygen saturation can also be used to assess the prognosis and efficacy of resuscitation in shock states including septic shock.[302,309,322,323] However, central venous saturation, which has been suggested to represent a reliable marker of resuscitation efficacy in sepsis,[302] does not appear to correlate well with lactate clearance in some sepsis studies, perhaps reflecting elements other than oxygen debt in those conditions.[320] Poor correlation with mixed venous oxygen saturation has also been noted in septic shock.[324]

IMAGING

A chest radiograph is useful in ruling out pneumonia as a source of septic shock, pulmonary edema as a manifestation of cardiogenic shock, tension pneumothorax, pericardial tamponade, and so on. Although abdominal views may be helpful on occasion, intra-abdominal processes resulting in shock are usually clinically apparent. Computerized axial tomograms may be helpful in directing management in specific instances (occult internal hemorrhage, aortic dissection, pulmonary embolus). Similarly, transthoracic and transesophageal echocardiography can diagnose with great accuracy the specific repairable cardiac or aortic lesions associated with shock and can be highly suggestive of other

important diagnoses including hemodynamically significant pulmonary embolus. Pulmonary perfusion scans are useful for confirming massive pulmonary embolism. Other imaging modalities have less of a role in the evaluation of acute shock.

INVASIVE HEMODYNAMIC MONITORING

All patients suspected of having circulatory shock should have an indwelling arterial pressure catheter placed. Blood pressure assessment by manual sphygmomanometry or automated noninvasive oscillometric techniques may be inaccurate during shock due to marked peripheral vasoconstriction.[325] In addition, neither technique supplies continuous monitoring of the rapidly changing hemodynamic status of unstable patients. Further, an arterial catheter allows ready access for arterial blood gas samples and other laboratory tests. In most cases, a peripheral site, such as the radial artery, is utilized. However, given the potential for disparity of pressures between central and peripheral sites,[326] if marked peripheral vasoconstriction due to either sympathetic stimulation or exogenous catecholamines obscures the peripheral pulses, a central site such as the femoral artery may be preferred.

Central venous pressure monitoring is frequently used during the perioperative period to assess the intravascular volume status in patients without critical illness. Because of the relatively stable hemodynamic status of these patients and the questionable benefit of pulmonary artery catheterization in these patients, such an approach is adequate. Similarly, CVP monitoring for otherwise healthy patients being resuscitated for hypovolemic shock may provide useful data. In the appropriate clinical context, CVP monitoring may also occasionally be useful in differentiating among different forms of shock (e.g., low CVP in hypovolemic shock, high CVP in cardiac tamponade). As a rule, though, CVP monitoring is inadequate for the hemodynamic assessment of critically ill patients, particularly those with shock. A number of studies have conclusively shown that central venous pressure does not accurately estimate left ventricular preload in critically ill patients.[327,328]

The use of the flow-directed balloon-tipped pulmonary artery catheters with thermodilution cardiac output determination capability has been the standard of practice for the hemodynamic assessment of circulatory shock. Their use is supported by a number of studies that demonstrate that experienced physicians cannot accurately determine cardiac filling pressures or cardiac output based on clinical evaluation alone.[329,330] In addition to cardiac output determination, pulmonary artery catheters provide continuous monitoring of central venous and pulmonary artery waveforms and pressures. Pulmonary artery occlusion pressure (as an estimate of left ventricular end-diastolic pressure and volume) and waveform can be obtained intermittently. Waveform analysis may be useful in cardiovascular diagnoses of cardiac tamponade, restrictive cardiomyopathy, congestive heart failure, ventricular hypertrophy, and mitral or tricuspid regurgitation. These devices also allow withdrawal of blood from the pulmonary artery, enabling the determination of MVo_2 in order to verify sufficient oxygen delivery during hypodynamic shock. In addition, they can demonstrate evidence of right heart and pulmonary artery oxygen saturation "stepups" for the diagnosis of left-to-right shunts associated with cardiac anatomic abnormalities such as ventricular septal defect. In shock, the flow-directed balloon-tipped pulmonary artery catheter is useful for etiologic classification, determination of optimal management, and to follow the response to therapy. Typical hemodynamic profiles of different forms of shock have been described in Table 21.1.

The utility of pulmonary artery catheterization has been questioned. In a case-matched study, researchers suggested that increased resource utilization and mortality were associated with the use of pulmonary artery catheters in the ICU.[331] A series of randomized studies performed since then have reported on the role of the pulmonary artery catheter (PAC) in the setting of major noncardiac surgery,[332] congestive heart failure (CHF),[333] sepsis and adult respiratory distress syndrome (ARDS),[334] acute lung injury,[335] and in the general ICU setting.[336,337] In the perioperative management of patients undergoing major noncardiac surgery, the use of a PAC did not impact mortality and was associated with a greater incidence of pulmonary embolism.[332] In critically ill patients diagnosed with CHF, management directed with the use of a PAC did not influence mortality but resulted in more in-hospital adverse events.[333] Another study comparing the use of a PAC versus central venous monitoring in acute lung injury found no difference in organ failure or mortality.[335] A large trial evaluating the role of the PAC in the management of patients with ARDS secondary to sepsis also found no significant differences in mortality if a PAC was utilized or not.[334] Two randomized studies of general ICU patients similarly concluded that the use of PAC among critically ill patients neither increased nor decreased mortality.[336,337] Most, although not all, meta-analyses have shown no consistent benefit with the PAC.[338-341] These studies failing to show a lack of clinical benefit have been paralleled by other studies questioning some of the basic premises of PAC utility. Several studies have shown a lack of correlation between PAOP/CVP and ventricular volumes in the critically ill.[342,343] One study has even demonstrated that PAOP and CVP fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal volunteer subjects.[344] Despite these data, no studies have examined the use of pulmonary artery catheters in cases of shock specifically. Nonetheless, the use of the PAC in the United States has decreased dramatically since the 1990s.[345]

One parameter that a pulmonary artery catheter uniquely provides is mixed venous oxygen saturation. This measure may assess the adequacy of resuscitation of low output states prior to the presence of anaerobic metabolism (as signified by increased lactate). MVo_2 rises with increases of perfusion above requirements and falls, with increasing oxygen extraction ratio, as perfusion becomes inadequate (Fig. 21.3). Normal MVo_2 falls within the 65% to 75% range. During myocardial infarction, saturations of less than 60% are found with congestive heart failure, and less than 40% with cardiogenic shock.[323] Lactate accumulation and supply-dependent oxygen consumption begin to appear as saturation levels fall below 30% to 40%.[346,347] MVo_2 is especially useful in determining whether low cardiac outputs indicate supply-dependent oxygen consumption (MVo_2 low) or normally depressed metabolic demands (normal MVo_2). Due to the maldistribution of perfusion in distributive shock (or

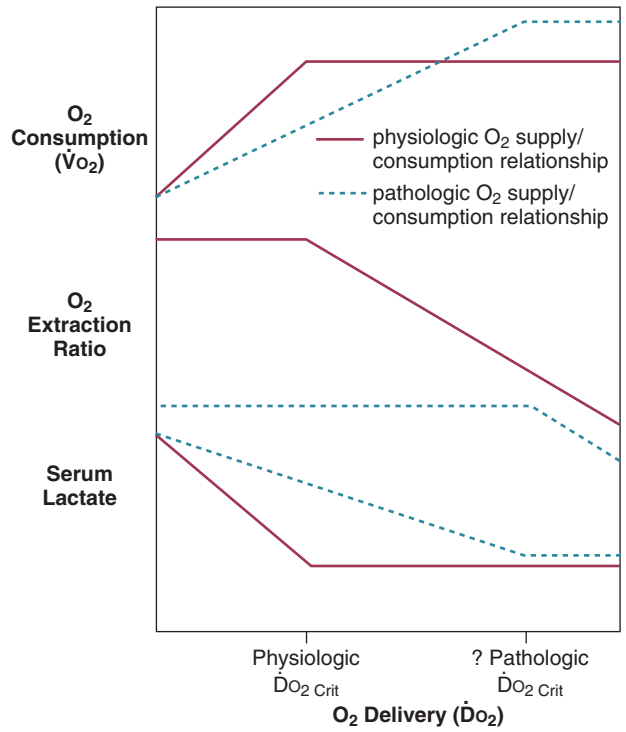

Figure 21.3 Oxygen supply–dependent oxygen consumption in shock. Physiologic supply–dependent oxygen consumption is characterized by a biphasic relationship between oxygen delivery (Do_2) and oxygen consumption (Vo_2). The inflection point defines the physiologic critical oxygen delivery (Do_{2crit}). Below this Do_{2crit}, Vo_2 is linearly dependent on Do_2, the oxygen extraction ratio is maximal, and lactate (indicating anaerobic metabolism) is produced. Above the physiologic Do_{2crit}, Vo_2 is independent of Do_2, the oxygen extraction ratio varies to maintain a constant Vo_2, and lactate is not produced.

substrate utilization defect in septic shock) and left-to-right shunting in cardiogenic shock associated with ventricular septal defects, MVo_2 is not useful in assessment in those conditions. Central venous oxygen saturation ($cSVo_2$) has been proposed as an alternate way to examine the adequacy of resuscitation.[302,309]

Oxygen delivery and oxygen consumption variables can also be determined using pulmonary artery catheter–derived data. Although such global perfusion data appear to have prognostic significance for large groups of the critically ill, their utility is controversial when applied to individual patients.

Modifications to the standard pulmonary artery flotation catheter allow continuous monitoring of MVo_2 or determination of right ventricular ejection fractions and volumes. Although both innovations have been utilized for clinical research purposes and each theoretically offers unique insights into shock, they have no defined role at this time in clinical shock management.

ANCILLARY MONITORING TECHNIQUES

OXIMETRY

Because oxygen delivery is dependent on arterial oxygen saturation, pulse oximetry should, in theory, provide useful data during circulatory shock. However, limitations of the technique include the fact that ambient light sources, dyshemoglobinemias (methemoglobin, carboxyhemoglobin), lipemia, and hypothermia can affect results.[348] Motion artifact may generate a false signal.[349] Shock-associated vasoconstriction also impairs signal aquisition. One study has shown that a cardiac index less than 2.4 L/min/m^2 is associated with signal loss.[350] Although these problems limit the utility of pulse oximetry in the acute management of circulatory shock, the technique may be more helpful during postresuscitation monitoring. At this time, sequential arterial blood gases provide more reliable data during acute shock.

Transcutaneous and transconjunctival oxygen tension measurement are newer noninvasive techniques used for determining tissue oxygen tension, which show some promise in the management of patients at risk for or following the resuscitation of circulatory shock. In the absence of shock, transcutaneous probes reflect arterial oxygenation.[351] A number of studies, however, have suggested that if arterial oxygen tension is stable, the devices may be of use in assessing global or regional changes in perfusion and oxygen metabolism.[352-355] Global hypoperfusion due to low output shock (as well as local vasoconstriction) results in decreased transcutaneous oxygen tension and a decreased ratio of transcutaneous to arterial oxygen tension.[353] Decreased transcutaneous oxygen tension, seen early in hemorrhagic shock, may precede hypotension.[354,355] Decreases in transconjunctival oxygen tension predict hemodynamic collapse in perioperative patients[352] and death in patients with cardiogenic shock.[355] Transcutaneous and transconjunctival measurement of oxygen tension may also be useful in assessing the adequacy of tissue perfusion during resuscitation from hypodynamic shock.[356,357]

As anaerobic glycolysis with lactate generation is paralleled by the production of hydrogen ions during hypodynamic shock, noninvasive measurement of tissue pH may provide an attractive, metabolism-based assessment of adequacy of tissue oxygenation/perfusion. Because the stomach is easily accessible, may reflect overall splanchnic perfusion during shock,[358] and splanchnic perfusion is known to be altered early in shock,[359] most clinical work has focused on gastric mucosal pH. Studies suggest that gastric intramucosal pH correlates closely with systemic and organ oxygen consumption, organ failure, and outcome in critically ill humans.[360,361] Normalization of gastric mucosal pH has been suggested as one appropriate target during resuscitation of circulatory shock.[362] Limited evidence suggests such an approach may be associated with improved survival.[363] However, further supportive studies are required before this can be accepted as an appropriate therapeutic target.

Near infrared spectroscopy (NIRS) is an innovative technique able to noninvasively monitor regional tissue blood flow, oxygen delivery, and oxygen utilization. Although several investigators have claimed the ability to examine mitochondrial oxidation state (particularly the redox state of cytochrome aa3, the terminal portion of the electron transport chain), these measurements may actually reflect only tissue oxygenation.

Normal tissue oxygenation is the ultimate expression of normal cardiopulmonary function. Any major perturbation of cardiopulmonary status including incipient shock should ultimately express decreased tissue oxygenation. Because peripheral tissue perfusion is, as part of normal

compensatory mechanisms, among the first to become restricted during cardiovascular stress, peripheral tissue oxygenation may serve as an excellent marker of cardiovascular stress. Near-infrared light is known to pass through biologic tissues such as skin and muscle. By illuminating a tissue with a known amount of incident light, the amount recovered depends on the degree of absorption by chromophores within the tissue and the amount of scattering. Only three chromophores are known to absorb light in the near-infrared wavelength spectrum: hemoglobin, myoglobin, and cytochrome aa3. All three are known to vary their absorption of near-infrared light depending on whether they are in an oxygenated or deoxygenated/reduced state. By monitoring these parameters, NIR spectroscopy is a unique tool that allows for real-time assessment of the adequacy of tissue perfusion during both the resuscitation and ongoing management of patients with shock. Studies in both animals and humans have suggested the potential utility of this technique in assessment of shock including hypovolemic/traumatic[364-369] and septic.[370,371]

The application of advanced echocardiography techniques to the ICU environment as intermittent monitoring tools may represent one of the most exciting developments in critical care management. A number of factors have hastened this development. These include questions regarding the safety and efficacy of routine pulmonary artery catheter utilization; the availability of relatively inexpensive, portable echocardiography systems; the application of advanced software algorithms to analyze data; and the development of new, high-resolution echocardiographic techniques including transesophageal and contrast echocardiography. The confluence of these factors has resulted in a substantial increase in the use of echocardiography in the ICU assessing hemodynamic instability and shock. In addition to its long-recognized ability to detect anatomic lesions (pericardial tamponade, pericardial effusion, septal defects, valvular disease, aortic dissection), new techniques allow for the assessment of cardiac output, stroke volume, preload (ventricular volumes), intravascular volume status (inspiratory inferior caval collapse), pulmonary artery pressures, systolic contractility (ejection fraction), diastolic function, and regional motion abnormalities at baseline and under stressed conditions.[372] The utility for diagnosis of hemodynamically significant pulmonary embolism has also been established.[373] The widespread dissemination of echocardiographic skills among the next generation of intensivists has allowed for a substantial reduction in the use of invasive monitoring techniques including pulmonary artery catheterization.

MANAGEMENT AND THERAPY

Patients suspected to be in circulatory shock should be managed in an intensive care unit with continuous ECG monitoring and close nursing support. Those whose etiologic diagnosis is in doubt, whose hemodynamic instability does not quickly resolve with intravenous fluids, or who are medically complicated should undergo invasive hemodynamic monitoring with arterial and pulmonary artery catheters. Laboratory tests, as mentioned earlier, should be performed at or before admission.

Management of shock can be divided into specific therapy for the triggering injury and general therapy of the shock syndrome. Examples of specific therapy include antibiotics and drotrecogin-alfa (activated) for treatment of septic shock, blood transfusion for hemorrhagic shock, thrombolysis for acute myocardial infarction or massive pulmonary embolus, and pericardial aspiration for pericardial tamponade. Specific therapy for different etiologies of shock will be discussed in their separate chapters.

AIMS

Because the shock syndrome shares many characteristics across different etiologies, the general management of shock is similar in all cases. The basic goal of circulatory shock therapy is the rapid restoration of effective perfusion to vital organs and tissues prior to the onset of cellular injury. Because effective tissue perfusion depends on both sufficient cardiac output and adequate driving pressure, therapy of shock requires maintenance of an appropriate cardiac index and mean blood pressure (Box 21.5). However, because for brief periods marked hypoperfusion is better tolerated than severe hypotension, the first specific resuscitative aim, support of blood pressure (>60 to 65 mm Hg in a baseline normotensive patient), may initially take priority over the second specific aim, maintenance of cardiac index. Finally, maintaining perfusion sufficiently high that arterial lactate concentration remains under 2.2 mmol/L is a generally accepted approach to avoiding anaerobic metabolism and ischemic tissue injury (see Box 21.5). The practice of targeting oxygen delivery to specified supranormal oxygen delivery goals or to evidence of supply-independent oxygen consumption in the ICU has been substantially discredited by clinical studies.[374-377] However, early targeting (<6 hr post presentation) to a central venous oxygen saturation ($cSVo_2$) of >70% using a defined protocol with fluids, blood transfusion, and dobutamine support has been shown to improve outcome in severe sepsis and septic shock.[302] This approach has not been validated in other forms of shock.

Box 21.5 General Approach to Shock: Immediate Goals

Hemodynamic

- MAP > 60 to 65 mm Hg (higher in the presence of coronary artery disease)
- CVP = 8 to 12 mm Hg/PAOP = 12 to 15 mm Hg (may be higher for cardiogenic shock)
- CI > 2.1 L/min/m^2

Optimization of Oxygen Delivery

- Hemoglobin > 9 g/dL; > 7 g/L postshock is sufficient
- Arterial saturation > 92%
- MVo_2 > 60%, $sCVo_2$ > 70%
- Normalization of serum lactate (to < 2.2 mM/L)

Reverse Organ System Dysfunction

- Reverse encephalopathy
- Maintain urine output > 0.5 mL/kg/hr

It is of note that one of the major achievements in shock therapy since the early 2000s has been the recognition that the speed of implementing supportive and specific therapies may be critical to an improvement in outcomes. This concept of a "golden hour" has long been recognized in the context of specific and resuscitative therapy of trauma-induced hypovolemic shock with blood products and surgical management[378,379] and then cardiogenic shock due to myocardial infarction with emergent primary angioplasty or thrombolysis.[380] A similar rapid treatment paradigm has been established for thrombolytic therapy for obstructive shock due to massive pulmonary embolus.[78,79,381] Similarly, rapid fluid resuscitation (<6 hours)[302] and antimicrobial therapy (<1 hour)[107] have been shown to be key to maximizing survival in cases of severe sepsis and septic shock. The accelerated provision of effective therapy probably accounts for reports of improved clinical outcomes with medical emergency response teams.[382-384] Variation in the baseline provision of effective therapy likely accounts for the inconsistent results seen with such teams.[385] The importance of early aggressive resuscitative and specific therapy of all shock states cannot be sufficiently emphasized.

RESUSCITATION

The universal basics of resuscitation underlie the initial management of circulatory shock. Because many patients with circulatory shock may have accompanying trauma and a decreased level of consciousness, the ventilatory status of the patient must be secured. This may involve tracheal intubation or mechanical ventilation, if necessary. Oxygen should be provided at a sufficiently high concentration to supply an arterial oxygen saturation of greater than 90% to 92%. Unintubated patients may require high flow (30 to 45 L/min) or rebreathing oxygen delivery systems, as many patients will have unusually high minute ventilation volumes. Intubated patients should initially receive full ventilatory support in order to decrease systemic oxygen demand. Given that pulmonary infiltrates (aspiration, pneumonia, or ARDS) are common, positive end-expiratory pressure (PEEP) may be necessary to ensure adequate oxygenation. Potential adverse hemodynamic effects from positive pressure ventilation (related primarily to decreased venous return) may be seen but can be minimized by fluid loading so that the patient is euvolemic or modestly hypervolemic.

Depending on the clinical situation, pain management may be necessary. Again, potential adverse hemodynamic effects may be seen if intravascular volume is inadequate because all measures result in some degree of venodilatation either directly or by decreasing sympathetic tone. Two- to 4-mg intravenous boluses of morphine are recommended. During circulatory shock, clearance of morphine by the liver may be impaired due to hepatic hypoperfusion. Besides relieving pain, analgesia should also decrease systemic oxygen consumption.

Management of lactic acidosis developing during circulatory shock is problematic. Bicarbonate therapy may have adverse effects on intracellular pH even while improving the pH of the extracellular fluid. Further, even when pH is extremely low, bicarbonate therapy does not improve systemic hemodynamics in shock associated with acidosis.[386] In addition, increasing serum pH may adversely affect the oxyhemoglobin dissociation relationship. The optimal approach to the management of lactic acidosis is to improve organ and systemic perfusion so that anaerobic metabolism is limited and the liver and, to a lesser extent, kidneys can clear the accumulated lactate. If this is not effective, restricting the use of sodium bicarbonate to situations in which pH is less than 7.1 to 7.15 may be appropriate.

Initial management of circulatory shock should almost always include a crystalloid fluid challenge. In the absence of invasive monitoring with a pulmonary artery catheter, the only practical exception is if clinical evidence strongly suggests ventricular filling pressures are already elevated. This is usually limited to clinical situations involving cardiogenic shock and marked pulmonary edema. Even then, if pulmonary edema is manageable, crystalloid challenge may be appropriate. The volume of the challenge is variable. Large volumes, on the order of 1 to 2 L given rapidly (0.5 to 1 L every 10 to 15 minutes), are frequently used in hemorrhagic and septic shock. One hundred– to 200-mL boluses may be used during cardiogenic shock. If shock does not resolve promptly after the initial fluid challenge, patients should undergo a more detailed invasive (central venous catheter) or noninvasive (echocardiographic) assessment. As previously discussed, a central role for pulmonary artery catheterization in shock is now questioned and highly controversial.

Although aggressive fluid resuscitation is well accepted in the therapy of shock, emerging data support more limited resuscitation in some contexts. Resuscitation to hypotensive targets (target systolic blood pressure 80 to 100 mm Hg) has been recommended in hemorrhagic shock due to penetrating trauma based on data showing improved survival using this approach.[387,388] In addition, a limited fluid resuscitation protocol for 7 days has been shown to improve the number of ventilator- and ICU-free days in acute lung injury without increasing the prevalence of shock or the mortality rate.[389] A more limited early fluid resuscitation has also been shown to be associated with improved survival in children with shock associated with infection in under-resourced settings.[390]

In addition, substantial controversy exists regarding the appropriate use of crystalloid and colloid fluids after initial resuscitation attempts. The basis of this controversy lies with the differing oncotic properties of the fluids. Crystalloid fluids (such as normal saline and lactated Ringer's solution) contain sodium chloride in a quantity that closely matches extracellular fluid. No large molecules are present. Thus, such fluids distribute into the extracellular space. Colloids, in addition, contain albumin or large osmotically active carbohydrates (hydroxyethyl starch, dextran), which may be held within the intravascular space resulting in an increase of the plasma oncotic pressure. It has been suggested that in shock associated with microvascular changes of permeability (such as sepsis), colloid fluids will remain in the intravascular space, leading to decreased tissue edema and noncardiogenic pulmonary edema.[391] However, the limited human studies available suggest that although radiographic infiltrates may appear more severe with crystalloid resuscitation of sepsis, gas exchange is comparable to colloid resuscitation.[41]

Importantly, it has been proposed that colloids may provide better outcomes in the resuscitation of shock due

to the rapidity and persistence of volume expansion compared to crystalloid infusion.[41,392] However, clinical studies for the most part have not supported this contention. Meta-analyses have largely failed to demonstrate the clinical outcome superiority of crystalloids compared to either albumin or synthetic colloids.[393] In fact, one meta-analysis of randomized, controlled studies examining the effect of fluid administration in critically ill patients with burn injury, hypovolemia, or hypoalbuminemia suggested increased mortality in patients treated with colloids.[394] In one large, randomized study of albumin versus normal saline, a trend toward improved outcomes with albumin in severe sepsis and saline in trauma failed to reach significance.[395] More recently, a substantial body of literature has shown that synthetic colloids increase the risk of renal injury and death, particularly in sepsis and septic shock.[396-398] An increased risk of renal injury/dialysis requirement and risk of death was shown for hydroxyethyl starch versus Ringer's solution therapy in two large randomized trials of sepsis.[397,398] There are some data, though, that suggest colloid resuscitation may clear lactate more quickly and result in less renal injury than crystalloid in penetrating trauma.[399] Given the much higher costs of colloids and the higher risk of renal injury and death with synthetic colloids, resuscitation of shock should generally focus on crystalloid solutions unless speed of resuscitation is paramount (i.e., there is acute major trauma or massive hemorrhage). In those settings, colloidal solutions may be initially favored until blood is available.

With respect to hemoglobin, one randomized trial has suggested that a hemoglobin level of 70 g/L is sufficient for most patients in the ICU (other than those with a high severity of illness or acute coronary syndrome).[400,401] Although several other studies have pointed out the potential risks associated with blood transfusion in the ICU setting,[402-405] no study has directly examined hemoglobin requirements during shock. The only study to (indirectly) examine blood transfusion in shock suggested that early augmentation of hematocrit to >30% during septic shock as part of a protocol to drive central venous oxygen saturation to >70% was associated with improved survival.[302] For that reason, it is reasonable to recommend that a hemoglobin of 90 to 100 g/L be maintained during acute shock.

Once intravascular volume is optimized, the next line of therapy of circulatory shock usually involves inotropes and vasopressors. Alternately, vasopressors may be occasionally required for brief periods of blood pressure support in extremely hypotensive patients prior to the initiation of fluid infusion.

Four major classes of agents are used clinically for inotropic or vasopressor support: sympathomimetics, phosphodiesterase inhibitors, cardiac glycosides, and vasopressin (anti-diuretic hormone) (Table 21.4). Sympathomimetics (catecholamines) may activate cardiac beta-1 and alpha adrenoreceptors, peripheral vascular alpha or beta-2 receptors, and vascular dopaminergic receptors. Cardiac beta-1 adrenoreceptors augment heart rate and myocardial contractility by increasing activity of adenylate cyclase resulting in increased generation of cyclic adenosine monophosphate (AMP).[406] Alpha receptors act through phospholipase C production of inositol triphosphate and diacylglycerol.[407-409] Peripheral vascular alpha receptors cause vasoconstriction, whereas peripheral beta-2 adrenoreceptors induce a mild vasodilatation. Cardiac alpha adrenoreceptors contribute to increased contractility (but not heart rate) when stimulated.[407,409] Dopaminergic adrenoreceptors, mediating dilatation, are found in the arterial vessels supplying vital organs (including the heart, brain, kidneys, and splanchnic organs).[410] Phosphodiesterase inhibitors such as amrinone and milrinone augment cardiac contractility by inhibition of cyclic AMP degradation. They also relax vascular smooth muscle.[411] Despite a long history of digitalis use in the management of congestive heart failure and data suggesting hemodynamic benefit in sepsis,[412] cardiac glycosides are rarely used for the acute management of circulatory shock due to their narrow therapeutic index and long half-life. Uncontrolled studies have shown that endogenous vasopressin concentrations may be relatively deficient in shock states and that infusion of vasopressin (which has little effect in healthy, normotensive subjects) can have a profound pressor effect during vasodilatory shock.[413-416]

Norepinephrine, an endogenous catecholamine, exerts both powerful inotropic (cardiac alpha and beta-1 adrenoreceptors) and peripheral vasoconstriction effects (alpha adrenoreceptors). It is currently the favored catecholamine for the initial management of shock. It can be used for persistent hypotension despite high-dose dopamine during septic and obstructive shock. It should generally be used only transiently in cardiogenic shock because it may dramatically reduce forward flow. Similarly, it should not be required during hemorrhagic shock except for extremely brief periods of blood pressure support pending volume infusion. Infusion rates of 2 to 20 μg/min are commonly used, but if necessary, higher rates may be tried. Suggestions that there is clinical utility in the concomitant use of "low"-dose dopamine with norepinephrine to generate sparing of pressor and shock-associated renal injury have been refuted.[417-419]

Dopamine has fallen out of favor as the initial vasopressor used for circulatory shock. A central and peripheral nervous system neurotransmitter and the biologic precursor of norepinephrine, it stimulates three different receptors: vascular dopaminergic, cardiac β1, and vascular α. In addition, a part of dopamine's myocardial effects is mediated by the release of endogenous norepinephrine. Dose-dependent maximal stimulation of each of dopamine's target receptors has been suggested to result in different typical hemodynamic responses at different infusion rates. At infusion rates of less than 4 to 5 μg/kg/min, dopaminergic effects have been said to dominate, but studies suggest this has little clinical relevance (although in the past it was the theoretical basis for the use of low-dose dopamine for renal protection).[418,419] Vascular DA2 receptors vasodilate the renal, mesenteric, myocardial, and cerebral vascular beds. In addition, renal DA1 receptors mediate a mild natriuresis.[420] β-adrenoreceptor-mediated cardiac inotropic effects have been suggested to dominate at doses below approximately 10 μg/kg/min with α-adrenoreceptor vasopressor effects more prominent at doses over 10 μg/kg/min.[410] It is important to note, however, that dopaminergic and cardiac adrenergic effects are not suppressed at higher doses but rather that additional effects are seen. In addition, there is substantial inter-individual variation in response with some showing substantial vasopressor or inotropic responses at low infusion rates. For management of circulatory shock, dopamine

Table 21.4 Relative Potency of Intravenously Administered Vasopressors/Inotropes Used in Shock*

		Cardiac		Peripheral Vasculature			
	Dose	Heart Rate	Contractility	Vasoconstriction	Vasodilation	Dopaminergic	Typical Clinical Use
Dopamine	1-4 µg/kg/min 5-10 µg/kg/min 11-20 µg/kg/min	1+ 2+ 2+	1-2+ 2+ 2+	0 1-2+ 2-3+	1+ 1+ 1+	4+ 4+ 4+	All shock
Norepinephrine	2-20 µg/min	2+	2+	4+	0	0	Refractory shock
Dobutamine	1-20 µg/kg/min	1-2+	3+	1+	2+	0	CHF; cardiogenic, obstructive and septic shock
Dopexamine†	0.5-6 µg/kg/min	2+	1+	0	3-4+	4+	CHF; cardiogenic shock
Epinephrine	1-8 µg/min	4+	4+	4+	3+	0	Refractory shock or anaphylactic shock
Phenylephrine	20-200 µg/min	0	1+	4+	0	0	Neurogenic or septic shock
Isoproterenol	1-8 µg/min	4+	4+	0	4+	0	Cardiogenic shock (bradyarrhythmia), torsades de pointes, ventricular tachycardia
Vasopressin	0.04-0.10 U/min (start 0.01-0.04 U/min; titrate up 0.02-0.04 U/min every 20-30 min)	0	0	4+	0	0	Vasodilatory (e.g., septic) shock
Milrinone	37.5-75 µg/kg bolus over 10 min; 0.375-0.75 µg/kg/min infusion	1+	3+	0	2+	0	CHF; cardiogenic shock

*The 1-4+ scoring system represents an arbitrary quantitation of the comparative potency of different vasopressors/inotropes.
†Not clinically released in the United States. CHF, congestive heart failure.

is often started at 5 μg/kg/min and increased rapidly (5 μg/kg/min every 2 or 3 minutes) to a maximum of 20 μg/kg/min until the target blood pressure is reached. If vasopressor effects are inadequate at these infusion rates, a norepinephrine infusion is begun.

Dobutamine, which is structurally derived from isoproterenol, is a racemic mixture of two synthetic stereoisomers. In combination, the stereoisomers increase myocardial contractility through alpha and beta-1 cardiac adrenoreceptors.[421,422] Weak arteriolar vasodilatory effects are mediated through the dominance of beta-2 adrenoreceptor-mediated vascular relaxation over alpha-adrenoreceptor-mediated vasoconstriction in the arterial circulation. Evidence suggesting that dobutamine induces vasoconstriction in the systemic venous bed (resulting in increased mean circulatory pressure and the augmentation of venous return/cardiac output) implies that alpha-adrenoreceptor-mediated effects may be dominant in small capacitance vessels.[167,421,422]

Although its hemodynamic effects are otherwise similar to isoproterenol, dobutamine has been reputed to exert minimal chronotropic effects.[422,423] This attribute has been questioned[424] and may have been based on the selection of congestive heart failure patients with beta-adrenoreceptor down-regulation and other potential alterations of adrenoreceptor signal transduction.[423,425] Dobutamine's powerful inotropic effect is due to a combination of its direct effect on myocardial contractility, its afterload reducing effect, and alpha-adrenoreceptor-mediated venoconstriction.[422,423] In contrast to dopamine, it causes a reduction in filling pressures and a greater increase in cardiac output at equivalent doses.[426,427] In addition, although it increases myocardial oxygen demand (like dopamine), myocardial perfusion is also augmented (in contrast to dopamine[428]). The most well-accepted use of dobutamine in circulatory shock relates to cardiac etiologies.[422,423] Once blood pressure is corrected, dobutamine may be used to increase cardiac performance and decrease elevated ventricular filling pressures associated with cardiogenic pulmonary edema. In this setting dobutamine may in fact increase blood pressure. Alternately, if myocardial damage is extensive, vasodilatory properties may dominate, resulting in hypotension. Dobutamine may also be of use in obstructive shock pending definitive intervention and can be used to augment low CI occasionally seen in fluid-resuscitated septic shock. Our own experience suggests that maintenance of a PAOP of at least 15 mm Hg is required during dobutamine infusion in order to avoid hypotension in patients with septic shock. Its use for augmenting oxygen delivery in septic shock has been substantially abandoned.[429,430]

Epinephrine is occasionally used when other inotrope/vasopressors have failed to support blood pressure or cardiac output in circulatory shock. It is the first-line agent for management of anaphylactic shock. In addition, it is used to support myocardial contractility postcardiopulmonary bypass.[431] Epinephrine stimulation of alpha, beta-1, and beta-2 receptors results in increases of myocardial contractility that are more pronounced than with any other inotrope. Nanogram/kg/min infusion rates result in significant increases in cardiac output.[431] Epinephrine is also frequently used in septic shock refractory to other inotropes/vasopressors. Effects attributable to impaired myocardial perfusion (chest pain, arrhythmias, ST depression) in patients with known coronary artery disease are usually limited to patients receiving more than 120 ng/kg/min.[432] Although the usual infusion rate is 1 to 8 μg/min, higher rates can be used with the potential for increasing toxicity.

Milrinone, a bipyridine phosphodiesterase inhibitor, increases intracellular concentrations of cyclic AMP by blocking cyclic AMP breakdown.[411] Although some controversy has existed regarding the relative contributions of increased myocardial contractility and decreased vascular tone with respect to the apparent inotropic properties of phosphodiesterase inhibitors, data confirm the presence of substantial increases of myocardial contractility[433]; these agents also produce substantial vasodilatation. The most accepted use for milrinone in the intensive care unit is in the management of congestive heart failure, cardiogenic shock, and postcardiopulmonary bypass myocardial dysfunction.[411] Experimental animal studies suggest phosphodiesterase inhibitors may exert beneficial hemodynamic effects in sepsis by augmenting cardiac output and increasing oxygen delivery without increasing consumption.[434] Occasional clinical reports suggest a potential management role in catecholamine-refractory septic shock.[435]

Phenylephrine is a synthetic catecholamine that is unique in its almost pure alpha-adrenergic agonist effects. Its most common uses are intraoperatively to counteract the vasodilatory effects of anesthetics and in septic shock where its lack of beta-adrenergic activity may help limit deleterious increases in heart rate seen with other agents. Isoproterenol is another synthetic catecholamine with dominant beta-1 and beta-2 activity. Its previous indications for use have largely been supplanted by dobutamine. Due to its powerful chronotropic effects, it can be useful in the management of bradyarrhythmias and torsades de pointes ventricular tachycardia (for overdrive pacing), but otherwise it has no specific role in the management of circulatory shock.

Vasopressin levels in septic shock have been shown to be significantly suppressed.[413] Studies have shown that intravenous infusion of vasopressin into patients with septic shock results in a profound pressor response.[414] This profound pressor response occurs despite the absence of such an effect with even larger amounts of vasopressin in normotensive patients. Investigators have also documented efficacy in other vasodilatory shock states with refractory hypotension including milrinone-induced shock in severe heart failure,[436] postcardiotomy vasodilatory shock,[437] unstable brain dead organ donors,[438] and late phase hemorrhagic shock.[416] Vasopressin (0.1 to 1 U/mL in normal saline or D5W) may be initiated at 0.02 to 0.04 U/min and titrated up every 20 to 30 minutes to 0.1 to 0.12 U/min. Few patients will respond with higher doses. It is of note that in large doses, vasopressin may produce bradycardia, minor arrhythmias, premature atrial contraction, heart block, peripheral vascular constriction or collapse, coronary insufficiency, decreased cardiac output, myocardial ischemia, and myocardial infarction. In patients with coronary artery disease, even small doses of the drug can precipitate angina. At the upper end of dosing, a significant subset of patients may develop digital, mesenteric, or myocardial ischemia, so it is imperative to use the minimal amount of vasopressin possible to achieve desired blood pressure goals. Published data suggest vasopressin can be used for up to 4 to 6 days if necessary. A

randomized, blinded study of vasopressin treatment of septic shock has shown that the addition of vasopressin (versus norepinephrine) to open label vasopressors offered no overall advantage.[439] Because of the limited experience with this compound and the relatively longer half-life of the drug, vasopressin should be utilized only after hemodynamic stabilization with standard agents (catecholamines) has been attempted.

CONCLUSION

Although the syndrome of shock ultimately involves common late pathologic elements, the early pathophysiologic processes underlying different conditions resulting in circulatory shock are both diverse and complex. Our concepts of shock, which once focused on broad cardiovascular physiologic mechanisms, have more recently centered on issues of microvascular function and cellular metabolism. In the future, this focus may evolve toward questions of altered cellular gene expression in a variety of tissues. Advances in therapy have developed in parallel to these changes in our understanding of shock pathophysiology. Early work on the therapy of shock concentrated on correcting hemodynamic derangements through the use of vasopressors and inotropes. Clinical trials over decades have centered on anticytokines such as anti-TNFα and various novel resuscitative compounds. The most advanced experimental therapies involve the direct manipulation of gene expression via antisense oligonucleotides and transcription factor inhibitors. Despite these advances, however, many questions remain. Only ongoing basic research and clinical trials will answer them.

KEY POINTS

- Shock is the final pathway through which a variety of pathologic processes lead to cardiovascular failure and death.
- Shock is the state in which the profound and widespread reduction of effective tissue perfusion leads to cellular injury. The inability of cells to obtain or utilize oxygen in sufficient quantity to optimally meet their metabolic requirements is common to all forms of shock. Hypotension alone does not define shock.
- Based on hemodynamic characteristics, shock is categorized as hypovolemic, cardiogenic, extracardiac obstructive, or distributive.
- Although one hemodynamic categorization dominates, most forms of clinical shock involve some cardiovascular characteristics of several categories.
- The clinical picture of shock is dependent on the etiology, the magnitude of the injury or insult, and the degree of physiologic compensation. Physiologic compensation is determined by the time course of the development of shock and the preexisting cardiovascular reserve.

KEY POINTS (Continued)

- The systemic hemodynamic aspects of shock can be described by the interactive contributions of cardiac and vascular function to blood pressure and cardiac output.
- Physiologically, blood pressure is dependent on cardiac output and vascular resistance; cardiac output is not dependent on blood pressure.
- Failure to maintain the blood pressure required for autoregulation during hypodynamic circulatory shock indicates a severe reduction in cardiac output.
- In a closed cardiovascular circuit, cardiac output as determined by heart rate, preload, afterload, and contractility equals venous return as determined by venous pressure (mean circulatory pressure), right atrial pressure, and venous resistance. Total systemic perfusion is therefore dependent on cardiac-vascular interactions.
- In addition to sufficient cardiac output at sufficient pressure, effective perfusion requires normal local and systemic microvascular function resulting in the appropriate distribution of cardiac output.
- During hypovolemic and other forms of hypodynamic shock, extrinsic blood flow regulatory mechanisms overwhelm the autoregulatory response of most vascular beds. Blood flow to vital organs such as the heart and brain is relatively well preserved due to dominant autoregulatory control.
- During distributive shock, particularly septic shock, organ blood flow is disturbed at higher mean arterial pressures, suggesting a primary defect of microvascular function.
- Cellular dysfunction and organ failure in shock involves the interactions of cellular ischemia, circulating or local inflammatory mediators, and free radical injury.
- All compensatory responses to shock support oxygen delivery to vital tissues. The mechanisms include support of venous pressure, maximization of cardiac function, redistribution of perfusion to vital organs, and optimization of oxygen unloading.
- Circulatory shock may be associated with encephalopathy, adult respiratory distress syndrome, acute tubular necrosis, ischemic hepatitis or intrahepatic cholestasis, thrombocytopenia, immunosuppression, and multiple organ dysfunction syndrome.
- Because early recognition and treatment are the keys to improved survival, the diagnosis of shock is primarily based on clinical criteria. Laboratory and radiologic data are used to confirm the diagnosis and to help clarify etiology.
- Clinically, shock is characterized by physiologic compensatory responses including tachycardia, tachypnea, oliguria, and signs of physiologic decompensation, particularly hypotension.

Continued on following page

KEY POINTS (Continued)

- Shock should be managed in an intensive care unit with continuous monitoring and close nursing support. Patients whose etiologic diagnosis is in doubt, whose hemodynamic instability does not quickly resolve with intravenous fluids, or who are medically complicated should undergo noninvasive (echo) or invasive hemodynamic monitoring with arterial and centrally placed catheters. Pulmonary artery catheters remain a reasonable option in some cases.
- The basic goal of therapy of circulatory shock is the restoration of effective perfusion to vital organs and tissues prior to the onset of cellular injury.
- The specific aims of resuscitation of shock include support of mean blood pressure above 60 to 65 mm Hg, maintenance of a cardiac index greater than 2.1 L/min/m^2, and restriction of arterial lactate concentrations to less than 2.2 mmol/L.

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22 Cardiogenic Shock

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CHAPTER OUTLINE

Cardiogenic shock is the syndrome that ensues when the heart is unable to deliver enough blood to maintain adequate tissue perfusion. Acute myocardial infarction (MI) is the leading cause, but other potential etiologic factors need to be considered.[1,2] Without prompt diagnosis and appropriate management, morbidity and mortality rates are substantial, approaching 60% for all age groups.[2,3] Rapid evaluation and prompt initiation of supportive measures and definitive therapy in patients with cardiogenic shock may improve both early and long-term outcomes.

DEFINITION

The clinical definition of cardiogenic shock includes decreased cardiac output and evidence of tissue hypoxia in the presence of adequate intravascular volume. The diagnosis of circulatory shock (Box 22.1) is made at the bedside by the presence of hypotension along with a combination of clinical signs indicative of poor tissue perfusion, including oliguria, clouded sensorium, and cool, mottled extremities. Hemodynamic criteria include sustained hypotension (systolic blood pressure < 90 mm Hg for at least 30 minutes) and a reduced cardiac index (<2.2 L/min/m^2) in the presence of elevated filling pressures (pulmonary capillary occlusion pressure > 15 mm Hg).[4] Cardiogenic shock is diagnosed after documentation of myocardial dysfunction and exclusion or correction of factors such as hypovolemia, hypoxia, and acidosis.

EPIDEMIOLOGY

Pump failure due to cardiogenic shock has long been known to carry a high mortality rate. The seminal article outlining prognosis after MI was a single center series of 250 patients reported by Killip in 1967.[5] Killip divided patients into four classes as follows:

Killip class I: no evidence of congestive heart failure
Killip class II: presence of an S_3 gallop and/or bibasilar rales
Killip class III: pulmonary edema (rales greater than halfway up the lung fields)
Killip class IV: cardiogenic shock

Nineteen percent of the 250 patients were in class IV at presentation, and their mortality rate was 81%.[5]

With the advent of right-sided heart catheterization, Forrester and Swan defined hemodynamic subsets after MI analogous to the clinical subsets outlined by Killip.[4] Subset I consisted of patients with normal pulmonary capillary wedge pressure (PCWP) and cardiac output, subset II consisted of patients with elevated PCWP and normal cardiac output, subset III consisted of patients with normal PCWP and decreased cardiac output, and subset IV consisted of patients with elevated PCWP and decreased cardiac output.[4]

Despite advances in management of heart failure and acute MI, the mortality rate of patients with cardiogenic shock has remained high.[2,6-8] Data suggest an increase in

Box 22.1 Diagnosis of Cardiogenic Shock

Clinical Signs

Hypotension
Oliguria
Clouded sensorium
Cool and mottled extremities

Hemodynamic Criteria

Systolic blood pressure < 90 mm Hg for > 30 min
Cardiac index < 2.2 L/min/m^2
Pulmonary artery occlusion pressure > 15 mm Hg

Box 22.2 Causes of Cardiogenic Shock

Acute Myocardial Infarction

Pump failure
  Large infarction
  Smaller infarction with preexisting left ventricular dysfunction
  Infarct extension
  Reinfarction
  Infarct expansion
Mechanical complications
  Acute mitral regurgitation due to papillary muscle rupture
  Ventricular septal defect
  Free wall rupture
  Pericardial tamponade
Right ventricular infarction

Other Conditions

End-stage cardiomyopathy
Myocarditis
Myocardial contusion
Prolonged cardiopulmonary bypass
Septic shock with severe myocardial depression
Left ventricular outflow tract obstruction
  Aortic stenosis
  Hypertrophic obstructive cardiomyopathy
Obstruction to left ventricular filling
  Mitral stenosis
  Left atrial myxoma
Acute mitral regurgitation (chordal rupture)
Acute aortic insufficiency

survival in the 1990s, coincident with the use of reperfusion strategies.[7-9] Cardiogenic shock, however, remains the most common cause of death in hospitalized patients with acute MI.

INCIDENCE

Accurate determination of the precise incidence of cardiogenic shock is difficult because patients who die of MI prior to reaching the hospital generally do not receive this diagnosis.[6,10-13] Nonetheless, estimates from a variety of sources have been fairly consistent. The Worcester Heart Attack Study,[6] a community-wide analysis, found an incidence of cardiogenic shock of 7.5%, an incidence that remained fairly stable from 1975 to 1997.[6,9] The incidence was similar in the randomized GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial (7.2%),[14] in other multicenter thrombolytic trials,[10-12] and in patients with ST-segment elevation MI in the National Registry of Myocardial Infarction (NRMI) database from 1995 to 2004 (8.6%).[7] More recently, however, the incidence of cardiogenic shock has fallen from about 8% to about 6% of MIs, with most of the change resulting from a decrease in cardiogenic shock developing after initial presentation, supporting the notion that early revascularization strategies are an important contributor to the decline.[3]

ETIOLOGY

The most common cause of cardiogenic shock is left ventricular failure in the setting of an extensive acute MI, although a smaller infarction in a patient with previously compromised left ventricular function may also precipitate shock. Cardiogenic shock can also be caused by mechanical complications such as acute mitral regurgitation, rupture of the interventricular septum, or rupture of the free wall—or by large right ventricular infarctions. In a report of the SHOCK (**SH**ould we emergently revascularize **O**ccluded **C**oronaries for shoc**K**) trial registry of 1160 patients with cardiogenic shock,[2] 78.5% of patients had predominant left ventricular failure, 6.9% had acute mitral regurgitation, 3.9% had ventricular septal rupture, 2.8% had isolated right ventricular shock, 1.4% had tamponade or cardiac rupture, and 6.5% had shock resulting from other causes.

Other causes of cardiogenic shock include myocarditis, end-stage cardiomyopathy, myocardial contusion, septic shock with severe myocardial depression, myocardial dysfunction after prolonged cardiopulmonary bypass, valvular heart disease, and hypertrophic obstructive cardiomyopathy (Box 22.2). An important consideration is that some cardiogenic shock may have an iatrogenic component. Early diagnosis of impending shock or of patients at high risk for development of shock is essential, both to speed intervention and to avoid therapies that may worsen hemodynamics. In many cases of cardiogenic shock in the setting of MI, the diagnosis is not made until the patient has been triaged and admitted to an inpatient setting. Patients may have received early beta blockade or angiotensin-converting enzyme inhibition, therapies that may impact hemodynamics substantially.

Patients may have cardiogenic shock at initial presentation, but most do not; shock usually evolves over several hours,[15,16] suggesting that early treatment may potentially prevent shock. In fact, some data indicate that early thrombolytic therapy may decrease the incidence of cardiogenic shock.[17] In the SHOCK trial registry, 75% of patients developed cardiogenic shock within 24 hours after presentation, with a median delay of 7 hours.[2] Results from the GUSTO trial were similar;[13] among patients with shock, 11% were in shock on arrival and 89% developed shock after admission.

Risk factors for the development of cardiogenic shock in MI generally parallel those for left ventricular dysfunction

and the severity of coronary artery disease. Shock is more likely to develop in patients who are elderly, are diabetic, and have anterior MI.[5,15,18,19] Patients with cardiogenic shock are also more likely to have histories of previous infarction, peripheral vascular disease, and cerebrovascular disease.[18,19] Decreased ejection fractions and larger infarctions (as evidenced by higher cardiac enzymes) are also predictors of the development of cardiogenic shock.[18,19] Analysis from the GUSTO-3 trial has identified age, lower systolic blood pressure, heart rate, and Killip class as significant predictors of the risk for development of cardiogenic shock after presentation with acute MI.[20] Use of a predictive scoring system derived from this study may be useful in identifying patients at high risk for the development of cardiogenic shock and targeting such patients for closer monitoring.[20]

Cardiogenic shock is most often associated with anterior MI. In the SHOCK trial registry, 55% of infarctions were anterior, 46% were inferior, 21% were posterior, and 50% were in multiple locations.[2] These findings were consistent with those in other series.[21] Angiographic evidence most often demonstrates multivessel coronary disease (left main occlusion in 20% of patients, three-vessel disease in 64%, two-vessel disease in 23%, and one-vessel disease in 13% of patients).[22] The high prevalence of multivessel coronary artery disease is important because compensatory hyperkinesis normally develops in myocardial segments that are not involved in an acute MI, and this response helps maintain cardiac output. Failure to develop such a response, because of previous infarction or high-grade coronary stenoses, is an important risk factor for cardiogenic shock and death.[16,23]

PATHOGENESIS

SYSTEMIC EFFECTS

Cardiac dysfunction in patients with cardiogenic shock is usually initiated by MI or ischemia. The myocardial dysfunction resulting from ischemia worsens that ischemia, creating a downward spiral[24] (Fig. 22.1). When a critical mass of ischemic or necrotic left ventricular myocardium fails to pump, stroke volume and cardiac output decrease. Myocardial perfusion, which depends on the pressure gradient between the coronary arterial system and the left ventricle and on the duration of diastole, is compromised by hypotension and tachycardia, exacerbating ischemia. The increased ventricular diastolic pressures caused by pump failure reduce coronary perfusion pressure, and the additional wall stress elevates myocardial oxygen requirements, further worsening ischemia. Decreased cardiac output also compromises systemic perfusion.

When myocardial function is depressed, several compensatory mechanisms are activated, including sympathetic stimulation to increase heart rate and contractility and renal fluid retention to increase preload. These compensatory mechanisms may become maladaptive and can actually worsen the situation when cardiogenic shock develops. Increased heart rate and contractility increase myocardial oxygen demand and exacerbate ischemia. Fluid retention and impaired diastolic filling caused by tachycardia and ischemia may result in pulmonary congestion and hypoxia. Vasoconstriction to maintain blood pressure increases

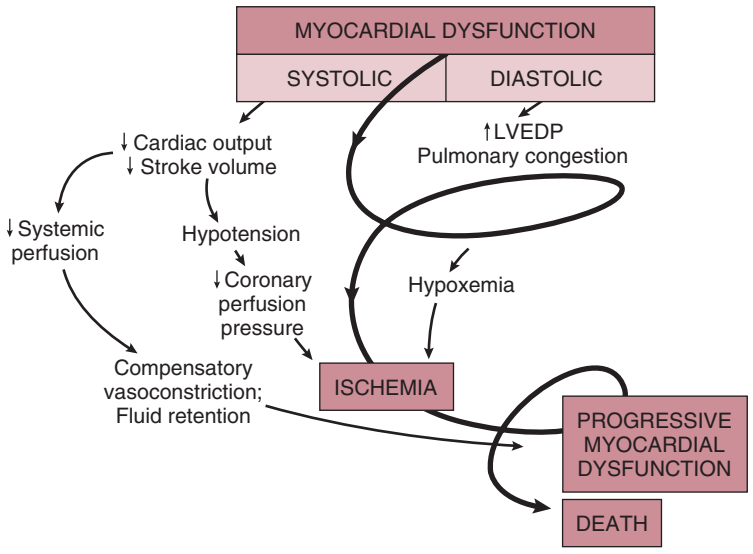

Figure 22.1 The "downward spiral" in cardiogenic shock. Cardiac dysfunction is usually initiated by myocardial infarction or ischemia. When a critical mass of left ventricular myocardium fails to pump, stroke volume and cardiac output decrease. Myocardial perfusion is compromised by hypotension and tachycardia, exacerbating ischemia. The increased ventricular diastolic pressures that result from pump failure further reduce coronary perfusion pressure, and the additional wall stress elevates myocardial oxygen requirements, also worsening ischemia. Decreased cardiac output also compromises systemic perfusion, which can lead to lactic acidosis and further compromise of systolic performance. When myocardial function is depressed, several compensatory mechanisms are activated, including sympathetic stimulation to increase heart rate and contractility and renal fluid retention to increase preload. These compensatory mechanisms may become dysfunctional and can actually worsen the situation when cardiogenic shock develops by increasing myocardial oxygen demand and afterload. Thus, myocardial dysfunction resulting from ischemia worsens that ischemia, setting up a vicious cycle that must be interrupted to prevent patient demise. LVEDP: left ventricular end-diastolic pressure. (Modified from Hollenberg SM, Kavinsky CJ, Parrillo JE: Cardiogenic shock. Ann Intern Med 1999;131:49.)

myocardial afterload, further impairing cardiac performance and increasing myocardial oxygen demand. This increased demand, in the face of inadequate perfusion, worsens ischemia and begins a vicious cycle that will end in death if not interrupted (see Fig. 22.1). The interruption of this cycle of myocardial dysfunction and ischemia forms the basis for the therapeutic regimens for cardiogenic shock.

Not all patients fit into this classic paradigm. In the SHOCK trial, the average systemic vascular resistance (SVR) was not elevated, and the range of values was wide, suggesting that compensatory vasoconstriction is not universal. Some patients had fever and elevated white blood cell counts along with decreased SVR, suggesting a systemic inflammatory response syndrome.[25] This has led to an expansion of the paradigm to include the possibility of the contribution of inflammatory responses to vasodilation and myocardial stunning, leading clinically to persistence of shock (Fig. 22.2).[25] Supporting this notion is the fact that the mean ejection fraction in the SHOCK trial was only moderately decreased (30%), suggesting that mechanisms other than pump failure were operative.[25] Immune activation appears to be common to a number of different forms of shock. Activation of inducible nitric oxide synthase (iNOS) with production of nitric oxide and peroxynitrate has been proposed as one potential mechanism.

MYOCARDIAL PATHOLOGY

Cardiogenic shock is characterized by both systolic and diastolic myocardial dysfunction.[16,26] Progressive myocardial necrosis has been observed consistently in clinical and pathologic studies of patients with cardiogenic shock.[16,27] Patients who develop shock after admission often have evidence of infarct extension, which can result from reocclusion of a transiently patent infarct artery, propagation of intracoronary thrombus, or a combination of decreased coronary perfusion pressure and increased myocardial oxygen demand.[18,19] Myocytes at the border zone of an infarction are more susceptible to additional ischemic episodes; therefore, these adjacent segments are at particular risk.[28] Mechanical infarct expansion, which is seen most dramatically after extensive anterior MI, can also contribute to late development of cardiogenic shock.[18,29]

Ischemia remote from the infarct zone may be particularly important in producing systolic dysfunction in patients with cardiogenic shock.[23,30] Patients with cardiogenic shock usually have multivessel coronary artery disease,[2,16] with limited vasodilator reserve, impaired autoregulation, and consequent pressure-dependent coronary flow in several perfusion territories.[31] Hypotension and metabolic derangements thus have the potential to impair the contractility of noninfarcted myocardium in patients with shock.[32] This can limit hyperkinesis of uninvolved segments, a compensatory mechanism typically seen early after MI.[23,30]

Myocardial diastolic function is also impaired in patients with cardiogenic shock. Myocardial ischemia causes decreased compliance, increasing the left ventricular filling pressure at a given end-diastolic volume.[33,34] Compensatory increases in left ventricular volumes to maintain stroke volume further increase filling pressures. Elevation of left ventricular pressures can lead to pulmonary edema and hypoxemia (see Fig. 22.1).

In addition to abnormalities in myocardial performance, valvular abnormalities can contribute to increased pulmonary congestion. Papillary muscle dysfunction caused by ischemia is common and can lead to substantial increases in left atrial pressure; the degree of mitral regurgitation may be lessened by afterload reduction. This mechanism is distinct from complete rupture of the papillary muscle, a mechanical complication that presents dramatically, with pulmonary edema and cardiogenic shock.

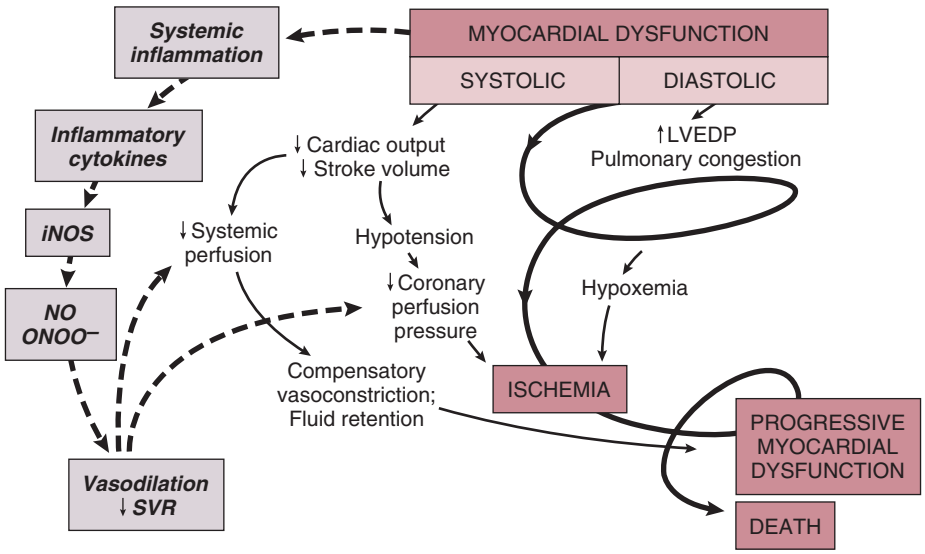

Figure 22.2 Expansion of the pathophysiologic paradigm of cardiogenic shock to include the potential contribution of inflammatory mediators. Inhibition of nitric oxide, however, has not been shown to be beneficial in patients with cardiogenic shock.[149] iNOS, inducible nitric oxide synthase; LVEDP, left ventricular end-diastolic pressure; NO, nitric oxide; $ONOO^-$, peroxynitrite; SVR, systemic vascular resistance. (Adapted from Hochman JS: Cardiogenic shock complicating acute myocardial infarction: Expanding the paradigm. Circulation 2003;107:2999.)

CELLULAR PATHOLOGY

Tissue hypoperfusion and consequent cellular hypoxia lead to anaerobic glycolysis, with depletion of adenosine triphosphate and intracellular energy reserves. Anaerobic glycolysis also causes accumulation of lactic acid and resultant intracellular acidosis. Failure of energy-dependent ion transport pumps decreases transmembrane potential, causing intracellular accumulation of sodium and calcium and myocyte swelling.[35] Cellular ischemia and intracellular calcium accumulation can activate intracellular proteases.[36] If the ischemia is severe and prolonged enough, myocardial cellular injury can become irreversible, with the classic pattern of myonecrosis: mitochondrial swelling, accumulation of denatured proteins and chromatin in the cytoplasm, lysosomal breakdown, and fracture of the mitochondria, nuclear envelope, and plasma membrane.[35,36]

Accumulating evidence indicates that apoptosis (programmed cell death) may also contribute to myocyte loss in MI.[28,36,37] Although myonecrosis clearly outweighs apoptosis in the core of an infarcted area, evidence for apoptosis has been found consistently in the border zone of infarcts after ischemia and reperfusion and sporadically in areas remote from the ischemia area.[28,37] Activation of inflammatory cascades, oxidative stress, and stretching of myocytes have been proposed as mechanisms that activate the apoptotic pathways.[36,37] Although the magnitude of apoptotic cell loss in MI remains uncertain, inhibitors of apoptosis have been found to attenuate myocardial injury in animal models of postischemic reperfusion; these inhibitors may also have therapeutic potential for myocyte salvage after large infarctions.[37]

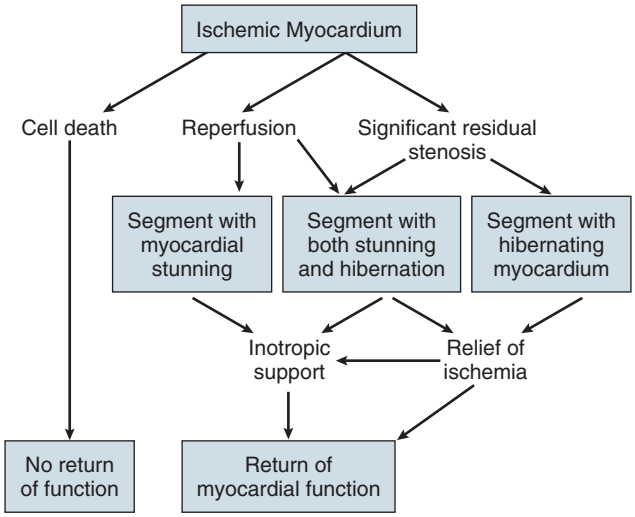

Figure 22.3 Possible outcomes after myocardial ischemia. After myocardial ischemia, either necrosis or reversible dysfunction may occur. Myocardial stunning represents postischemic dysfunction that persists despite restoration of normal flow. These segments respond to inotropes and will recover function if supported. Hibernating myocardium is a state of persistently impaired myocardial function at rest due to residual stenosis; function can be restored to normal by relieving ischemia. Repetitive episodes of stunning can coexist with or mimic myocardial hibernation. The concept that stunned or hibernating segments can recover contractile function emphasizes the importance of measures to support hemodynamics in patients with cardiogenic shock. (Modified from Hollenberg SM, Kavinsky CJ, Parrillo JE: Cardiogenic shock. Ann Intern Med 1999;131:50.)

REVERSIBLE MYOCARDIAL DYSFUNCTION

A key to understanding the pathophysiology and treatment of cardiogenic shock is to realize that large areas of nonfunctional but viable myocardium can also cause or contribute to the development of cardiogenic shock in patients after MI (Fig. 22.3). This reversible dysfunction can be described in two main categories: stunning and hibernation.

Myocardial stunning represents postischemic dysfunction that persists despite restoration of normal blood flow; eventually, however, myocardial performance recovers completely.[38] Originally defined in animal models of ischemia and reperfusion,[39] stunning has been recognized in the clinical arena.[38,40] Direct evidence for myocardial stunning in humans has been found using positron emission tomography (PET) scanning in patients with persistent wall motion abnormalities after angioplasty for acute coronary syndromes; perfusion measured by ^{13}N-ammonia was normal in the presence of persistent contractile dysfunction.[41] The pathogenesis of stunning has not been conclusively established but appears to involve a combination of oxidative stress,[42] perturbation of calcium homeostasis, and decreased myofilament responsiveness to calcium.[38,43,44] In addition to these direct effects, data from studies in isolated cardiac myocytes suggest that circulating myocardial depressant substances may contribute to contractile dysfunction in myocardial stunning.[45] The intensity of stunning is determined primarily by the severity of the antecedent ischemic insult.[38]

Myocardial hibernation comprises segments with persistently impaired function at rest due to severely reduced coronary blood flow; inherent in the definition of hibernating myocardium is the notion that function can be normalized by improving blood flow.[46-48] Hibernation can be seen as an adaptive response to reduce contractile function of hypoperfused myocardium and restore equilibrium between flow and function, thereby minimizing the potential for ischemia or necrosis.[49] Revascularization of hibernating myocardium can lead to improved myocardial function,[50] and improved function appears to translate into improved prognosis.[51,52]

Although hibernation is conceptually and pathophysiologically different from myocardial stunning, the two conditions are difficult to distinguish in the clinical setting and may in fact coexist.[38,52] Repetitive episodes of myocardial stunning can coexist with or mimic myocardial hibernation.[38,46,53] Consideration of myocardial stunning and hibernation is vital in patients with cardiogenic shock because of their therapeutic implications. Hibernating myocardium improves with revascularization, and stunned myocardium retains inotropic reserve and can respond to inotropic stimulation.[38] In addition, the fact that the severity of the antecedent ischemic insult determines the intensity of stunning[38] provides one of the rationales for reestablishment of patency of occluded coronary arteries in patients with cardiogenic shock. Finally, the notion that some myocardial tissue may recover function emphasizes the importance of measures

to support hemodynamics and thus minimize myocardial necrosis in patients with shock.

CLINICAL ASSESSMENT

EVALUATION

Cardiogenic shock is an emergency. The clinician must initiate therapy before shock irreversibly damages vital organs; at the same time, he or she must perform the clinical assessment required to understand the cause of shock and to target therapy to that cause. A practical approach is to make a rapid initial evaluation on the basis of a limited history, physical examination, and specific diagnostic procedures (Fig. 22.4).[24] Cardiogenic shock is diagnosed after documentation of myocardial dysfunction and exclusion of alternative causes of hypotension such as hypovolemia, hemorrhage, sepsis, pulmonary embolism, tamponade, aortic dissection, and preexisting valvular disease.

Patients with shock are usually ashen or cyanotic and can have cool skin and mottled extremities. Cerebral hypoperfusion may cloud the sensorium. Pulses are rapid and faint and may be irregular in the presence of arrhythmias. Jugular venous distention and pulmonary rales are usually present, although their absence does not exclude the diagnosis. A precordial heave resulting from left ventricular dyskinesis may be palpable. The heart sounds may be distant, and third or fourth heart sounds are usually present. A systolic murmur of mitral regurgitation or ventricular septal defect may be heard, but these complications may occur without an audible murmur.

An electrocardiogram should be performed immediately; other initial diagnostic tests usually include chest radiography and measurement of arterial blood gas, electrolytes, complete blood count, and cardiac enzymes.

Echocardiography is an excellent initial tool for confirming the diagnosis of cardiogenic shock and ruling out other causes of shock (Box 22.3); therefore, early echocardiography should be routine. Echocardiography provides information on overall and regional systolic function, and can rapidly diagnose mechanical causes of shock such as papillary muscle rupture and acute mitral regurgitation, acute ventricular septal defect, and free wall rupture and tamponade.[54,55] Unsuspected severe mitral regurgitation is not uncommon. In some cases, echocardiography may reveal findings compatible with right ventricular infarction.

Box 22.3 Role of Echocardiography in Cardiogenic Shock

- Evaluate overall systolic performance
- Delineate regional wall motion abnormalities
- Rule out mechanical causes of shock
  - Papillary muscle rupture
  - Ventricular septal rupture
  - Free wall rupture
  - Tamponade
- Diagnose right ventricular infarction

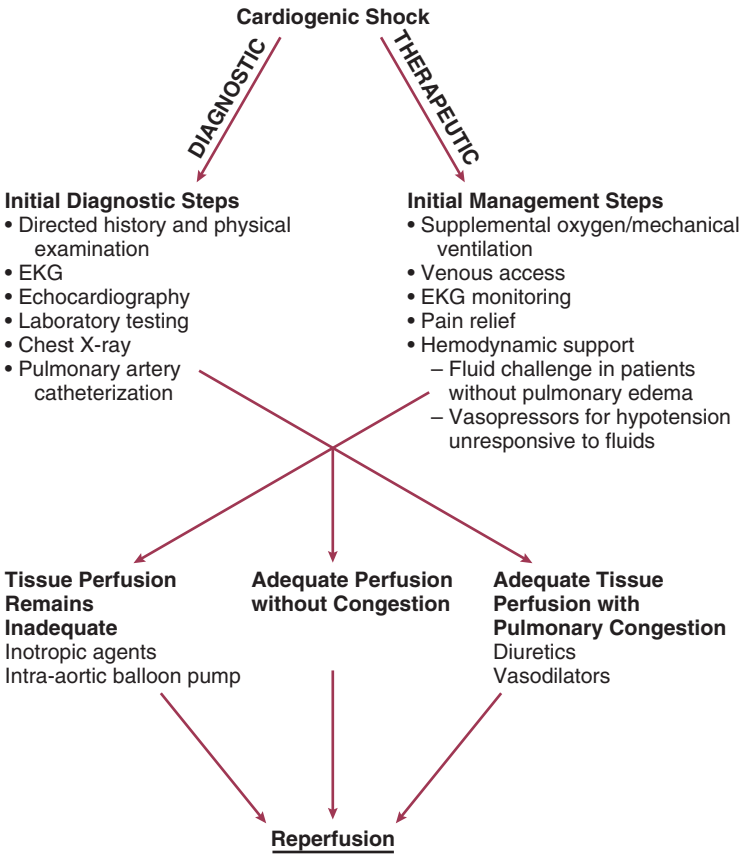

Figure 22.4 An approach to the diagnosis and treatment of cardiogenic shock caused by myocardial infarction. Right ventricular infarction and mechanical complications are discussed in the text. CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pumping. (Modified from Hollenberg SM, Kavinsky CJ, Parrillo JE: Cardiogenic shock. Ann Intern Med 1999;131:51.)

Invasive hemodynamic monitoring can be quite useful to exclude volume depletion, right ventricular infarction, and mechanical complications.[16,35] The hemodynamic profile of cardiogenic shock includes a pulmonary capillary occlusion pressure greater than 15 mm Hg and a cardiac index less than 2.2 L/min/m^2. It should be recognized that optimal filling pressures may be greater than 15 mm Hg in individual patients due to left ventricular diastolic dysfunction. Right-sided heart catheterization may reveal an oxygen step-up diagnostic of ventricular septal rupture or a large v wave that suggests severe mitral regurgitation. The hemodynamic profile of right ventricular infarction includes high right-sided filling pressures in the presence of normal or low occlusion pressures.[56,57]

Coronary angiography is usually performed as a precedent to revascularization, and will be considered later.

INITIAL MANAGEMENT

Maintenance of adequate oxygenation and ventilation are critical; intubation and mechanical ventilation are often required, if only to reduce the work of breathing and facilitate sedation and stabilization before cardiac catheterization. Central venous and arterial access, bladder catheterization, and pulse oximetry are routine. Electrolyte abnormalities should be corrected. Hypokalemia and hypomagnesemia are predisposing factors to ventricular arrhythmias, and acidosis can decrease contractile function. Relief of pain and anxiety with morphine sulfate (or fentanyl if systolic pressure is compromised) can reduce excessive sympathetic activity and decrease oxygen demand, preload, and afterload. Arrhythmias and heart block may have major effects on cardiac output, and should be corrected promptly with antiarrhythmic drugs, cardioversion, or pacing. Cardiology consultation has been shown to be associated with improved outcomes in patients with MI and is strongly indicated in the setting of cardiogenic shock.[58] In addition, measures proven to improve outcome after MI, such as nitrates, beta blockers, and angiotensin-converting enzyme inhibitors,[59] have the potential to exacerbate hypotension in cardiogenic shock and should be stopped until the patient stabilizes.

THERAPY

Following initial stabilization and restoration of adequate blood pressure, tissue perfusion should be assessed (see Fig. 22.4). If tissue perfusion remains inadequate, inotropic support or intra-aortic balloon pumping (IABP) should be initiated. If tissue perfusion is adequate but significant pulmonary congestion remains, diuretics may be employed. Vasodilators can be considered as well, depending on the blood pressure.

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 the original description of hemodynamic subsets in MI, approximately 20% of patients had low cardiac index and low PCWP; most had reduced stroke volume and compensatory tachycardia.[60] Some of these patients would be expected to respond to fluid infusion with an increase in stroke volume, although the magnitude of such a response depends on the degree of ischemia and cardiac reserve.

Fluid infusion is best initiated with predetermined boluses titrated to clinical end points of heart rate, urine output, and blood pressure.[61] 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, titrated not only to blood pressure but to clinical indices of perfusion and mixed venous oxygen saturation, may be required to maintain coronary perfusion pressure. Maintenance of adequate blood pressure is essential to break the vicious cycle of progressive hypotension with further myocardial ischemia. Norepinephrine is preferable to dopamine for hypotension in this situation. Dopamine acts as both an inotrope (particularly 3-10 μg/kg/minute) and a vasopressor (10-20 μg/kg/minute). Norepinephrine (0.02-1.0 μg/kg/minute) acts primarily as a vasoconstrictor, has a mild inotropic effect, and increases coronary flow. A recent randomized trial comparing norepinephrine and dopamine in 1678 patients with shock found no significant difference in 28-day mortality rate in the overall trial, but a prespecified subgroup analysis did find increased mortality rate with dopamine in the 280 patients with cardiogenic shock.[62] Phenylephrine, a selective α_1-adrenergic agonist, may be employed to support blood pressure when tachyarrhythmias limit therapy with other vasopressors, although it does not improve cardiac output. Vasopressin, which causes vasoconstriction, has a neutral or slightly depressant effect upon cardiac output, and increases vascular sensitivity to norepinephrine, may be added to catecholamines if needed.

In patients with inadequate tissue perfusion and adequate intravascular volume, cardiovascular support with inotropic agents should be initiated. Dobutamine, a selective β_1-adrenergic receptor agonist, can improve myocardial contractility and increase cardiac output without markedly changing heart rate or SVR; it is the initial agent of choice in patients with systolic pressures greater than 90 mm Hg.[63-65] Dobutamine may exacerbate hypotension in some patients and can precipitate tachyarrhythmias. Phosphodiesterase inhibitors such as milrinone increase intracellular cyclic adenosine monophosphate (cAMP) by mechanisms not involving adrenergic receptors, producing both positive inotropic and vasodilatory actions. Milrinone has fewer chronotropic and arrhythmogenic effects than catecholamines.[66] In addition, because milrinone does not stimulate adrenergic receptors directly, its effects may be additive to those of the catecholamines.[67] Milrinone, however, has the potential to cause hypotension and has a long half-life; in patients with tenuous clinical status, its use is often reserved for

situations in which other agents have proved ineffective.[16] Standard administration of milrinone calls for a loading dose followed by an infusion, but most clinicians eschew the loading dose in patients with marginal blood pressure.

Levosimendan, a calcium sensitizer, has both inotropic and vasodilatory properties and does not increase myocardial oxygen consumption. Levosimendan reduces the calcium-binding coefficient of troponin C by stabilizing the conformational shape, which enhances myocardial contraction with lower intracellular calcium concentrations.[68] Several relatively small studies have shown hemodynamic benefits with levosimendan in cardiogenic shock after MI,[69] one suggesting a better hemodynamic effect than dobutamine,[70] but survival benefits with use of levosimendan have not been shown in either cardiogenic shock or acute heart failure.[71] Levosimendan has the potential to cause hypotension and thus should be used with some caution in patients with cardiogenic shock. Levosimendan is not available in the United States.

Infusions of vasoactive agents need to be titrated carefully in patients with cardiogenic shock to maximize coronary perfusion pressure with the least possible increase in myocardial oxygen demand. Invasive hemodynamic monitoring can be extremely useful in allowing optimization of therapy in these unstable patients, because clinical estimates of filling pressure can be unreliable;[72] in addition, changes in myocardial performance and compliance and therapeutic interventions can change cardiac output and filling pressures precipitously. Optimization of filling pressures and serial measurements of cardiac output (and other parameters, such as mixed venous oxygen saturation) allow for titration of the dosage of inotropic agents and vasopressors to the minimum dosage required to achieve the chosen therapeutic goals. This control minimizes the increases in myocardial oxygen demand and arrhythmogenic potential.[61,73]

Diuretics should be used to treat pulmonary congestion and enhance oxygenation. Vasodilators should be used with extreme caution in the acute setting owing to the risk of precipitating further hypotension and decreasing coronary blood flow. After blood pressure has been stabilized, however, vasodilator therapy can decrease both preload and afterload. Sodium nitroprusside is a balanced arterial and venous vasodilator that decreases filling pressures and can increase stroke volume in patients with heart failure by reducing afterload.[74] Nitroglycerin is an effective venodilator that reduces the pulmonary capillary occlusion pressure and can decrease ischemia by reducing left ventricular filling pressure and redistributing coronary blood flow to the ischemic zone.[75] Both agents may cause acute and rapid decreases in blood pressure and dosages must be titrated carefully; invasive hemodynamic monitoring can be useful in optimizing filling pressures when these agents are used.

THROMBOLYTIC THERAPY

Although it has been demonstrated convincingly that thrombolytic therapy reduces mortality rates in patients with acute MI,[10,76-78] the benefits of this therapy in patients with cardiogenic shock are less certain. It is clear that thrombolytic therapy can reduce the likelihood of subsequent development of shock after initial presentation.[14,76,77,79] This is important because most patients develop cardiogenic shock more than 6 hours after hospital presentation.[2,14]

Nonetheless, no trials have demonstrated that thrombolytic therapy reduces mortality rate in patients with established cardiogenic shock. The numbers of patients are small because most thrombolytic trials have excluded patients who have cardiogenic shock at presentation.[80] In the GISSI (Gruppo Italiano per lo Studio della Streptochinasi Nell'Infarto Miocardico) trial,[10,80] 30-day mortality rates were 69.9% in 146 patients with cardiogenic shock who received streptokinase and 70.1% in 134 patients receiving placebo. The International Study Group reported a mortality rate of 65% in 93 patients with shock treated with streptokinase and a mortality rate of 78% in 80 patients treated with recombinant tissue plasminogen activator (rt-PA).[12] In the GUSTO trial,[13] 315 patients had shock on arrival; mortality rate was 56% in patients treated with streptokinase and 59% in patients treated with rt-PA.[14,81]

The failure of thrombolytic therapy to improve survival in patients with cardiogenic shock may seem paradoxical in light of evidence that the absolute reduction in mortality rate with thrombolytics is greatest in those at highest risk at presentation. The meta-analysis performed by the Fibrinolytic Therapy Trialists (FTT) Collaborative Group demonstrated a reduction in mortality rate from 36.1% to 29.7% when thrombolytic therapy was used in patients with initial systolic blood pressures less than 100 mm Hg. In patients with initial heart rates greater than 100 beats per minute the mortality rate decreased from 23.8% to 18.9%.[82] However, most patients in these subgroups did not meet criteria for cardiogenic shock.

Consideration of the efficacy of thrombolytic therapy once cardiogenic shock has been established makes the disappointing results in this subgroup of patients easier to understand. The degree of reperfusion correlates with outcome,[79,83] and reperfusion has been shown to be less likely for patients in cardiogenic shock.[21,83,84] When reperfusion is successful, mortality rate has been shown to be significantly reduced.[21] The lower rates of reperfusion in patients with shock may explain some of the disappointing results in this subgroup in the thrombolytic trials.

The reasons for decreased thrombolytic efficacy in patients with cardiogenic shock include hemodynamic, mechanical, and metabolic factors. Decreased arterial pressure limits the penetration of thrombolytic agents into a thrombus.[85] Passive collapse of the infarct artery in the setting of hypotension can also contribute to decreased thrombolytic efficacy, as can acidosis, which inhibits the conversion of plasminogen to plasmin.[85] Two small studies support the notion that vasopressor therapy to increase aortic pressure improves thrombolytic efficacy.[86,87]

INTRA-AORTIC BALLOON PUMPING

IABP reduces systolic afterload and augments diastolic perfusion pressure, increasing cardiac output and improving coronary blood flow.[88,89] These beneficial effects, in contrast to those of inotropic or vasopressor agents, occur without an increase in oxygen demand. IABP is efficacious for initial stabilization of patients with cardiogenic shock.[90,91] Small

randomized trials in the prethrombolytic era, however, failed to show that IABP alone increases survival.[92,93] IABP alone does not substantially improve blood flow distal to a critical coronary stenosis.[94]

IABP is probably not best used as an independent modality to treat cardiogenic shock. It may, however, be an essential support mechanism to allow definitive therapeutic measures to be undertaken. In the GUSTO trial, patients who presented with shock and had early IABP placement showed a trend toward lower mortality rates, even after exclusion of patients who underwent revascularization.[13,95] A similar trend was seen in the SHOCK trial registry, although it did not persist after adjustment for age and catheterization.[2] Several observational studies have also suggested that IABP can improve outcome in patients with shock, although revascularization procedures are a confounding factor in these studies.[96-99] IABP has been shown to decrease reocclusion and cardiac events after emergency angioplasty for acute MI.[100,101] The TACTICS trial randomized 57 patients with MI complicated by hypotension or cardiogenic shock to IABP or placebo in conjunction with fibrinolysis; the trial was terminated early due to difficulties with enrollment and was thus underpowered.[102] Although there was no difference in the primary end point of 6-month mortality rate (34% versus 43%, $p = 0.23$), patients presenting in Killip class III or IV heart failure showed a trend toward benefit with IABP (39% versus 80%, $p = 0.05$).[102]

REVASCULARIZATION

Pathophysiologic considerations and extensive retrospective data favor aggressive mechanical revascularization for patients with cardiogenic shock due to MI. Emergency percutaneous revascularization is the only intervention to date that has been shown to consistently reduce mortality rates in patients with cardiogenic shock.

DIRECT CORONARY ANGIOPLASTY

Reestablishment of brisk (TIMI [Thrombolysis in Myocardial Infarction] grade 3) flow in the infarct-related artery is an important determinant of left ventricular function and survival after MI.[79] Direct percutaneous transluminal coronary angioplasty (PTCA) can achieve TIMI grade 3 flow in 80% to 90% of patients with MI[103-105] compared with rates of 50% to 60% 90 minutes after thrombolytic therapy.[79,106] In addition to improving wall motion in the infarct territory, increased perfusion of the infarct zone has been associated with augmented contraction of remote myocardium, possibly due to recruitment of collateral blood flow.[23]

Use of angioplasty in patients with cardiogenic shock grew out of its use as primary therapy in patients with MI.[21,107-117] Observational studies from registries of randomized trials, most notably the GUSTO-1 trial, have also reported improved outcomes in patients with cardiogenic shock selected for revascularization,[14,84,118] and these findings have also been confirmed in reports from NRMI.[119]

RANDOMIZED STUDIES

Prompt revascularization is the only intervention that has been shown consistently to reduce mortality rates in cardiogenic shock. In the landmark SHOCK trial, patients with shock caused by left ventricular failure complicating ST-segment elevation myocardial infarction (STEMI) were randomized to emergency revascularization ($n = 152$), accomplished by either coronary artery bypass grafting (CABG) or angioplasty, or initial medical stabilization ($n = 150$). IABPs were used in 86% of patients in both groups. The landmark "Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock" (SHOCK) study [120,121] was a randomized, multicenter international trial that assigned patients with cardiogenic shock to receive optimal medical management—including IABP and thrombolytic therapy—or to cardiac catheterization with revascularization using PTCA or CABG.[120] The trial enrolled 302 patients and was powered to detect a 20% absolute decrease in 30-day all-cause mortality rates. Mortality rate 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 ($p = 0.11$).[120] It is important to note that the control group (patients who received medical management) had a lower mortality rate than that reported in previous studies; this may reflect the aggressive use of thrombolytic therapy (64%) and balloon pumping (86%) in these control subjects. These data provide indirect evidence that the combination of thrombolysis and IABP may produce the best outcomes when cardiac catheterization is not immediately available. At 6 months, mortality rate in the SHOCK trial was reduced significantly (50.3% compared with 63.1%, $p = 0.027$),[120] and this risk reduction was maintained at 12 months (mortality rate 53.3% versus 66.4%, $p < 0.03$) (Fig. 22.5).[121] Encouragingly, this 13% absolute improvement in survival remained stable at both 3 and 6 years of follow-up.[122] In addition, most survivors have good functional status.[123]

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%, $p = 0.01$) and 6 months

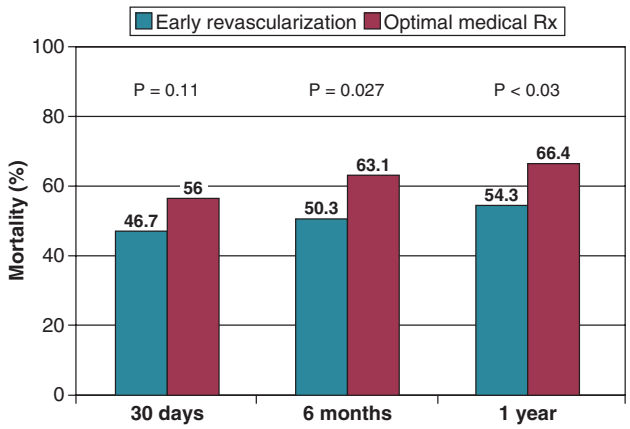

Figure 22.5 Mortality rates in the randomized SHOCK trial at 30 days, 6 months, and 1 year in the early revascularization and optimal medical management groups. (Data from Hochman JS, Sleeper LA, Webb JG, et al: Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med 1999;341: 625-634; and Hochman JS, Sleeper LA, White HD, et al: One-year survival following early revascularization for cardiogenic shock. JAMA 2001;285:190-192.)

(44.9% versus 65.0%, $p = 0.003$).[120] For patients older than 75, no benefit of revascularization was demonstrated in the SHOCK trial, although this was a small subgroup, and further analysis suggested baseline differences so that the elderly patients randomized to medical therapy appeared to have been a lower-risk group.[124] In the SHOCK trial registry, elderly patients treated with early revascularization had better outcomes than those treated medically, suggesting that it is possible to select elderly patients who will benefit from aggressive treatment.[125]

The SMASH (Swiss Multicenter Trial of Angioplasty for Shock) 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.[126] The trial was terminated early due to difficulties in patient recruitment for two different reasons: Early on, several centers declined to participate because it was felt that it would not be ethical to undertake early invasive evaluation in such extremely ill patients, and then, after publication of several encouraging studies documenting the superiority of percutaneous coronary intervention (PCI) over thrombolysis for acute MI, many centers felt that it had become unethical *not* to proceed to early evaluation and revascularization.[127] In the SMASH trial, although the patient numbers were very small (55 patients in all), an absolute reduction in 30-day mortality rate similar to that seen in the SHOCK trial was observed (69% mortality rate in the invasive group versus 78% in the medically managed group, RR [relative risk] = 0.88, 95% CI [confidence interval] = 0.6-1.2, p = NS [not significant]).[126] 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 MI, an important point emerges: Despite the moderate *relative* risk reduction (for the SHOCK trial, RR 0.72, CI 0.54-0.95; for the SMASH trial, RR 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 of 7.6, one of the lowest figures ever observed in a randomized, controlled trial of cardiovascular disease. In our judgment, these data strongly support the superiority of a strategy of early revascularization in most patients with cardiogenic shock (see Fig. 22.4). In the latest ACC/AHA guidelines for the management of acute MI, primary coronary intervention was given a class I indication for patients younger than 75 and a class IIa indication for patients older than 75.[128]

CORONARY ARTERY BYPASS SURGERY

Analysis of the SHOCK trial helps to define the indications for CABG in the setting of cardiogenic shock. CABG should be the first line of therapy offered in cases of left main artery disease or triple-vessel disease as well as in cases in which the patient has sustained mechanical complications necessitating surgical repair. In patients with multivessel disease in the SHOCK trial, complete revascularization was achieved more frequently (87% versus 23%). Long-term mortality rates were similar in the CABG and PCI groups despite worse coronary anatomy and more diabetes in the surgical group.[129]

OTHER CAUSES OF CARDIOGENIC SHOCK

RIGHT VENTRICULAR INFARCTION

Right ventricular infarction occurs in up to 30% of patients with inferior infarction and is clinically significant in 10%.[130] Patients present with hypotension, elevated jugular venous pressure, and clear lung fields. The diagnosis is made by identifying ST-segment elevation in right precordial leads or by characteristic hemodynamic findings on right-sided 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.[57] Patients with cardiogenic shock on the basis of right ventricular infarction have a better prognosis than those with left-sided pump failure.[130] This difference may be due in part to the fact that right ventricular function tends to return to normal over time with supportive therapy,[131] although such therapy may need to be prolonged.

Supportive therapy for patients with right ventricular infarction begins with maintenance of right ventricular preload 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.[131] 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.[131] Maintenance of atrioventricular synchrony is also important in these patients to optimize right ventricular filling.[57] For patients with continued hemodynamic instability, IABP 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. Restoration of normal flow by direct angioplasty 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%.[132] Prompt revascularization of patients with right ventricular infarction is a class I recommendation in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the treatment of acute MI.[133]

ACUTE MITRAL REGURGITATION

Ischemic mitral regurgitation is usually associated with inferior MI and ischemia or infarction of the posterior papillary muscle, which has a single blood supply, usually from the posterior descending branch of a dominant right coronary artery.[134] Papillary muscle rupture typically occurs 2 to 7 days after acute MI 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.[135]

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 IABP 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 because clinical deterioration can be sudden.[135,136] Although mortality rate is 20% to 40%, survival and ventricular function are improved compared with medical therapy.[137]

VENTRICULAR SEPTAL RUPTURE

Patients who have ventricular septal rupture have severe heart failure or cardiogenic shock, with a pansystolic murmur and a parasternal thrill. The hallmark finding is a left-to-right intracardiac shunt ("step-up" in oxygen saturation from right atrium to right ventricle). On pulmonary artery catheter tracing, it can be difficult to distinguish ventricular septal rupture from mitral regurgitation, because both can produce dramatic v waves. The diagnosis is most easily made with echocardiography.

Rapid stabilization, using IABP and pharmacologic measures followed by operative repair, is the only viable option for long-term survival. Because perforations are exposed to shear forces, the rupture site can expand abruptly. Repair can be technically difficult owing to the need to suture in areas of necrosis. Surgical mortality rate is 20% to 50%, especially for serpiginous inferoposterior ruptures, which typically are less well circumscribed than anteroapical ruptures. Right ventricular function is an important determinant of outcome in this setting. Timing of surgery has been controversial, but guidelines now recommend that operative repair should be undertaken early, within 48 hours of the rupture.[59] Placement of a septal occluding device may be helpful in selected patients.

FREE WALL RUPTURE

Ventricular free wall rupture usually occurs during the first week after MI; the classic patient is elderly, female, and hypertensive. The early use of thrombolytic therapy reduces the incidence of cardiac rupture, but late use may increase the risk, particularly in older patients.[138] Free wall rupture presents as a catastrophic event with a pulseless rhythm. Salvage is possible with prompt recognition, pericardiocentesis to relieve acute tamponade, and thoracotomy with repair.[139]

MYOCARDIAL DYSFUNCTION AFTER CARDIOPULMONARY BYPASS

Transient depression of ventricular contractility is common after cardiopulmonary bypass, and can represent a significant clinical problem. The differential diagnosis includes inadequate operation, cardiac tamponade (which may be localized and difficult to detect), and increased right ventricular afterload, but most cases likely result from myocardial stunning. The heart is rendered globally ischemic during aortic cross-clamping and then reperfused, and because demonstrable myocardial necrosis is rare, stunning can be implicated. Stunning after bypass has been documented in a study in which an ultrasonic probe was left on the epicardial surface for 2 to 3 days in 31 patients following bypass surgery; left ventricular wall thickening fell after surgery, reached a nadir at 2 to 6 hours, and subsequently improved, usually returning to baseline by 24 to 48 hours.[140]

The degree of myocardial dysfunction after cardiac surgery is variable, and may depend on the cardioplegia solution, the method of administration (antegrade or retrograde), the mode of administration (continuous or intermittent), and the temperature of the solution and of the patient during surgery.[38] In the clinical setting, transient depression of ventricular contractility is common and usually reversible within 24 to 48 hours. The depression of contractility can be severe to cause cardiogenic shock. In this event, therapy with inotropic agents, vasodilators, and IABP is necessary. Occasionally, even a left ventricular assist device may be employed.[40] Better understanding of the mechanisms of post–cardiopulmonary bypass myocardial dysfunction may lead to better preventive and therapeutic approaches.

MYOCARDITIS

Acute myocarditis can be benign and self-limited or fulminant, with severe congestive heart failure or atrial and ventricular arrhythmias. After acute myocarditis, patients can recover completely, or they can have severe left ventricular dysfunction. In some patients with acute inflammatory myocarditis, an aberrant immune response occurs, with continuing inflammation, and this can result in the eventual development of a dilated cardiomyopathy.

Evidence exists that some patients with myocarditis will benefit from immunosuppressive therapy, but how to identify which patients should be treated remains controversial. A trial initiated at the National Institutes of Health randomized 102 patients with dilated cardiomyopathy, no significant coronary artery disease, and ejection fraction less than 35% to oral prednisone or placebo.[141] The prospectively defined end point, an increase in radionuclide-measured ejection fraction of more than 5 percentage points, was observed in 53% of patients treated with prednisone compared to only 27% of control subjects at 3 months ($p < 0.05$), but the improvement did not persist at 9 months when patients were switched to alternate-day prednisone therapy.[141] Another clinical trial of immunosuppressive therapy for myocarditis showed no improvement in mean ejection fraction with immunosuppression, although the admission criteria in this trial were quite restrictive, the therapeutic regimens heterogeneous, and the incidence of definitive myocarditis uncertain.[142] We advocate consideration of corticosteroids in patients with myocarditis who do not respond to conventional heart failure therapies.

Although it might seem that patients with fulminant myocarditis might be the best candidates for immunosuppressive therapy, a recent series confounds this notion by reporting excellent long-term survival in patients with

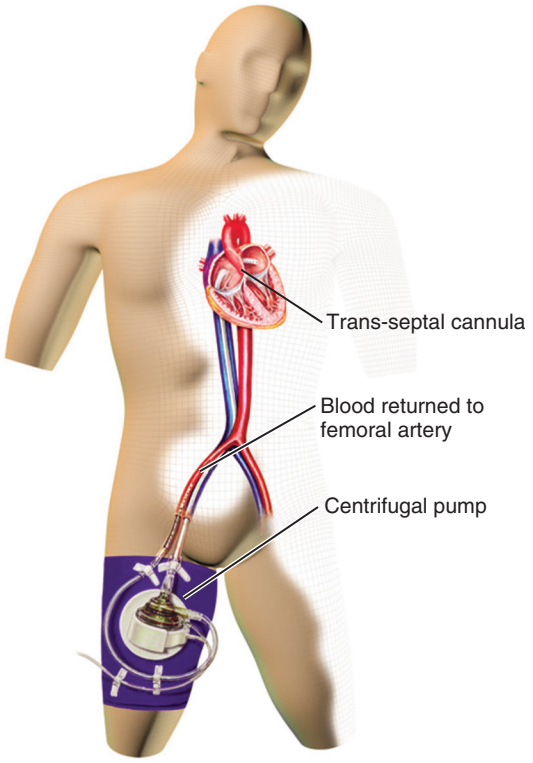

Figure 22.6 The TandemHeart percutaneous left ventricular assist device in situ. Blood is removed from the left atrium using a catheter placed from the femoral vein across the interatrial septum and pumped into the femoral artery. (Image courtesy of CardioAssist, Pittsburgh, PA.)

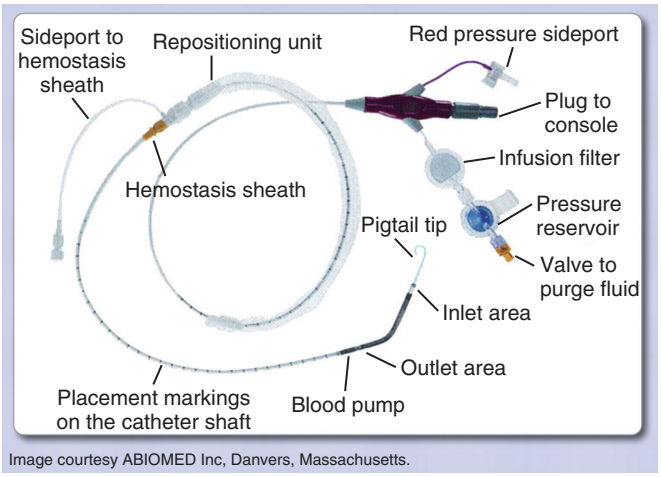

Figure 22.7 The Impella catheter when placed across the aortic valve (*left*). The inflow port is positioned within the left ventricle, and the outflow port is just above the valve. Impella catheter with introducer and sheath (*right*). (Images courtesy of Abiomed, Danvers, MA.)

myocarditis and a fulminant course.[143] Patients with acute myocarditis without a fulminant course had a much worse prognosis in this series,[143] pointing up the need for further research to identify subgroups of patients with dilated cardiomyopathy who may benefit from adjunctive therapies.

LEFT VENTRICULAR ASSIST DEVICES

In patients with potentially reversible causes of myocardial dysfunction, aggressive cardiovascular support with a combination of inotropic agents and intra-aortic balloon counterpulsation may be required for hours or days to allow sufficient time for recovery. If these measures fail, mechanical circulatory support with left ventricular assist devices (LVADs) can be considered.[144] Mechanical support with LVADs can interrupt the downward spiral of myocardial dysfunction, hypoperfusion, and ischemia in cardiogenic shock, allowing time for recovery of stunned or hibernating myocardium.

Percutaneously implanted LVADs are used in situations of cardiogenic shock, during high-risk percutaneous interventions, in postcardiotomy shock, and in fulminant myocarditis. Two currently approved devices, the TandemHeart (Fig. 22.6) and the Impella (Fig. 22.7), can be placed in the cardiac catheterization laboratory. The TandemHeart device is a bypass system with inflow of oxygenated blood from the left atrium and outflow to the femoral artery using a centrifugal flow pump; it can provide blood flow up to 5 L/minute. The Impella device is inserted across the aortic valve and pumps blood from a distal port from within the ventricle out to the ascending aorta through a proximal port of the device; there are two versions, one capable of pumping 2.5 L/minute, and one with a larger diameter that can provide up to 5 L/minute, although the actual flow is dependent on afterload. The inflow cannula with its pump is under fluoroscopic guidance. The device sits across the aortic valve. These devices augment cardiac output and blood pressure while decreasing myocardial oxygen demand. Both devices offer the potential for near-complete cardiac support but do require adequate right ventricular function. Known complications of percutaneous LVAD use include limb ischemia and bleeding.

Two recent trials compared the use of IABP to the TandemHeart for patients with cardiogenic shock,[145,146] and another compared use of the Impella to IABP therapy;[147] the results of these trials were combined in a meta-analysis that included 100 patients.[148] Hemodynamic benefits for the percutaneous LVADs compared with IABP were shown, with higher cardiac indices and mean arterial pressures as well as lower PCWPs. However, LVAD use showed no mortality rate benefit over IABP at 30 days.[148]

For patients with end-stage heart failure and refractory shock, a variety of surgically placed assist devices can be employed for circulatory support. These devices retrieve blood from the left ventricular apex and use a pumping device, either continuous or pulsatile, to return the blood into the ascending aorta. Full consideration of these devices is beyond the scope of this chapter; in cardiogenic shock, they are usually used as a bridge to recovery or transplantation, although in other contexts they may be used as destination therapy.

CONCLUSION

Cardiogenic shock remains a prevalent and dangerous syndrome that requires accurate and efficient diagnosis. Mortality rates in patients with cardiogenic shock have improved but remain frustratingly high. Its pathophysiology involves

a downward spiral in which ischemia causes myocardial dysfunction, which in turn worsens ischemia. Areas of nonfunctional but viable myocardium can also cause or contribute to the development of cardiogenic shock. Expeditious coronary revascularization is crucial, and the randomized multicenter SHOCK trial[120] has provided important data that help clarify the appropriate role and timing of revascularization in patients with cardiogenic shock. The potential for reversal of myocardial dysfunction with revascularization provides the rationale for supportive therapy to maintain coronary and tissue perfusion until more definitive revascularization measures can be undertaken. Application of a thorough understanding of the essentials of pathophysiology, diagnosis, and treatment of cardiogenic shock can allow for expeditious management and improved outcomes.

KEY POINTS

- Cardiogenic shock is a state of inadequate tissue perfusion due to cardiac dysfunction. Acute MI is the leading cause.
- The pathogenesis of cardiogenic shock is a "downward spiral" in which MI or ischemia causes myocardial dysfunction and compromised myocardial perfusion, exacerbating ischemia.
- Large areas of nonfunctional but viable myocardium (either stunned, hibernating, or both) can also cause or contribute to the development of cardiogenic shock in patients after MI.
- The challenge in initial management of cardiogenic shock is that evaluation and therapy must begin simultaneously. The clinician must perform the clinical assessment required to understand the cause of shock while initiating supportive therapy before shock causes irreversible damage.
- Thrombolytic therapy alone has less efficacy in patients with cardiogenic shock than in other settings; this is due to a combination of hemodynamic, mechanical, and metabolic factors.
- IABP alone has not been shown to decrease mortality rate in cardiogenic shock, but it may be an essential support mechanism to allow definitive therapeutic measures to be undertaken.
- Pathophysiologic considerations and extensive retrospective data favor aggressive mechanical revascularization for patients with cardiogenic shock due to MI. Results of the recent SHOCK study support a strategy of early revascularization in most patients with cardiogenic shock.
- Other acute mechanical causes of low cardiac output must be excluded. If present, urgent surgery may be required.
- In patients with potentially reversible causes of myocardial dysfunction (including severe myocarditis), aggressive cardiovascular support with a combination of inotropic agents and intra-aortic balloon counterpulsation may be required for hours or days to allow sufficient time for recovery.

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23 Septic Shock

Stephen Trzeciak | R. Phillip Dellinger | Joseph E. Parrillo

CHAPTER OUTLINE

OVERVIEW

This chapter pertains to pathophysiology, assessment, and management of septic shock, the most severe and overt manifestation of the septic condition. This discussion will specifically focus on cardiovascular and hemodynamic aspects. Other critically important elements of sepsis pathophysiology, assessment, and management (i.e., beyond the cardiovascular and hemodynamic aspects) will be addressed in a separate chapter (see Chapter 25, Sepsis and Multiple Organ Dysfunction). This chapter is also focused specifically on the adult patient with septic shock, as principles and evidence may differ in important ways in the pediatric population.

HISTORICAL PERSPECTIVE

The word *sepsis* originated from the Greek language. *Sepsis* was synonymous with putrefaction and pertained to the bacteria-mediated decomposition of organic matter.[1] The term persisted for more than 2700 years with essentially unchanged meaning.[2] In the twentieth century, our modern understanding of the term *sepsis* became rooted in a disease in which the clinical manifestations were attributed to severe infection and the release of pathogenic bacterial products into the patient's bloodstream.[3,4]

The term *shock* comes from the French word "choquer," meaning "to collide with." This is particularly appropriate terminology for shock due to sepsis, given our modern understanding of the sepsis pathophysiology, whereby the body's host defenses essentially collide with the invading microorganism, triggering a profound proinflammatory host response.[1]

CONTEMPORARY DEFINITIONS

Shock is defined as a failure of the cardiovascular system to maintain effective tissue perfusion. If effective tissue perfusion is not promptly restored, cellular dysfunction and acute organ failure may occur and may become irreversible, leading to acute organ system failure. When shock develops because of a systemic inflammatory response to infection, it is termed *septic shock*. The American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) first published consensus conference definitions for sepsis syndromes more than 20 years ago,[5] and these definitions were revisited and further developed by international consensus in 2003.[6] *Septic shock* was defined as infection-induced hypotension (systolic blood pressure <90 mm Hg [or a drop of >40 mm Hg] plus signs of tissue hypoperfusion despite adequate fluid resuscitation). The concurrent presence of clinical signs of tissue hypoperfusion (e.g., metabolic acidosis, encephalopathy, acute lung injury, oliguria, acute kidney injury, peripheral extremity discoloration, or impaired capillary refill) is an integral component of making the diagnosis of septic shock, because baseline blood pressure can vary among patients, and patients with lower baseline blood pressure may tolerate an arterial pressure lower than the values stated here without being in circulatory shock. The overarching purpose and major impact of the efforts to establish the contemporary definitions given here was the promotion of uniformity in inclusion criteria for sepsis clinical trials.[7]

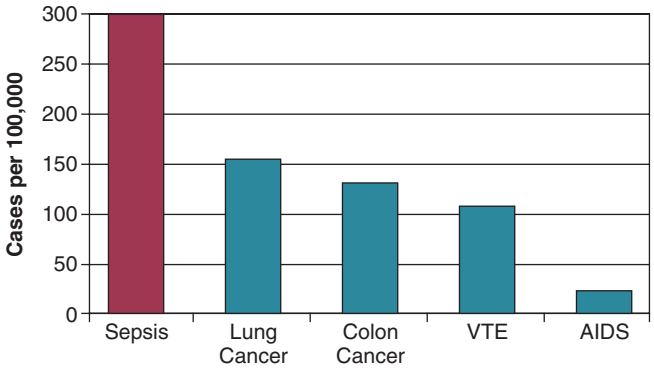

Figure 23.1 Incidence (cases per 100,000 population) of severe sepsis in the United States compared to four high-profile diseases.[8-11] AIDS, acquired immune deficiency syndrome; VTE, venous thromboembolic disease.

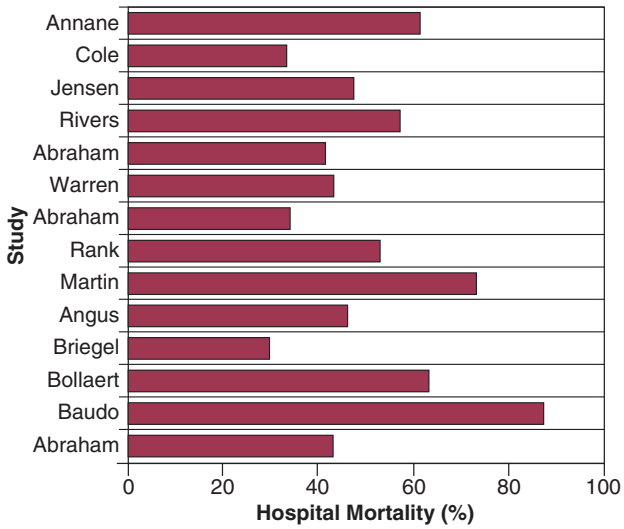

Figure 23.2 A compilation of septic shock mortality rates taken from the placebo arms of sepsis clinical trials published over the past decade (listed by first author). (Adapted from Dellinger RP: Cardiovascular management of septic shock. Crit Care Med 2003;31(3):946-955.)

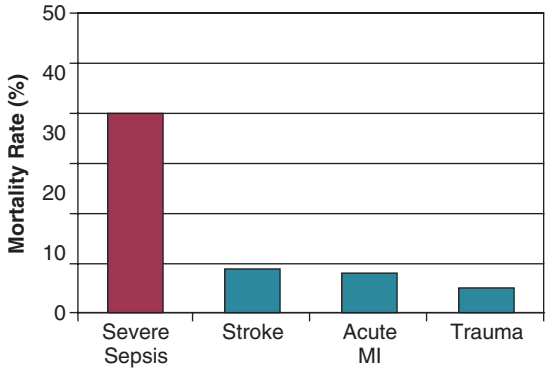

Figure 23.3 Mortality rate of severe sepsis in the United States compared to three diseases that are treated aggressively with time-sensitive interventions.[8,15-17] MI, myocardial infarction.

EPIDEMIOLOGY

Severe sepsis (sepsis plus acute organ system dysfunction) is a common and deadly disease with major public health implications. Although heterogeneity of definitions of sepsis has historically made the incidence of severe sepsis and septic shock difficult to precisely measure, estimates of the incidence have been possible. Using the International Classification of Diseases (ICD)-9 codes for infection and organ dysfunction, Angus and coworkers estimated that 751,000 cases of severe sepsis occur in the United States every year.[8] Figure 23.1 displays the incidence of severe sepsis in the United States compared to other common diseases. The incidence of severe sepsis currently exceeds the incidence of lung and colon cancer, venous thromboembolic disease, and acquired immune deficiency syndrome (AIDS),[8-11] and the incidence is projected to increase by 1.5% per year, resulting in more than 1 million cases of severe sepsis annually by the year 2020.[8] The incidence of sepsis and septic shock is known to be increasing because of a longer lifespan for patients with severe chronic medical conditions that predispose them to acquiring sepsis. This includes an increase in the number of immunocompromised patients in the community, number of infections caused by resistant organisms, increased use of intravascular catheters, and aging of the population.[8]

Sepsis is the leading cause of death among critically ill patients[12] and is responsible for as many deaths annually in the United States as acute myocardial infarction.[8] Figure 23.2 displays control arm mortality rates in septic shock clinical trials.[1] In a recent large multicenter registry study, septic patients with both arterial hypotension and severe lactic acidosis experienced a 46% mortality rate, whereas the mortality rate for arterial hypotension or severe lactic acidosis alone was 37% and 30%, respectively.[13] Overall, severe sepsis in general ranks as the tenth leading cause of death in the United States, with 215,000 deaths annually and an estimated 30% in-hospital mortality rate.[8,14] Figure 23.3 displays the mortality rate for severe sepsis compared to other high-profile diseases that may require critical care (acute ischemic stroke, acute myocardial infarction, and trauma).[8,15-17] The apparent disparity in mortality rates across these diseases may be explained in part by differences in the conventional approach to treatment, as acute ischemic stroke, acute myocardial infarction, and trauma are all typically treated with aggressive interventions in a time-sensitive fashion. Similar to the "golden hour" concept for trauma care that was first recognized more than 30 years ago[18] we are now beginning to understand that early aggressive interventions for sepsis can also have an impact on outcome.

It is also important to recognize that, in addition to a high mortality rate, severe sepsis and septic shock are associated with serious risk of morbidity among survivors.[19,20] A systematic review of the literature found that sepsis survivors had substantially diminished quality of life and a sharply reduced long-term survival after typical short-term (i.e., 28-day) outcomes are assessed.[19] Among older adults, severe sepsis has been associated with major persistent cognitive impairment and functional disability that could have a substantial impact on those patients' ability to live independently.[20] Taken together, even among patients who survive the sepsis insult, the development of severe sepsis or septic shock can represent a pivotal event in the trajectory of a patient's life.

PATHOGENESIS

Septic shock results when infectious microorganisms in the bloodstream induce a profound inflammatory response causing hemodynamic decompensation. The pathogenesis involves a complex response of cellular activation that triggers the release of a multitude of proinflammatory mediators. This inflammatory response causes activation of leukocytes and endothelial cells, as well as activation of the coagulation system. The excessive inflammatory response that characterizes septic shock is driven primarily by the cytokines tumor necrosis factor-alpha (TNF-α) and interleukin 1 (IL-1) that are produced by monocytes in response to an infection. Although TNF-α and IL-1 are central to the pathophysiology of septic shock and act synergistically to induce hypotension in experimental models, a number of other vital mediators are also known to play a major role, including high-mobility group box 1 (HMGB1) protein.[21] Another important recent advance in our understanding of septic shock pathophysiology has been identification of the close link that exists between the proinflammatory response of septic shock and activation of the coagulation system (e.g., clinical or subclinical disseminated intravascular coagulation [DIC]).[22] Although the systemic inflammatory response of sepsis triggers profound macrocirculatory and microcirculatory changes that impair tissue perfusion, another important mechanism playing a role in the development of acute organ dysfunction in septic shock is apoptosis (programmed cell death). Accelerated apoptosis is known to be a critical pathogenic event in this disease. In addition, certain genetic polymorphisms are becoming recognized as major determinants of susceptibility to infection, as well as risk of death from septic shock. Key steps in the pathogenesis of septic shock are shown in Figure 23.4.

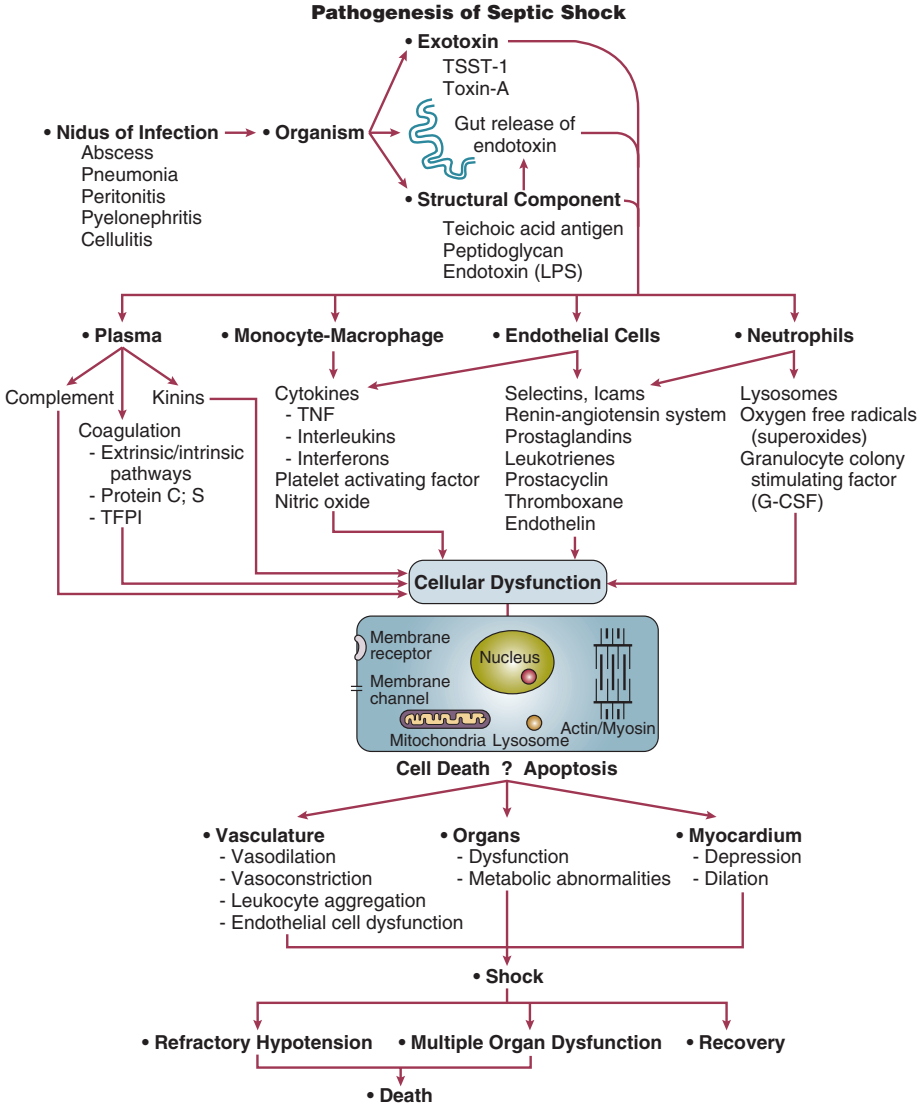

Figure 23.4 Pathogenetic sequence of the events in septic shock. LPS, lipopolysaccharide; TFPI, tissue factor pathway inhibitor; TNF, tumor necrosis factor; Toxin A, *Pseudomonas aeruginosa* toxin A; TSST-1, toxic shock syndrome toxin 1. (Data from Parrillo JE: Pathogenetic mechanisms of septic shock. N Engl J Med 1993;328:1471-1477.)

CLINICAL PRESENTATION

Patients with septic shock will typically manifest signs of systemic inflammation including fever or hypothermia, tachycardia, tachypnea, and elevation or reduction of the white blood cell count. Although the absence of arterial hypotension does not necessarily exclude the possibility of subclinical tissue hypoperfusion,[23] the hallmark of septic shock is arterial hypotension despite adequate volume resuscitation requiring vasoactive drugs for hemodynamic support. Other signs of potential tissue hypoperfusion may include lactic acidosis, oliguria, encephalopathy, or diminished capillary refill in the extremities. Patients with septic shock typically have multiple organ system dysfunctions; clinical evidence of other organ system dysfunction may range from subtle abnormalities to overt organ failure. Multiorgan system involvement in sepsis may include cardiovascular, respiratory, renal, central nervous system, hepatic, metabolic, or hematologic dysfunction. Respiratory system dysfunction manifests as acute lung injury or, in the most extreme cases, the acute respiratory distress syndrome (ARDS). Sepsis-induced renal dysfunction typically manifests with oliguria and may progress to acute renal failure requiring dialysis. Central nervous system dysfunction will manifest as encephalopathy, which may range from mild cognitive impairment to overt coma. Cholestasis is a common manifestation of hepatic dysfunction in sepsis, but in the presence of severe shock, ischemic hepatitis ("shock liver") may occur. Metabolic derangements of septic shock include a loss of glycemic control (hyper- or hypoglycemia) as well as metabolic acidosis. Septic shock is commonly associated with a consumptive coagulopathy, which is likely present in almost all patients at least subclinically,[24] but may also manifest clinically with thrombocytopenia, prolongation of the prothrombin time, or in the most severe cases, overt DIC.

The multiple organ dysfunction associated with septic shock is not only a critical event in the pathogenesis of this disease, but is also closely linked with mortality rate.[8,25,26] There is an approximate 20% increase in septic shock mortality rate with each additional organ system that fails.[8] *Early* evidence of organ failure is an especially strong predictor of death.[26,27] Early improvement in organ function (e.g., 0-24 hour improvement in the Sequential Organ Failure Assessment [SOFA] score[28,29]) is closely related to sepsis survival, whereas later improvement after the first 24 hours has little predictive value.[27] These data, garnered largely from observational studies as well as placebo arms of interventional trials, support the concept that aggressive therapy for sepsis to reverse (or prevent the development of) acute organ system failure within the first 24 hours is closely associated with eventual outcome.

HEMODYNAMIC PROFILE OF SEPTIC SHOCK

The hemodynamic profile of septic shock is the most complex hemodynamic profile of all shock etiologies (Fig. 23.5). What sets septic shock apart from other causes of circulatory shock is the fact that there may be multiple different mechanisms of circulatory shock occurring simultaneously.[1,30] Septic shock may have features of (1) hypovolemic shock (poor cardiac filling secondary to severe systemic capillary leak and increased venous capacitance), (2) cardiogenic shock (infection-induced myocardial depression), and (3) distributive shock (arteriolar vasodilation with tissue hypoperfusion in the face of an adequate cardiac output).[1]

HYPOVOLEMIA

The release of proinflammatory mediators into the circulation causes injury to the integrity of the endothelial cell surface throughout the systemic microvasculature, resulting in severe capillary leak and extravasation of fluid into tissues. Venodilation also compromises venous return. These are major factors in producing hypovolemia in the patient with septic shock. The septic shock patient may have a markedly decreased cardiac preload, especially in the initial phase of therapy. Aggressive resuscitation with intravenous volume expansion modulates the hemodynamic profile of septic shock and allows the patient to achieve a hyperdynamic (i.e., high cardiac output) state.[1] The combination of a decreased preload and myocardial depression means that in the early phase of sepsis resuscitation, patients may initially be hypodynamic (i.e., low cardiac output) prior to receiving adequate volume resuscitation. Capillary leak is an ongoing process in the course of septic shock therapy, and therefore hypovolemia may recur later in the course of the disease, even after adequate cardiac filling has been initially achieved. Fluid balance (input of intravenous fluids and output of urine) is an unreliable parameter for assessing adequacy of fluid resuscitation in septic shock.

MYOCARDIAL DYSFUNCTION

Septic shock is associated with depression of biventricular function with a decrease in the ejection fraction. Ventricular dilation occurs as a compensatory mechanism and raises end-diastolic volume so that stroke volume can be preserved, taking advantage of the Starling principle. When myocardial dysfunction occurs, a high cardiac output can still be achieved in many circumstances because of biventricular dilation, tachycardia, and arteriolar dilatation, as long as the patient is adequately volume resuscitated and does not have a severe cardiac suppression (related either to previously existing cardiac dysfunction or overwhelming sepsis-induced suppression of cardiac systolic function).[30] The most important inflammatory mediators that induce myocardial depression are TNF-α, IL-1, and perhaps nitric oxide.[31,32] Coronary blood flow is typically normal or increased in septic shock.[33] Although coronary blood flow can be diminished by severe arterial hypotension that compromises coronary perfusion pressure (especially if there is preexisting coronary artery disease), myocardial ischemia does not appear to be the causative factor of the depression in myocardial performance. It has been reported that nearly half of patients with septic shock will have echocardiographic evidence of some degree of depression of systolic function, even in the absence of preexisting cardiac disease.[34] However, myocardial depression is typically not the predominant feature of the septic shock hemodynamic profile.[30]

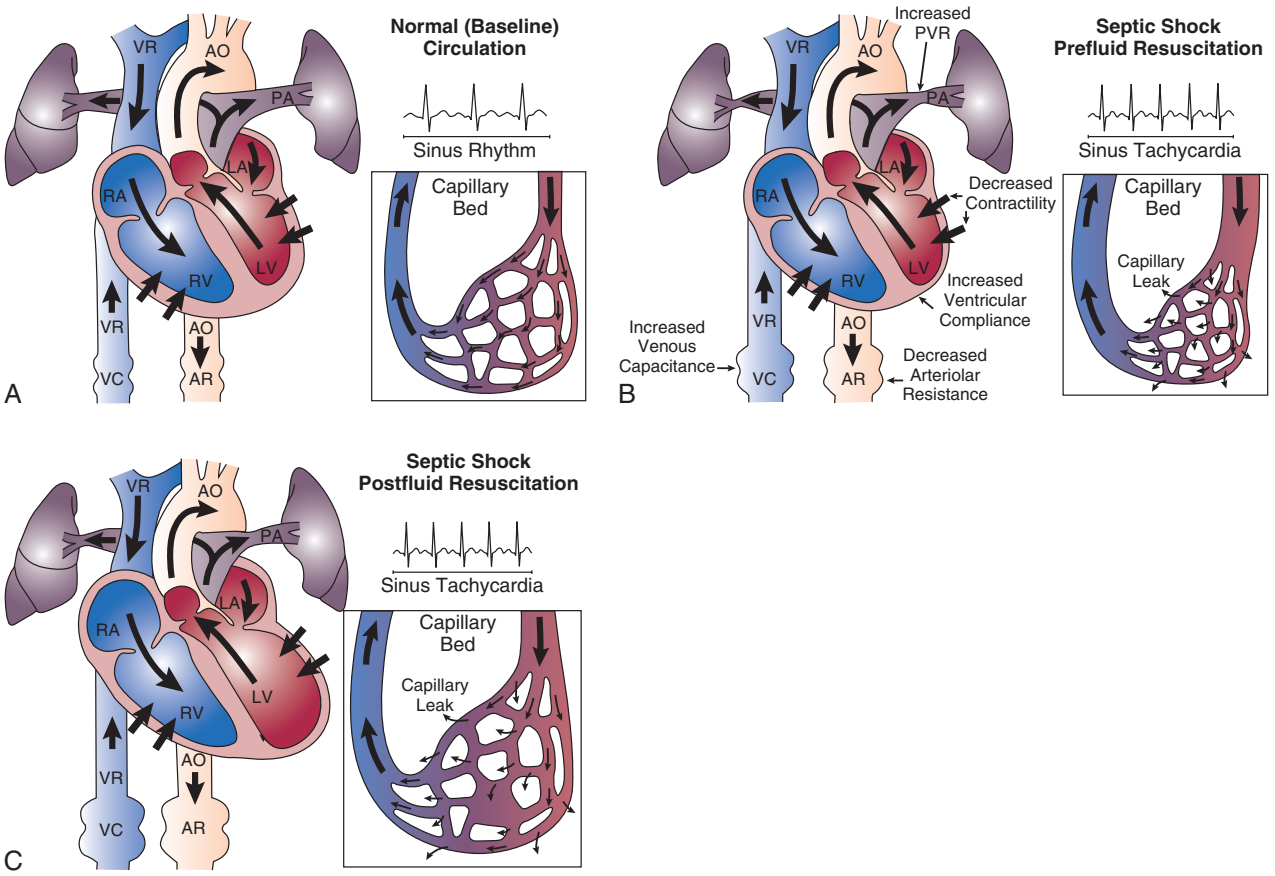

Figure 23.5 Cardiovascular changes associated with septic shock and the effects of fluid resuscitation. **A,** Normal (baseline) state. **B,** In septic shock, left ventricular blood return is reduced owing to a combination of capillary leak (*inset*), increased venous capacitance (VC), and increased pulmonary vascular resistance. The stroke volume is further compromised by a sepsis-induced decrease in left and right ventricular (RV) contractility. Tachycardia and increased left ventricular compliance serve as countermeasures to combat low cardiac output, the latter by increasing left ventricular preload. However, cardiac output remains low to normal. Finally, a decrease in arteriolar (systemic vascular) resistance allows a higher stroke volume at any given contractility and left ventricular filling state, but also the potential for severe hypotension, despite restoration of adequate left ventricular filling. **C,** Aggressive fluid resuscitation compensates for capillary leak, increased venous capacitance, and increased pulmonary vascular resistance by reestablishing adequate left ventricular blood return. Decreased arteriolar resistance (AR), tachycardia, and increased left ventricular compliance compensate for decreased ejection fraction. Ejection fraction increases as left ventricular filling increases. The net result is that after adequate volume resuscitation, most patients with severe sepsis have a high cardiac output and low systemic vascular resistance state. AO, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; VR, venous return; →, blood flow (cardiac output); ⇒, contractility. (From Dellinger RP: Cardiovascular management of septic shock. Crit Care Med 2003;31(3):946-955.)

For the majority of patients, aggressive intravascular volume expansion to restore adequate cardiac filling pressures will be enough to achieve a reasonable cardiac output.

DISTRIBUTIVE SHOCK

Septic shock is characterized by peripheral maldistribution of blood flow to tissues such that tissue hypoperfusion abnormalities can persist despite a normal or high cardiac output. This is called "distributive shock."[30] This maldistribution of blood flow may occur at both microcirculatory and macrocirculatory levels. The role of microcirculatory dysfunction is discussed in detail in the next section of this chapter. At the level of the macrocirculation, the autoregulation of blood flow within any single organ system in a normal host can typically maintain effective tissue perfusion over a wide range of systemic pressures (usually ranging from a mean arterial pressure [MAP] of 50 mm Hg to 150 mm Hg). However, there is heterogeneity of blood flow distribution throughout the body in septic shock due to preferential shunting of blood flow to vital organs (e.g., the brain and myocardium). The gastrointestinal tract may be the earliest organ system to experience tissue hypoperfusion in septic shock, as blood is shunted away from the splanchnic circulation in order to preserve blood flow to the brain, myocardium, and skeletal muscles. Ischemic injury to the gastrointestinal tract may be a source of ongoing systemic inflammation in septic shock.

The three components of the hemodynamic profile of septic shock are displayed in Figure 23.6.

MICROCIRCULATORY AND MITOCHONDRIAL DYSFUNCTION

After restoration of adequate cardiac filling pressures and achievement of optimal cardiac output in patients with septic shock, tissue dysoxia may still occur via a number of

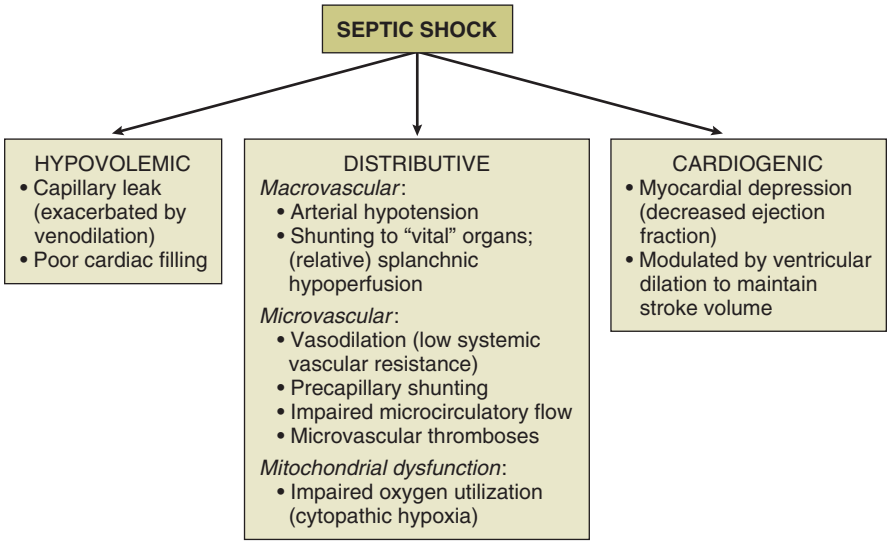

Figure 23.6 Major components of the hemodynamic profile in septic shock. (From Trzeciak S, Parrillo JE: Septic shock. In Society of Critical Care Medicine 8th Adult Critical Care Refresher Course. Chicago, Society of Critical Care Medicine, 2004.)

pathogenic mechanisms. These mechanisms of tissue dysoxia in the face of a normal or a supranormal cardiac output may be due to either (1) microcirculatory dysfunction or (2) mitochondrial dysfunction. These pathogenic mechanisms impair the way in which individual cells can either receive or utilize oxygen, respectively.

MICROCIRCULATORY DYSFUNCTION

Microcirculatory dysfunction is a pivotal element of the pathogenesis of septic shock.[35-38] Although the macrocirculation (heart and large arteries) regulates the global distribution of blood flow throughout the body, it is the microcirculation that controls the delivery of blood flow to tissues. Using intravital videomicroscopy, experimental models of sepsis have demonstrated impaired microcirculatory flow velocity, "stopped-flow" microvessels, increased heterogeneity of regional perfusion, and low density of perfused capillaries.[39-42] These derangements can cause marked alterations of oxygen transport including impaired tissue oxygen extraction.[43] With the advent of new investigational videomicroscopy techniques, it is now possible to study the microcirculatory network in human subjects with septic shock. Microcirculatory failure appears to be one of the critical pathogenic events in sepsis that is associated with acute multiorgan dysfunction and death.[35-38] As these alterations of microcirculatory flow in sepsis can occur in the *absence* of global hemodynamic perturbations (i.e., absence of low arterial pressure or low cardiac output),[36,42,44] derangements of small vessel perfusion are largely a function of intrinsic events in the microcirculation.

The causes of microcirculatory flow alterations in sepsis (Fig. 23.7) are multifactorial and include endothelial cell dysfunction, increased leukocyte adhesion, microthrombi formation, rheologic abnormalities, altered local perfusion pressures due to regional redistribution of blood flow, and functional shunting.[39,45] The proinflammatory cytokines released in sepsis cause diffuse endothelial cell activation, which is associated with neutrophil activation, expression of endothelial adhesion molecules (i.e., integrins and selectins), and localization of white blood cells to areas of

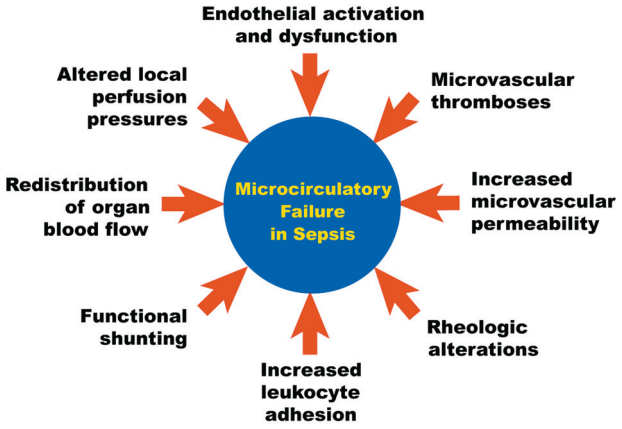

Figure 23.7 Causes of microcirculatory failure in sepsis. (Adapted from Spronk PE, Zandstra DF, Ince C: Bench-to-bedside review: Sepsis is a disease of the microcirculation. Crit Care 2004;8(6):462-468.)

microvascular injury. Pan-endothelial cell injury increases microvascular permeability with the influx of proinflammatory cells into the tissues; this is hypothesized to be an important pathogenic step in the development of acute system organ dysfunction in sepsis. Leukocyte adhesion of white blood cells to the microvessel endothelial surface (primarily in the postcapillary venule) further impedes microcirculatory blood flow. The endothelial injury also triggers the activation of the coagulation cascade via expression of tissue factor on the microvascular endothelium, resulting in fibrin deposition and microvascular thrombosis that may further impair microcirculatory flow. All of these mechanisms collectively contribute to microcirculatory failure in septic shock.[37,39]

Although septic shock research has classically been focused on macrocirculatory hemodynamic parameters that reflect the distribution of blood flow globally throughout the body, a functional microcirculation is another critical component of the cardiovascular system that is necessary for *effective* blood flow to tissues. This conceptual framework is depicted in Figure 23.8. Although a shift of research focus

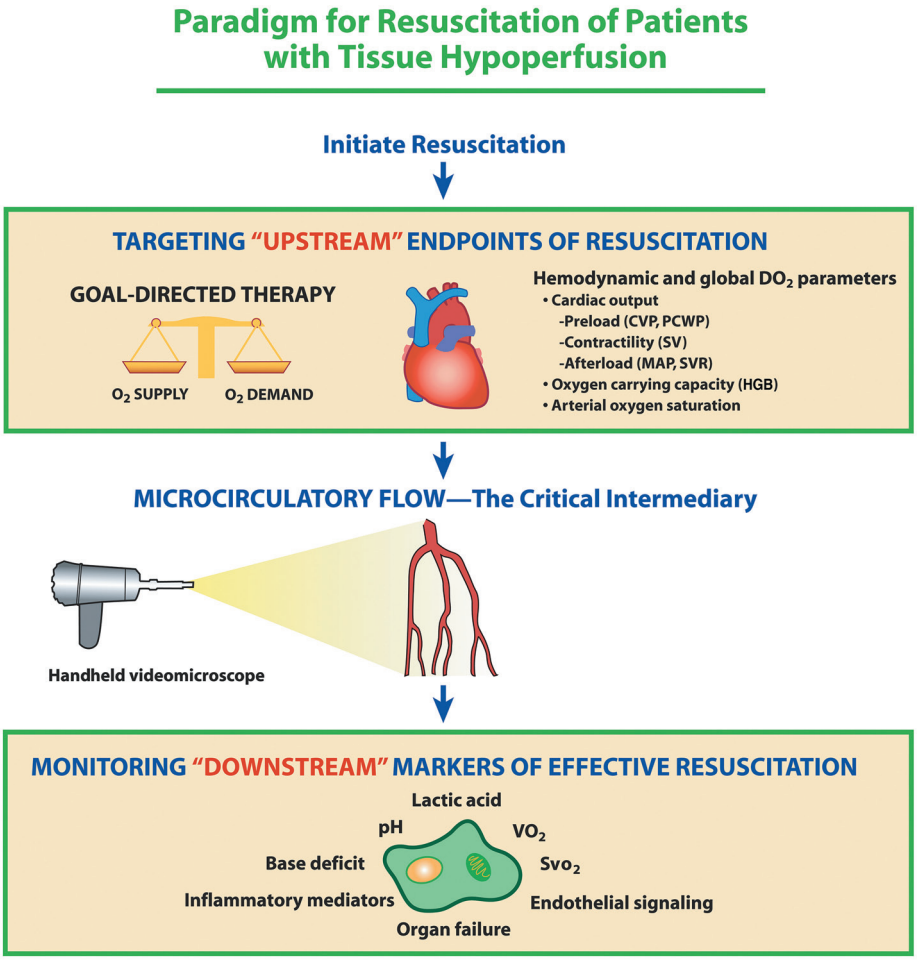

Figure 23.8 New paradigm of the cardiovascular profile of septic shock featuring the importance of the microcirculation. Conventional resuscitation targets the optimization of macrocirculatory (i.e., "upstream") hemodynamic parameters, with the monitoring of "downstream" surrogates of tissue perfusion to determine the effectiveness of resuscitation. The microcirculation is the critical intermediary. Although the macrocirculation (heart and large arteries) regulates the global distribution of blood flow throughout the body, an intact and functional microcirculation is necessary for the effective delivery of blood flow to tissues. Intrinsic microcirculatory dysfunction can be a pivotal pathogenic event in the development of sepsis-associated tissue hypoperfusion. Using new videomicroscopy techniques, microcirculatory flow can now be studied in human subjects with septic shock. CVP, central venous pressure; Do_2, oxygen delivery; HGB, hemoglobin; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; SV, stroke volume; $S\bar{v}o_2$, mixed venous oxygen saturation; SVR, systemic vascular resistance; Vo_2, oxygen consumption.

from global hemodynamic parameters to indices of microvascular perfusion could potentially be viewed as a major change of direction for septic shock research, the microcirculation likely represents a logical next frontier in the evolution of our understanding of circulatory failure in shock states.[37,46] Although there are currently no therapies to specifically target microcirculatory dysfunction in sepsis, going beyond optimization of macrocirculatory hemodynamics and developing new innovative strategies to reverse microcirculatory failure could (in the future) potentially represent a cutting edge method to augment tissue perfusion in sepsis.

MITOCHONDRIAL DYSFUNCTION

There is strong evidence that cellular utilization of oxygen can be markedly impaired in septic shock.[47] Bioenergetic failure can occur even after effective restoration of blood flow to tissues has been achieved, and this has been termed "cytopathic hypoxia." Despite the current absence of therapies to reverse cytopathic hypoxia, this phenomenon does have some relevance for clinical practice, as impaired cellular oxygen extraction and utilization can manifest clinically with acute organ system failure in the setting of markedly elevated values for mixed (or central) venous oxygen saturation. This venous hyperoxia likely reflects bioenergetic failure and identifies a population at exceptionally high risk of death.[48] Cytopathic hypoxia has been associated with acute organ dysfunction, but the extent to which this does or does not represent a cause-and-effect relationship has not yet been fully elucidated.

Microcirculatory and mitochondrial dysfunction likely coexist in septic shock. Both of these pathogenic mechanisms can impair tissue oxygen delivery and utilization, but the relative contribution of either mechanism is difficult to discern and may vary considerably.

MANAGEMENT OF SEPTIC SHOCK

OVERVIEW AND MANAGEMENT GUIDELINES

The Surviving Sepsis Campaign (SSC) first published comprehensive international consensus guidelines for sepsis management in 2004.[49,50] The SSC guidelines have been updated over time as the best evidence for sepsis management continues to evolve. The critical care practitioner should be familiar with the concepts in the SSC guidelines and is referred to the most recent update for a comprehensive review including evaluation of the strength of evidence for each recommendation.[50a] The SSC guidelines writing committee comprised representatives from numerous medical professional societies that relate to the care of the septic patient, and these medical professional societies have endorsed the guidelines.

The treatment recommendations in the SSC guidelines are intended to provide guidance for clinicians. However, treatment decisions must be individualized to the patient, and the recommendations cannot replace a clinician's decision-making capability when he or she is presented with a patient's unique set of clinical data. In addition, resource limitations in some institutions may prevent physicians from accomplishing some treatment recommendations. Thus, the SSC guidelines are intended to represent "best practice" recommendations for the management of sepsis rather than standard of care.

GENERAL PRINCIPLES

The patient with septic shock should be brought to a critical care area as quickly as possible to facilitate rapid resuscitation and optimal hemodynamic support. Continuous electrocardiographic monitoring and pulse oximetry are useful tools in the management of critically ill patients with sepsis.[51,52] In addition, a variety of more invasive devices may be of use. The arterial catheter has two functions: It allows frequent blood sampling and continuous assessment of arterial pressure. The pulmonary artery catheter (PAC) can provide data such as cardiac filling pressures, cardiac index, and systemic vascular resistance. The data gathered from the PAC can be useful for titrating vasoactive medications in septic shock. Although indications for PAC utilization are controversial and are often debated, it is important to recognize that the PAC represents a tool for guiding therapy rather than being a therapeutic intervention in itself. Monitoring venous oxygen saturation (either mixed venous oxygen saturation [$S\bar{v}O_2$] or central venous oxygen saturation [$ScvO_2$]) can yield information on the oxygen supply/demand relationship, especially in the early resuscitation phase of septic shock therapy.[23] A markedly low value for either $S\bar{v}O_2$ or $ScvO_2$ indicates a significant imbalance in the oxygen supply/demand relationship, and likely indicates a need for augmenting global oxygen delivery.

Metabolic parameters to monitor the effectiveness of resuscitation and cardiovascular support are limited; however, measurement of blood lactate can provide important information. In 1964, Weil first proposed the utilization of blood lactate levels as a surrogate of adequacy of tissue perfusion.[53] It is important to realize, however, that elevation of blood lactate does not necessarily indicate ineffective tissue perfusion, as metabolic derangements and altered cellular metabolism may cause hyperlactatemia and can be responsible for the elevation of blood lactate observed in sepsis. Despite this, blood lactate levels still have prognostic value in septic patients. Regardless of the cause of lactate elevation in sepsis, markedly elevated blood lactate (e.g., lactate ≥4 mmol/L) signals an increased risk of death.[54-58]

ANTIBIOTIC THERAPY AND SOURCE CONTROL

Early administration of empiric antibiotic therapy and expeditious source control to eliminate any nidus of infection are imperative in the management of septic shock. Appropriate antibiotics given early may substantially improve the likelihood of survival.[59,60] A choice of antibiotics is usually empiric because the organism is not yet identified when antibiotics must be delivered. Failure to include antibiotic coverage for what is later identified to be the offending organism has been associated with increased risk of death;[61] therefore, broad-spectrum antibiotics are necessary as soon as septic shock is identified. Kumar and associates performed a large-scale multicenter retrospective study of patients with septic shock and found a linear association between the duration of hypotension prior to first dose of antibiotic administration and risk of death.[62] One recent prospective emergency department (ED)–based study from Puskarich and colleagues found higher survival rates if antibiotics were administered prior to shock onset compared to after shock onset, but in contrast to the Kumar data the authors did not find a measurable effect of incremental time to administration of antibiotics on survival.[63] One potential reason to explain these results is that the Kumar study was a heterogeneous population and the therapeutic interventions (e.g., early resuscitation and hemodynamic support) that the patients received were not standardized, whereas all the patients in the Puskarich study were ED patients treated according to a standardized early resuscitation protocol.

The SSC currently recommends that intravenous antimicrobial therapy be started as soon as possible, preferably within an hour of recognition of septic shock. Even though a 1-hour time window is deemed desirable, the SSC acknowledges that longer time frames are common in real-world clinical practice, and practice surveys verify that a 1-hour window is currently not standard of care.[13] One reason for this could be the fact that sepsis often mimics other disorders, and the diagnosis of sepsis as the cause of the illness is often not obvious at the time of initial presentation. As such, the need for antimicrobial agents in the treatment of the patient may also not be immediately obvious. Once the diagnosis is made (or strongly suspected), antimicrobial therapy should be started promptly. Initial empiric antimicrobial selection should be broad enough to cover all likely pathogens based on clinical circumstances. In patients with septic shock, de-escalation or restriction of antibiotic therapy as a strategy to reduce the development of antimicrobial resistance is not recommended until after a causative organism has been identified or after the patient's condition has markedly improved.

Pertaining to source control, the SSC recommends that a specific anatomic diagnosis of infection requiring

consideration for emergent source control (e.g., laparotomy for intra-abdominal source) be sought and diagnosed or excluded as rapidly as possible. Thus, imaging studies, if needed, should be performed as soon as possible to make the diagnosis. One important caveat to this is the inherent hemodynamic instability and overall severity of illness in septic shock that may make invasive procedures or transport of patients outside the intensive care unit for imaging studies potentially unsafe. Balancing potential risks and benefits in that scenario is very important. When a procedure for source control is found to be necessary, the surgical drainage should be undertaken for source control as soon as feasible following successful initial resuscitation. Specifically, the SSC recommends that this occur within the first 12 hours after the diagnosis is made. One exception to this may be necrotizing pancreatitits with suspected infection, for which a delayed approach to surgical management (i.e., intravenous antimicrobial therapy only at first, in addition to supportive care) may be preferred.

EARLY RESUSCITATION

One of the initial goals in the early management of a patient with septic shock is effective resuscitation to restore adequate tissue perfusion and decrease the risk of organ system injury. A number of hypotheses have been developed to explain the relationship between shock and the development of organ failure in critical illness. One hypothesis suggests that organ failure during critical care occurs as a consequence of inadequate oxygen delivery. Based on this hypothesis, a number of investigators have suggested that patients should be resuscitated to supranormal goals of systemic oxygen delivery in an attempt to prevent organ failure and improve outcome. The concept of supranormal oxygen delivery refers to the use of fluid resuscitation and inotropic drugs to drive up the oxygen delivery to achieve a predefined target. Several studies have examined this concept, although it is important to recognize that some studies have been performed in heterogeneous populations of critically ill patients rather than sepsis populations. The earliest clinical trials in perioperative high-risk surgery patients demonstrated an outcome benefit.[64,65] Subsequently, however, numerous trials of supranormal oxygen delivery in critically ill patients failed to demonstrate any benefit. In the largest of these studies, Gattinoni and coworkers found no difference in survival or organ failure in a large number of critically ill patients when comparing patients resuscitated to supranormal end points to those receiving standard care.[66] In a study by Hayes and associates, increasing oxygen delivery to supranormal levels with the use of high-dose dobutamine was associated with a reduction in survival.[67] A meta-analysis concluded that supranormal oxygen delivery in critically ill patients was not beneficial[68] and this concept largely fell out of favor in the 1990s.

For goal-oriented hemodynamic optimization to be beneficial, it has become clear that *timing* is critical. In contrast to the trials in perioperative high-risk surgery patients, subjects in the Gattinoni study were randomized much later, up to 72 hours after initial presentation.[66] In a meta-analysis of critically ill patients that stratified studies by severity and the timing of interventions (early versus late), an outcome benefit was identified in the subset of patients with a high severity of illness and early initiation of interventions.[69] A recent meta-analysis, this time specifically focused on patients with sepsis, found that quantitative resuscitation (i.e., early hemodynamic optimization targeting predefined quantitative end points of resuscitation) was associated with lower mortality rate in sepsis patients, but only if applied early, defined as less than 24 hours after presentation.[70] These data suggest that quantitative resuscitation in the treatment of severe sepsis and septic shock can in fact be beneficial—in the right patient.

This early intervention concept was the rationale behind the study of early goal-directed therapy (EGDT) for severe sepsis and septic shock by Rivers and colleagues.[23] EGDT is a type of quantitative resuscitation for septic patients that involves targeting central venous oxygen saturation ($Scvo_2$) as a monitor of the adequacy of oxygen delivery. In a single-center randomized controlled trial of 263 ED patients with severe sepsis and septic shock, Rivers and colleagues targeted predefined end points of resuscitation including central venous pressure (CVP) 8 to 12 mm Hg, MAP 65 mm Hg or greater, and $Scvo_2$ 70% or greater in the ED. The authors reported that the EGDT protocol was associated with a 16% absolute risk reduction for mortality rate (30.5% vs. 46.5%). This study was an important contribution to the literature in showing that early interventions in the resuscitation phase of therapy can be associated with a significant improvement in long-term survival for patients with sepsis.

Recently, a multicenter ED-based randomized trial from Jones and associates compared lactate clearance (defined as a decrease by ≥10% in the serum lactate concentration) versus $Scvo_2$ as an end point of sepsis resuscitation.[71] Among 300 patients with sepsis-induced tissue hypoperfusion, the authors found that lactate clearance was noninferior to $Scvo_2$ for the primary outcome of all-cause in-hospital deaths. These data suggest that, in addition to ensuring adequate cardiac preload and arterial blood pressure, lactate clearance has potential as a resuscitation target in sepsis-induced tissue hypoperfusion.

The data are conflicting as to what therapeutic interventions are typically needed beyond intravascular volume expansion and vasopressor agents in the early resuscitation of patients with sepsis. In the Jones trial, after aggressive administration of intravenous crystalloid to achieve a CVP of 8 to 12 mm Hg and vasopressor agents to achieve an arterial pressure of 65 mm Hg or greater in a stepwise resuscitation algorithm, very few patients required additional therapies for augmentation of oxygen delivery to achieve either lactate clearance or $Scvo_2$ goals (i.e., only 7% required packed red blood cell transfusion and 3% required inotropes). In contrast, 64% of patients in the EGDT ($Scvo_2$ targeted) arm in the Rivers study were treated with blood transfusions and 14% were treated with inotropic support. The Rivers data would suggest that packed red blood cell transfusions and inotropes are commonly required therapies for optimization of oxygen delivery in sepsis resuscitation, whereas the Jones trial (and multiple other recent observational clinical studies) suggests that these additional therapies are rarely required to achieve resuscitation goals. Although the optimal end points of quantitative resuscitation for sepsis remain controversial, it is generally accepted that the earlier the therapeutic interventions are delivered,

the greater the capacity for benefit. Therefore, the resuscitation phase of therapy appears to be an important window of opportunity for impact on outcome.

Currently, the SSC recommends the following end points for quantitative resuscitation: CVP 8 to 12 mm Hg, MAP 65 mm Hg or greater, urine output 0.5 mL/kg/hour or greater, and $Scvo_2$ 70% or greater (or mixed venous oxygen saturation [$S\bar{v}O_2$] ≥ 65%). Although arterial pressure and urine output are routinely monitored in critical care practice, targeting CVP and central or mixed venous oxygen saturation necessitates invasive hemodynamic monitoring. If invasive hemodynamic monitoring is not yet in place (or is not established for any reason), aggressive empiric resuscitation should still be performed because it is possible that empiric resuscitation can optimize cardiac filling pressure and oxygen delivery even if the specific values for CVP or central/mixed venous oxygen saturation are not recorded. The SSC also recommends targeting resuscitation to lactate normalization as soon as possible in patients with elevated serum lactate levels, especially if $Scvo_2$ values are not available. Targeting both $Scvo_2$ at 70% or greater and lactate normalization as a combined end point is also an option if both are available.

The SSC acknowledges limitations with utilizing static ventricular pressure estimates (e.g., CVP) for assessing intravascular volume status in septic shock patients. Specifically, measuring CVP in a range that is typically thought to be normal (or even high) does not necessarily exclude the possibility of preload-dependent cardiac output, especially in patients with preexisting chronically elevated cardiac filling pressures (e.g., cardiomyopathy or pulmonary artery hypertension). However, a markedly low value for CVP can be helpful in that it can reliably indicate the presence of hypovolemia in patients with circulatory shock. Targeting dynamic measures of fluid responsiveness during resuscitation and perhaps volumetric indices (e.g., pulse pressure variation, stroke volume variation) may eventually prove to be advantageous, but these newer techniques of intravascular volume assessment have not yet been widely adopted in practice and require future research.

The SSC also acknowledges that achievement of quantitative resuscitation goals can be challenging in routine clinical practice. Although some centers have been successful in implementing programs for quantitative resuscitation,[72] a recent large multicenter observational study of the translation of SSC recommendations to clinical practice found that clinicians currently achieve all recommended end points of resuscitation less than 50% of the time.[13] The reasons for this are likely multifactorial but may include the fact that from a practical standpoint the provision of quantitative resuscitation at the bedside can be relatively resource intensive, and some institutions may not have the necessary infrastructure to provide this service consistently at the present time.

CARDIOVASCULAR SUPPORT

The main goal of cardiovascular support in septic shock is to use intravascular volume expansion and vasoactive agents to help restore and maintain effective tissue perfusion. The main components of cardiovascular support in septic shock can be grouped into three separate and distinct categories: volume resuscitation, vasopressor therapy, and inotropic support. The goal of volume resuscitation is to optimize cardiac filling in order to augment cardiac output. Although many vasoactive drugs have both vasopressor and inotropic activity, this distinction is made on the basis of intended goals of therapy. Vasopressor activity primarily raises the arterial pressure, whereas inotropic activity augments myocardial contractility and raises cardiac output.

VOLUME RESUSCITATION

Aggressive intravascular volume expansion is another cornerstone of septic shock management and is the best initial therapy for the cardiovascular instability of sepsis. The initial hypotension observed in many patients with sepsis-induced cardiovascular instability may be reversed with volume infusion alone. A reasonable approach to initial volume resuscitation in the adult patient is the rapid administration of 2 to 3 L of crystalloid solution (e.g., 0.9% NaCl or lactated Ringer's solution). If (after initial volume infusion) the hemodynamic instability has resolved, further aggressive resuscitation may be unnecessary and the patient may be relegated to a somewhat higher maintenance fluid.

Because there is no proven benefit of colloid therapy over crystalloids in resuscitation,[73] the SSC currently recommends initiating volume resuscitation with crystalloid for patients with septic shock and suspicion of hypovolemia. The SSC-recommended volume of crystalloid is a minimum of 30 mL/kg fluid challenge. If there is hemodynamic improvement with this initial fluid challenge, clinicians may continue repeated fluid challenges to see if further hemodynamic improvement occurs. The SSC further suggests consideration of the addition of albumin infusion to initial crystalloid resuscitation if the initial crystalloids are judged to be ineffective. The SSC recommends against the use of synthetic hydroxyethyl starches in volume resuscitation because these agents have been associated with increased risk of acute kidney injury.

If a PAC is in place, the target for pulmonary capillary wedge pressure in a patient without preexisting cardiopulmonary disease is likely in the range of 12 to 15 mm Hg;[74] however, it is imperative to remember that the "optimal" cardiac filling pressure may vary widely from patient to patient. One prudent strategy of volume resuscitation (rather than targeting a predefined cardiac filling pressure) would be to continue fluid bolus administration until the cardiac index fails to rise with additional intravascular volume expansion, indicating optimization of cardiac preload. An extremely high left ventricular filling pressure should be avoided because it could contribute to pulmonary capillary leak and cause impairment of oxygenation if the patient has concomitant acute lung injury. In the absence of a PAC to guide therapy, and if a patient has persistent hypotension refractory to an initial 30 mL/kg crystalloid intravascular volume infusion, it would be prudent to continue administering fluid boluses in attempts to raise the arterial pressure (unless the patient is manifesting clinical signs that pulmonary edema is developing, [e.g., increasing supplemental oxygen requirement]).[75] Decisions on aggressiveness of fluid resuscitation should be made with consideration of oxygenation status. Patients with minimal supplemental oxygen requirements can be

more aggressively fluid resuscitated with minimal concern for deleterious effects of intravascular volume expansion, but more cautious fluid administration is required in patients requiring higher F_{IO_2} to maintain adequate oxygenation. Because the intravascular volume that optimizes stroke volume may produce worsening of oxygenation in patients with acute lung injury, intubation and mechanical ventilation may be required in order to assure adequate tissue perfusion.

VASOPRESSOR THERAPY

In addition to fluid administration, pharmacologic support of blood pressure is frequently necessary in both the initial resuscitation and subsequent support of patients with septic shock. These agents are, after fluids, the next most important interventions for the initial management of the hemodynamically unstable patient. Restoration of adequate arterial pressure is the end point of vasopressor therapy. The SSC recommends targeting a MAP of 65 mm Hg; however, blood pressure does not always equate to systemic blood flow, and the precise MAP to target may not necessarily be the same for all patients. LeDoux, Astiz, and coworkers demonstrated that, in septic shock patients treated with norepinephrine to maintain target MAP, MAPs of 65, 75, and 85 mm Hg achieved equivalent indices of tissue perfusion.[76] In an observational study of patients with septic shock Varpula and associates found that an area under the curve of 65 mm Hg was the best predictor of positive outcome and showed that among multiple hemodynamic variables, a MAP above 65 mm Hg was the best predictor of a favorable outcome.[77] It is notable that a MAP of 65 mm Hg may be inadequate for a patient with preexisting poorly controlled essential hypertension and associated vascular disease. Similarly, it should be recognized that in some patients it is possible to have arterial pressures lower than 65 mm Hg without tissue hypoperfusion. It is hypotension in the presence of tissue hypoperfusion that merits therapy with vasopressor agents. End points of resuscitation such as arterial pressure should be combined with assessment of regional and global perfusion. Other bedside indicators of persistent tissue hypoperfusion (besides hypotension) include oliguria, encephalopathy, poor capillary refill, and metabolic acidosis. Thus, even though the SSC recommends targeting a MAP of 65 mm Hg for most patients, the optimal MAP should be individualized based on the clinical considerations noted here.

The appropriate use of vasopressors may require accurate assessment of a patient's cardiovascular status with invasive hemodynamic monitoring. However, in the earliest stage of therapy, it is common to institute vasopressor therapy when invasive monitoring data is not immediately available if a patient remains hypotensive despite adequate intravascular volume expansion. If the MAP remains low (e.g., <65 mm Hg) with evidence of ongoing tissue hypoperfusion despite adequate fluid resuscitation, vasopressor therapy is indicated. In some circumstances, patients with sepsis may require vasopressor support even if hypovolemia has not yet been resolved. Below a threshold blood pressure, autoregulation of blood flow in vascular beds may be lost and linearly dependent on blood pressure; thus the administration of vasopressor agents to achieve a minimal perfusion pressure and maintain adequate flow is reasonable as an emergency measure in some situations while fluid resuscitation is ongoing.

INDIVIDUAL VASOACTIVE AGENTS

Multiple different vasoactive agents including norepinephrine, epinephrine, vasopressin, dopamine, and phenylephrine can achieve arterial pressure goals in the management of patients with septic shock. The different catecholamine agents have different effects on α- and β-adrenergic receptors. The hemodynamic actions of these receptors is well described: α-adrenergic receptors promote vasoconstriction, but β_1-adrenergic receptors increase heart rate and myocardial contractility and β_2-adrenergic receptors cause peripheral vasodilation. Given the differential effects of vasopressor drugs upon adrenergic receptors, these different agents have different effects upon arterial pressure and systemic blood flow. In this context, the quintessential question as to which catecholamine is the best initial choice for treating septic shock is best framed as a question of which agent is most appropriate for a given therapeutic strategy in an individual patient, and is largely dependent upon that individual patient's hemodynamic status. Rather than a "one size fits all" strategy, vasoactive agents should be carefully selected based on the intended goals of therapy.

Vasoactive agents and their characteristics are summarized in Table 23.1. The selection of one of these drugs over the other as a first-line agent is a controversial and an often debated subject in the field of critical care medicine. Both norepinephrine and dopamine will effectively raise the

Table 23.1 Vasoactive Agents Commonly Used for Hemodynamic Support in Sepsis

Agent	Typical Dose	Chronotropic Effects	Inotropic Effects	Vasoconstriction
Dopamine	6-20 μg/kg/min	++	++	+/++ (dose-dependent)
Epinephrine	1-10 μg/min	++	++	++
Norepinephrine	2-30 μg/min	+	+	++
Phenylephrine	20-200 μg/min	–	–	++
Vasopressin	0.01-0.03 U/min	–	–	++
Dobutamine	2-15 μg/kg/min	++	++	–

From Trzeciak S, Parrillo JE. Septic shock. In Society of Critical Care Medicine, 8th Adult Critical Care Refresher Course. Chicago: Society of Critical Care Medicine, 2004, used with permission.

blood pressure and the cardiac index, but the rise in cardiac index will be greater with dopamine. Dopamine, however, may cause or exacerbate tachycardia or dysrythmias.[78] Norepinephrine is a more potent drug than dopamine in achieving a target MAP.[1] Information from five randomized trials (n = 1993 patients with septic shock) comparing norepinephrine and dopamine does not support the routine use of dopamine in the management of septic shock.[79]

Epinephrine is a potent α- and β-adrenergic agent that increases MAP by vasoconstriction and also increases the cardiac index. Although epinephrine is a potent agent in raising the arterial pressure, the chief concern with the use of epinephrine has been the potential for impaired splanchnic perfusion.[80-82] A large-scale randomized controlled trial comparing epinephrine to norepinephrine plus dobutamine reported no difference in vasopressor withdrawal, organ failure, and mortality rate. There was also no difference in the rates of serious adverse events. The authors concluded that there is no difference in efficacy and safety for epinephrine versus norepinephrine plus dobutamine in the management of septic shock.[83]

Vasopressin is an agent that has both vasoconstriction and antidiuretic properties. Vasopressin constricts vascular smooth muscle directly via V_1 receptors, and may also increase the responsiveness of the vasculature to endogenous or exogenous catecholamines.[84,85] Normally, endogenous vasopressin levels are very low, and there is essentially no vasoconstriction effect in a normal host. However, in septic shock vasopressin levels are initially extremely elevated. In prolonged septic shock, a relative vasopressin deficiency can develop. It has been postulated that this relative vasopressin deficiency may be the result of the depletion of the pituitary stores or the downregulation of vasopressin production by the pituitary via the effects of nitric oxide.[84] Exogenous administration of low-dose vasopressin can have a dramatic hemodynamic response in this scenario, rapidly restoring arterial pressure.[86,87] A large randomized clinical trial compared vasopressin to norepinephrine in 776 subjects with vasopressor-dependent septic shock. Patients were randomized to vasopressin (0.03 U/minute) or norepinephrine (15 μg/minute). For the group as a whole (intent-to-treat analysis) there was no difference in the primary end point of 28-day mortality rate. It appears that vasopressin (up to 0.03 U/minute) may be equally safe and effective as norepinephrine in patients with septic shock after fluid resuscitation.[88] Doses of vasopressin higher than 0.04 U/minute are not recommended due to concerns of coronary, digital, and mesenteric ischemia.

Phenylephrine is a pure vasoconstrictor with α-adrenergic effects alone. Although one potential advantage of using phenylephrine is that it will not cause or exacerbate tachycardia, the increase in peripheral resistance may produce a deleterious lowering of cardiac output. Phenylephrine may be useful in select patients with severe dysrhythmias associated with catecholamine infusion because it has no β-adrenergic effects, as well as in patients with refractory hypotension in the presence of a known high cardiac index.

The SSC recommends norepinephrine as the first-line vasopressor agent in septic shock. The SSC further recommends the addition of either epinephrine or vasopressin (0.03 U/minute) if a second vasopressor agent is needed to support the blood pressure.

INOTROPIC SUPPORT

Inotropic support may be required for patients with septic shock. In the context of severe sepsis-induced myocardial depression, or if the patient has severe preexisting myocardial dysfunction, an inotrope may be necessary to augment cardiac output (typically in combination with a drug that is supporting the MAP). The SSC recommends that dobutamine be the inotrope selected. When used beyond early quantitative resuscitation (first 6 hours of therapy) inotropic therapy is guided by measurements of cardiac index. A reasonable goal for inotropic therapy would be a cardiac index of 3.0 L/minute/m^2 or greater.

CORTICOSTEROIDS

Administering high doses of steroids (30 mg/kg of methylprednisolone) failed to show an outcome benefit in septic shock in large-scale randomized controlled trials in the 1980s.[89,90] These studies used large doses of steroids over a short time period in an attempt to blunt the proinflammatory response of sepsis. In contrast, an alternative strategy of administering low-dose (i.e., "stress" or "physiologic" dose) steroids appeared to be promising in multiple small studies in the 1990s.[91,92] Despite the fact that septic shock patients typically have elevated serum cortisol levels, it was identified that some patients with septic shock may have "relative adrenal insufficiency," as evidenced by failure to mount a significant elevation of serum cortisol in response to intravenous adrenocorticotropic hormone (ACTH) stimulation. Relative adrenal insufficiency in the context of septic shock may predispose a patient to persistent cardiovascular failure that is refractory to conventional hemodynamic support therapies, and administration of exogenous low-dose steroids could help achieve shock reversal. On the other hand, administration of exogenous steroids could be associated with deleterious effects such as immunosuppression or myopathy.

In 2000, Annane and colleagues performed an observational study focusing on the ability to respond to an ACTH stimulation test in septic shock.[93] The highest 28-day mortality rate (75%) was observed in patients who did not increase serum cortisol level greater than 9 μg/dL. Being a "nonresponder" was a better predictor of death than an initially low cortisol value. In a randomized controlled trial by the same investigators in 2002, 300 severely ill (persistent hypotension despite fluid resuscitation and vasopressor initiation) septic shock patients were randomized to 7 days of hydrocortisone plus fludrocortisone versus placebo.[94] The study found that in the 229 nonresponders administration of low-dose steroids was associated with an improvement in time to shock reversal and mortality rate. Patients who responded appropriately to ACTH stimulation test did not demonstrate a benefit with low-dose steroids.

The concept of low-dose steroid administration was further tested in a multicenter randomized controlled trial (CORTICUS).[95] This study found no difference in the primary outcome measure of mortality rate between those treated with steroids compared to placebo. However, it is notable that (1) in contrast to the Annane study in which all subjects had vasopressor-refractory septic shock, the CORTICUS study tested a more diverse patient population

with overall lower severity sepsis, and (2) randomization in the Annane study occurred within 8 hours of developing shock as opposed to CORTICUS, which randomized subjects up to 72 hours after shock onset. Despite the fact that low-dose steroids do not appear to improve outcome in diverse, less severely ill populations of patients with sepsis, patients with vasopressor-unresponsive septic shock likely benefit. In summary, although steroid therapy should not be used in all patients with septic shock, it could be considered in those with persistent circulatory shock despite the administration of vasopressor agents.

The SSC recommends that intravenous hydrocortisone not be administered to septic shock patients if fluid resuscitation and vasopressor agents can restore an adequate arterial pressure. If arterial pressure cannot be successfully restored and maintained, the SSC suggests intravenous hydrocortisone at a maximum dose of 200 mg per day. The SSC does not recommend the use of an ACTH stimulation test to identify candidates for steroid therapy, but rather using bedside clinical criteria such as the presence of vasopressor-refractory shock. The SSC does not recommend the addition of fludrocortisone to hydrocortisone when steroids are administered. Hydocortisone should be tapered off when vasopressor agents are no longer required.

SUMMARY

Successful management of the patient with septic shock continues to be a major clinical and public health challenge, as evidenced by persistently high mortality rates associated with this disease. The principal goals of sepsis therapy remain early identification, early empiric antibiotic therapy and infection source control, aggressive resuscitation, and effective cardiovascular support. The hemodynamic profile of septic shock is the most complex of all shock profiles and may be characterized by simultaneous hypovolemia, myocardial depression, and peripheral vascular dysfunction. Clinicians should define goals and end points of hemodynamic support in individual patients, titrate therapies to those end points, and evaluate the effectiveness of their interventions based on improving indices of tissue perfusion.

KEY POINTS

- Septic shock is a clinical syndrome resulting from a systemic infection that triggers an excessive inflammatory response and produces cardiovascular instability.

KEY POINTS (Continued)

- The initial management of the patient with septic shock is aggressive resuscitation and cardiovascular support, as well as early empiric administration of broad-spectrum antibiotics.
- Initial cardiovascular support is achieved with aggressive intravascular volume expansion.
- Vasopressors are administered to patients who remain hypotensive despite fluid administration. Although the selection of vasopressors must be individualized, norepinephrine is typically considered a first-line agent.
- End points of resuscitation should be physiologic values that reflect adequacy of regional and global perfusion. Clinicians should define goals and end points of hemodynamic support, titrate therapies to those end points, and evaluate the results of their interventions on improving indices of tissue perfusion.

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24 Cardiac Tamponade

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CHAPTER OUTLINE

FUNDAMENTALS OF TAMPONADE

Cardiac tamponade is a condition characterized by an increase in pressure external to the heart resulting in impaired filling of the cardiac chambers. In the typical scenario, as fluid in the pericardium accumulates, cardiac output falls. The diagnosis represents a continuum from mild tamponade with subtle diagnostic findings to a critical clinical setting with imminent mortality.[1] The variability in presentation, including diagnostic findings and course, and the morbidity and mortality associated with treatment make this a particularly challenging clinical problem in critical care medicine.

PERICARDIAL ANATOMY

The pericardium consists of a visceral and a parietal pericardial segment, the former being composed of a single layer of cells that adhere to the cardiac epicardial surface.[2,3] The parietal pericardium is the structure responsible for the clinically relevant features of tamponade; it is a relatively noncompliant structure composed of collagen and elastin and normally is less than 2 mm thick. The mechanical properties of the pericardium—in particular, those reflected by its pressure-volume curve (Fig. 24.1)—are responsible for the clinical features seen in cardiac tamponade.

The pericardium extends from the lower third of the superior vena cava to the apex of the heart. It is attached to the sternum, the diaphragm, and the great vessels. Because it extends beyond the heart border, trauma to not only the heart but also the great vessels approaching the heart borders can lead to cardiac tamponade.[4]

PHYSIOLOGY

Cardiac tamponade is a result of decreased transmural pressure, typically from the accumulation of fluid in the pericardial space (Fig. 24.2). Other causes of "tamponade-like physiology" are related to extrinsic compression of the heart,[5] although these pathologic processes should be separated from those causing constriction rather than true tamponade. Differentiating these two distinct physiologic entities, constriction and tamponade, is essential to diagnosis and management.

The fluid accumulating in the pericardial space can be blood, serous fluid, purulent material, clot, or rarely gas. As fluid accumulates, the pericardium stretches, until it reaches a point (see Fig. 24.1) at which its degree of compliance is exhausted, so that it has become largely inelastic. At this point, any further increase in intrapericardial fluid is associated with a decrease in intracardiac chamber volume, because the total volume of pericardial fluid, heart muscle, and the cardiac chambers becomes fixed by pericardium no longer able to stretch. This in turn results in decreased filling of the heart and consequently decreased stroke volume. To maintain cardiac output, an early compensatory mechanism is an increase in heart rate. Subsequent adaptations to maintain blood flow to central end organs (heart, brain, kidneys) are venous pressure rise, peripheral vasoconstriction, increase in ejection fraction, and selective shunting of blood to preserve flow to the essential end

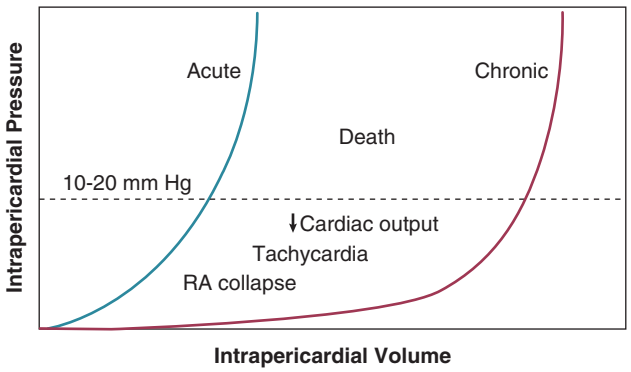

Figure 24.1 Pressure-volume curves for normal pericardium on the *left* and compliant pericardium on the *right*. In the setting of rapid onset of effusion in the normal pericardium, low volumes, typically starting from less than 50 mL, lead to a rise in pressure that exceeds the limit of pericardial stretch, with early onset of tamponade physiology. With more compliant pericardium, a result of chronic stretching, critical extramural pressures do not result until substantially higher volumes are achieved, in some cases more than 1 L.

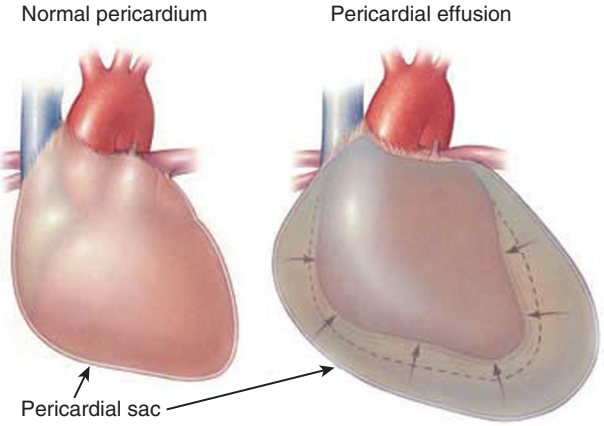

Figure 24.2 The pericardium surrounding the heart in a normal physiologic setting and in tamponade. The pericardium can be seen to extend to the proximal great vessels. Note the large amount of effusion in the image on the *right,* consistent with chronic pericardial stretch, which leads more slowly to tamponade. (From Holmes DR Jr, Nishimura R, Fountain R, Turi ZG. Iatrogenic pericardial effusion and tamponade in the percutaneous intracardiac intervention era. JACC Cardiovasc Interv 2009;2(8):705-717.)

organs. Venous pressure increase is accomplished by fluid retention and peripheral venoconstriction. In severe tamponade, equalization of right atrial, right ventricular diastolic, pulmonary diastolic, pulmonary artery wedge, and intrapericardial pressures occurs. Both pulmonary and systemic arterial and pulse pressures fall. Tamponade is a continuum, ranging from a primarily echocardiographic finding of right-sided chamber collapse to shock and pulseless electrical activity.

PERICARDIAL PRESSURE

The normal pericardium contains a small amount of fluid, typically in a range of 20 to 50 mL, resulting in no more than 5 mm of separation between the visceral and the parietal pericardial surfaces. Pressure in the normal pericardium reflects intrathoracic pressure, which in turn reflects atmospheric pressure, with variation influenced by respiration. During inspiration, the pressure falls a few millimeters below atmospheric pressure (by convention, 0 mm Hg); during expiration, it falls a few millimeters above. The difference between intracardiac and intrapericardial pressures, the transmural pressure, in turn distends or compresses the cardiac chambers. Because intrapericardial mean pressure in patients breathing unassisted typically is the same as atmospheric pressure, whereas right atrial pressure is normally in the range of 2 to 8 mm Hg, the latter is the typical range of net right atrial transmural pressure. When intrapericardial pressure rises to the level of right atrial pressure, the right atrium collapses, a typical feature of early cardiac tamponade, though this nonspecific finding can be seen with hypovolemia alone.

The normal parietal pericardium, because of its limited compliance, limits abrupt expansion of the heart as a whole.[6] Thus, in the setting of right ventricular infarction, for example, acute dilation of the right ventricle is at the cost of left ventricular volume decrease—a ventricular interdependence phenomenon similar to that illustrated in Figure 24.3. Acute chamber enlargement resulting from other etiologic conditions or disorders, such as abrupt volume loading or sudden onset of severe valvular regurgitation, is impeded by the constraint of pericardium that has reached the limits of its intrinsic elasticity. Because right-sided heart filling occurs preferentially with inspiration, when negative intrathoracic pressures result in increased venous return and higher right-sided chamber volume, left ventricular stroke volume and hence systolic blood pressure tend to fall as left atrial and left ventricular volumes decrease. This exaggerates the normal respiratory variation, and systemic pressure falls with inspiration to a level at which pulsus paradoxus, defined by convention as a greater than 10 mm Hg decrease in systolic pressure, is seen. In addition, decreased intrathoracic pressure has a disproportionate effect on the pulmonary venous circulation, which is not exposed to the high pericardial pressures; hence, a disproportionate fall during inspiration in the pulmonary vein to left atrial gradient further exacerbates the decrease in left atrial filling.[7] The fall in systolic pressure is not in fact a paradox but rather an exaggeration of normal respiratory variation of approximately 3%[8] with associated inspiratory decrease in left ventricular stroke volume. With severe tamponade, total elimination of pulse pressure can be seen with individual heartbeats, as in the example in Figure 24.4.

The inability to dilate further means that additional volume beyond the intrinsic stretch limit of the pericardium, such as from bleeding into the pericardial sac, results in increasing compression of heart chambers as volume expands in the pericardial space. Because the right-sided chambers have the lowest intracardiac pressures, in particular the right atrium, those are the first chambers showing collapse, in particular in diastole, when the tricuspid valve is open and the right atrium can decompress into the right ventricle. With a progressive increase in intrapericardial pressure, compression of the right ventricle in diastole occurs during pressure equalization with the right atrium. Eventually, as intrapericardial pressure continues to rise, compression of the left-sided chambers ensues.

In contrast with acute tamponade physiology, in which hemodynamic decompensation may occur after only a

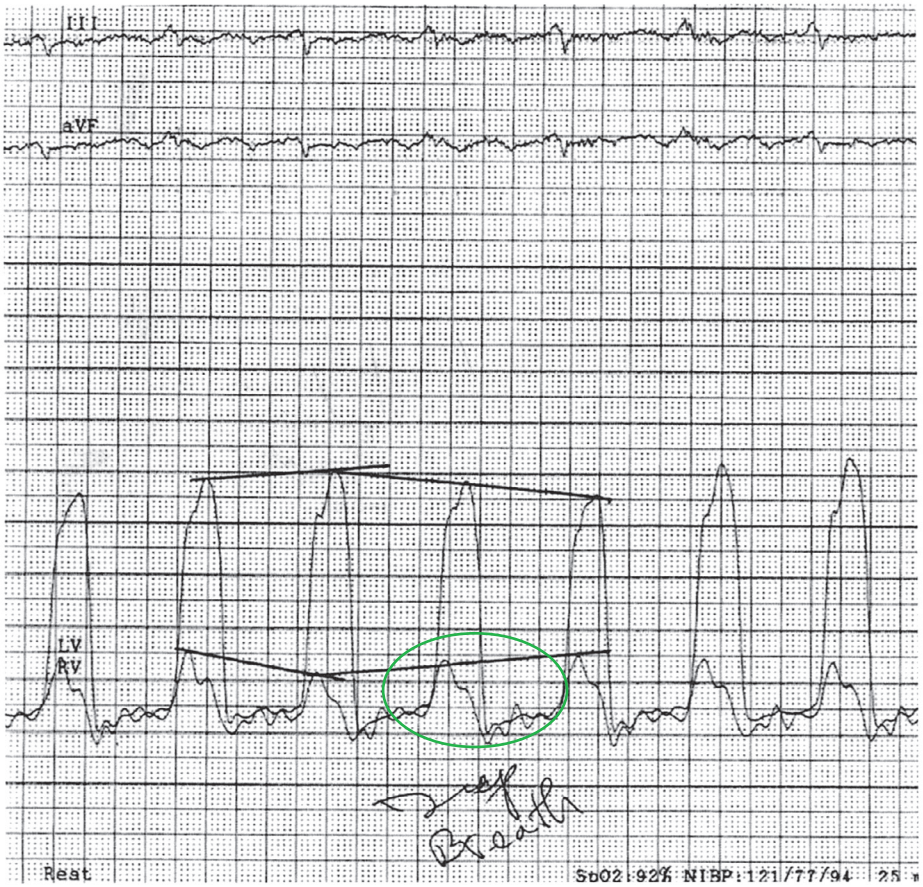

Figure 24.3 Hemodynamic tracings from a patient with ventricular interdependence (200–mm Hg scale). With inspiration, left ventricle (LV) systolic pressure falls as right ventricle (RV) systolic pressure increases. Because of ventricular interdependence, the right ventricular and left ventricular systolic pressures trend in opposite directions (lines connecting peak systolic pressures diverge during phases of the respiratory cycle). Diastolic pressures in both ventricles are essentially identical *(green oval)*. Absence of pulsus paradoxus and preserved systolic pressure make this physiology consistent with constriction rather than tamponade. The patient had a clot in the pericardial space after prior cardiac trauma.

modest accumulation of fluid, generally in the range of 100 to 200 mL, chronic pericardial effusion results in a gradual increase in distensibility of the pericardium. With increasing compliance, large amounts of fluid can accumulate at low pressure without decreasing transmural pressure or compressing the cardiac chambers (see Fig. 24.1). Even in chronic low pressure–high volume tamponade, a limit of distensibility is eventually reached that results in similar pathophysiology as with acute tamponade, in some cases only after a liter or more of fluid has accumulated. Once the steep portion of the pressure-volume curve is reached, it is important to appreciate that with accumulation of another 50 to 100 mL of pericardial fluid, hemodynamic decompensation can occur rapidly, with similar outcomes as in patients who suffer from acute tamponade, such as is seen with penetrating trauma, coronary artery perforation, aortic dissection, or cardiac rupture.

ETIOLOGY

Pericardial effusions generally can be characterized as transudate or exudate, infectious or bloody, with tamponade occurring with variable frequency depending both on the rapidity of fluid accumulation and, to a somewhat lesser degree, on characteristics of the effusion and physiology determined by its etiology. Transudates are characteristic of congestive heart failure, radiation, and uremia; exudates are characteristic of infections, malignancy, and connective tissue disorders. Laboratory testing may help differentiate exudates from transudates; pericardial and serum protein, albumin, lactate dehydrogenase (LDH), cholesterol, and glucose should be obtained,[9] although some of the differentiating characteristics applicable to pleural effusions may not be discriminatory in pericardial effusions.[10] In addition, pericardial fluid total and differential cell count, Gram stain, aerobic and anaerobic culture, and mycobacterial and fungal evaluation should be performed along with cytology when malignancy is considered. Molecular techniques can be useful in diagnosing otherwise occult infections.[11] Amylase is reserved for cases where pancreatic disease or esophageal rupture are part of the differential diagnosis.

Conditions predisposing to slow accumulation such as heart failure, myxedema, chronic renal failure, and connective tissue disorders in general are less likely to cause acute tamponade, whereas those associated with rapid development, such as malignancy, infection (including bacterial, fungal, and human immunodeficiency virus related), or particularly hemorrhage, commonly result in abrupt

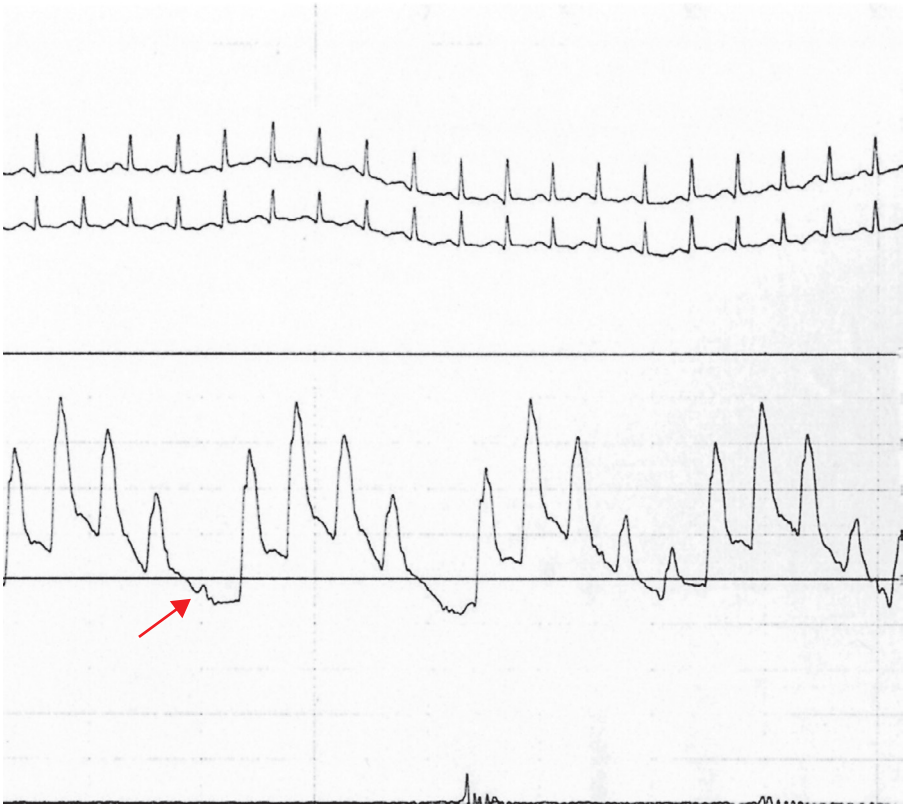

Figure 24.4 Hemodynamic tracing of systemic pressure in cardiac tamponade, 100–mm Hg scale. Systolic pressure variation is nearly 40 mm Hg, and pulse pressure is markedly reduced during inspiration. Note the complete obliteration of the systemic pressure during deep inspiration in the beat highlighted by the *arrow.* Because of low stroke volume, cardiac output is being maintained to some extent by a high heart rate (146 beats per minute).

hemodynamic deterioration. The effect of inflammation in decreasing compliance of the pericardium exacerbates the hemodynamic effects of effusions associated with pericarditis.[12] The potential etiologic disorders are highly variable, with significant influence of demographics and geography, so that tamponade secondary to tuberculous pericardial effusion in immune-compromised patients is a not uncommon presentation in Africa,[13] whereas in industrialized nations malignant effusions are a far more common cause.[14] Large and usually benign pericardial effusions are seen frequently after heart transplantation, possibly immune mediated.[15] Large pleural effusions can cause sufficient compression of the heart that tamponade physiology occurs.[16] The most common etiologic disorders are listed in Table 24.1; more detailed discussion of the various causes is presented later in the chapter, organized by the hospital setting in which presentation typically is seen.

HISTORY AND PHYSICAL EXAMINATION

Dyspnea is the most common symptom of tamponade, although its etiology sometimes is unexplained and it usually is not associated with significant concomitant pulmonary vascular congestion. It is likely to be secondary to decreased cardiac output and encroachment on lung volume by the expanding pericardium as well as any simultaneous pleural effusions. The patient may describe a sensation of fullness in the chest or abdomen and dysphagia, associated with venous engorgement and passive congestion, stretching of the richly innervated pericardium, and occasionally vagal stimulation.[17] Because most patients with tamponade have comorbid conditions accounting for their effusion, additional signs and symptoms are likely to be related to pericarditis, malignancy, or other concomitant conditions.

The hallmarks of cardiac tamponade on physical examination relate to features associated with venous hypertension, low cardiac output, and effects of the layer of fluid between the heart and the chest wall. In patients with tamponade, the general appearance changes substantially during progressive increase in pericardial pressure. Because tamponade represents a continuum, some patients with early tamponade physiology look well, whereas patients with more advanced tamponade show features of a low-output state, with clinical manifestations reflecting the high catecholamine levels required to maintain cardiac output. They become progressively more anxious and agitated and less communicative and may be struggling to breathe. Patients may complain of chest pain associated with pericardial irritation, not infrequently radiating to the neck, jaw, or shoulder[18]; if venous congestion is acute, patients may experience pain from stretching of Glissen's capsule around the liver.

PULSUS PARADOXUS

The physical examination in significant tamponade can include Beck's triad, described in 1935 by the surgeon C. S.

Table 24.1 Etiology of Cardiac Tamponade

Causative Disorder/Condition	Frequency (%)
Most Common*	
Idiopathic	23
Malignancy	22
Iatrogenic	18
Acute myocardial infarction	8
Purulent (including tuberculous)	8
Renal failure	3
Miscellaneous	**18**
Aortic dissection	
Myxedema	
Trauma	
Connective tissue disorders	
Radiation therapy	

*Frequency of common etiologies of tamponade is based on 119 cases in Barcelona, Spain. Other relatively common causes of effusion include congestive heart failure, hypoalbuminemia, coagulopathy, and postcardiotomy and Dressler's syndromes. Etiologies of tamponade will be dependent on geography and patient demographics and also will be strongly influenced by the presence of oncology, trauma, or dialysis units. For a comprehensive list of tamponade etiologies based on prior data, see Box 6.1.

Data from Sagrista-Sauleda J, Merce J, Permanyer-Miralda G, et al: Clinical clues to the causes of large pericardial effusions. Am J Med 2000;109:95-101.

Box 24.1 Tamponade Settings in Which Pulsus Paradoxus May Not Be Present

- Nonrestrictive (large) atrial septal defect
- Severe aortic insufficiency
- Loculated effusion
- Left ventricular hypertrophy and other causes of elevated left ventricular diastolic pressure
- Shock due to hypovolemia, or profound circulatory collapse with tamponade
- Severe left ventricular dysfunction
- Low-pressure tamponade
- Right ventricular hypertrophy or other cause of impaired right ventricular filling
- Positive-pressure ventilation
- Arrhythmias

Beck.[19] This entity features jugular venous distention, decreased arterial pressure, and a small, quiet heart. As described earlier, pulsus paradoxus is the result of cardiac chamber interdependence and a decrease in left ventricular chamber volume with inspiration. It can be detected at the bedside by auscultation of Korotkoff sounds, identifying the highest and lowest pressures at which sounds are first heard during inspiration and expiration; alternatively, a simpler and more useful technique is to palpate the radial artery pulse with the cuff inflated to the maximum pressure at which the pulse appears and then to lower the cuff pressure in increments of 10 mm Hg to detect the pressure at which pulses are continuously noted throughout the respiratory cycle. In the patient whose systolic pressure is shown in Figure 24.4, simple palpation of the radial pulse would detect the loss of pulse pressure in the beat flagged by the red arrow. It is important to recognize that although pulsus paradoxus is a classic feature of severe tamponade, as a diagnostic feature it is of limited sensitivity and specificity.

Various thresholds other than the relatively arbitrary 10 mm Hg threshold have been proposed to increase specificity, including a 10% decrease, rather than a 10 mm Hg fall.[20] A drop in *systolic* pressure greater than 50% of the *pulse* pressure also has been proposed.[1] Use of a 15 or 20 mm Hg fall in pressure by physical examination is a less sensitive but far more specific finding for tamponade but may result in delayed diagnosis. Pulsus paradoxus may be present in other conditions that result in an exaggerated decrease in systolic pressure with inspiration, such as massive pulmonary embolism, severe chronic obstructive pulmonary disease (which also can feature constrictive physiology because of limited expansion of the heart in the setting of hyperexpanded lungs),[20] and right ventricular infarction.[21] Furthermore, other features of the systemic blood pressure and pulse are important to consider. With a progressive decrease in cardiac filling overall, a decline in systemic pressure (regardless of phase of the respiratory cycle) as well as a decrease in pulse pressure (the difference between systolic and diastolic pressures) occurs, reflecting decreasing stroke volume and decreasing cardiac output. Thus, it may be impossible to palpate radial artery pulsations; with severe tamponade, the patient is likely to feel cool and clammy, a finding consistent with severe peripheral vasoconstriction.

Tachycardia is almost invariable, except for comorbid conditions associated with a decrease in heart rate, such as electrical conduction disturbances, severe hypothyroidism, or aggressive β-blockade. Tachycardia is a compensatory mechanism for decreased stroke volume, is also caused by high catecholamine levels, and may result from pericardial irritation of the sinus node that stimulates a higher heart rate. On occasion, acute bradycardia may be seen in tamponade, sometimes the first finding after hemorrhage into the pericardial sac. Although a well-preserved systolic pressure and a wide pulse pressure are uncommon in tamponade, neither a low pressure nor a narrow pulse pressure is completely specific. Further, early in the course of tamponade, acute surge in catecholamine levels may result in hypertension rather than shock; in addition, patients with tamponade in the setting of renal disease and chronic hypertension appear to present more often with elevated systolic pressures.[22]

The pulsus paradoxus may be absent in conditions in which ventricular interdependence is masked[23] (Box 24.1), such as a nonrestrictive atrial septal defect, in which inspiration also increases left atrial filling, or aortic insufficiency, in which left ventricular filling in diastole is increased by regurgitation from a high-pressure source: the aorta. Localized tamponade may have some general tamponade features (such as decreased stroke volume) but may not result in ventricular interdependence—hence, the clinical picture may be that of a sick patient with tamponade but without pulsus paradoxus. Markedly elevated left-sided

heart diastolic pressures in severe left ventricular hypertrophy and other disease states may exceed the elevated right atrial and intrapericardial pressures in tamponade, decreasing the effect of inspiration on the interdependence of the right and left sides of the heart. An example in which both pulse pressure and pulsus paradoxus would be insensitive markers of tamponade is aortic dissection that combines aortic insufficiency with tamponade, in which a wide pulse pressure may be seen in some patients with partial compensation, and in which pulsus paradoxus, as discussed, may be masked. By contrast, conditions resulting in impaired right ventricular filling, such as right ventricular hypertrophy in severe pulmonary hypertension, also may result in the absence of a pulsus paradoxus[24]; furthermore, in settings such as cor pulmonale, the dramatic elevation in right-sided diastolic pressures will delay onset of the otherwise highly sensitive and early finding of right atrial and right ventricular diastolic collapse until tamponade is severe.[25] A substantial number of case reports describe physiologic conditions in which the classic findings for tamponade are not seen or are attributable to other etiologic disorders.[26]

VENOUS PRESSURE

Because impairment of right-sided filling is usually the first manifestation of increasing pericardial pressure, high jugular venous pressure manifested by prominent venous pulsations may be the earliest finding on physical examination, occurring with increasing intrapericardial and right atrial pressures. Jugular venous distention may, however, be simultaneously absent because venoconstriction, a common finding with acute tamponade, makes detection of elevated venous pressures difficult. It also will be masked by low-volume tamponade, including volume-depleted states such as trauma, when, in addition to hemorrhage into the pericardium, significant blood loss has occurred. Other settings in which venous distention may not be observed are post-dialysis in patients with uremic pericardial effusions, and excessive diuresis, sometimes as part of treatment for symptoms of congestive heart failure when the cause of elevated filling pressures has not been appreciated.[27] In general, lack of venous engorgement in tamponade, particularly when the latter is acute, is not uncommon. Thus, prominent jugular venous distention may suggest an alternative diagnosis, such as severe right-sided heart failure. Increased venous pressure with inspiration, Kussmaul's sign, is a feature of constriction, reflecting increased venous return to the thorax without increased right atrial filling, because the latter is constricted by the pericardium. This is in contrast with tamponade, in which negative intrathoracic pressure is transmitted through the pericardial effusion, and results in increased right-sided heart filling with decrease in venous pressure. Because these findings are difficult to differentiate in most acutely ill patients, much of the subsequent description about right atrial pressure is based on catheter based hemodynamic findings rather than the physical examination.

The Y descent, in contrast with pericardial constriction, in which it is prominent, typically is limited or absent (Fig. 24.5). Unlike in pericardial constriction, filling of the right ventricle (and hence emptying of the right atrium) is impaired throughout the cardiac cycle, because extrinsic compression by pericardial fluid results in elevated diastolic pressures in the right ventricle when rapid filling would otherwise occur. Because the pericardium allows additional atrial expansion during ventricular ejection (when ventricular volume decreases), the X descent is typically the more prominent negative pressure wave seen. The classic square

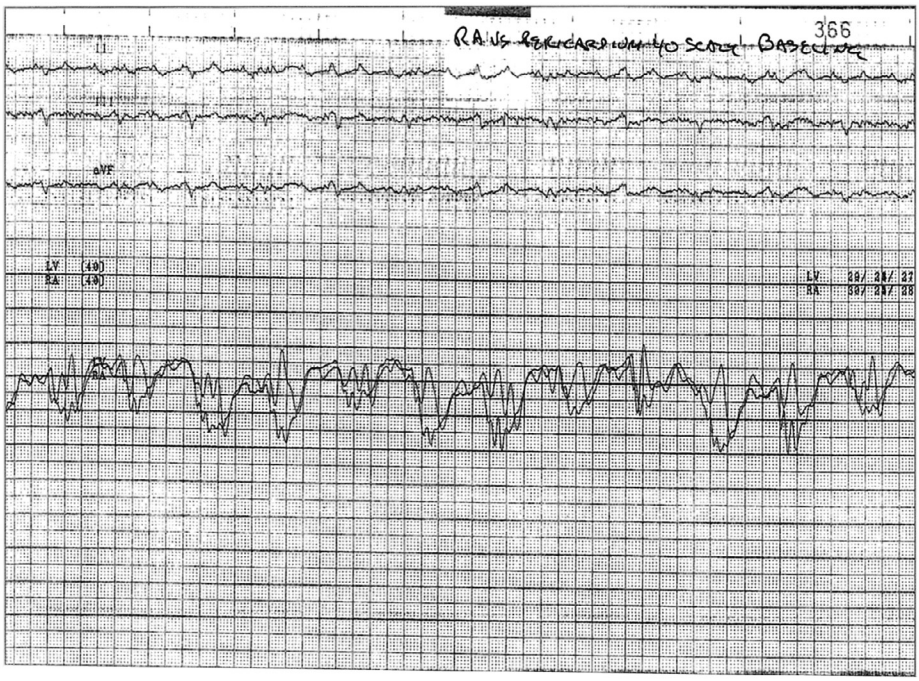

Figure 24.5 Hemodynamic tracings showing right atrial (RA) and intrapericardial pressures (incorrectly labeled LV) on a 40–mm Hg scale. Note the equivalence of pressures as well as the high mean pressure, 27 mm Hg, consistent with tamponade and hemodynamic decompensation. The Y descent is nearly absent.

root sign seen in the right ventricular pressure tracing in constriction is absent in tamponade.

In contrast with acute tamponade, with chronic effusion persistent elevation in pericardial pressure leads to a parallel rise in central and peripheral venous pressure, as well as fluid retention with elevated intravascular volume. Venous congestion as well as peripheral edema and end-organ signs of chronic venous hypertension, such as passive congestion of the liver, become more common in this setting.

CARDIAC AND CHEST EXAMINATION

The quiet heart in Beck's triad relates to several features that tend to muffle the intensity of heart sounds. First, the insulating effects of pericardial fluid on sound waves tend to decrease the sound volume transmitted to the chest wall. Second, low stroke and filling volumes tend to decrease the forces that cause the sounds generated by heart valve closure, with low pulse pressure in both the aortic and the pulmonary arteries. Because the S3 gallop is created by rapid ventricular filling, a phenomenon absent in tamponade, it would not be expected, nor would an S4, because the hemodynamic characteristics of late diastolic atrial emptying that causes the fourth heart sound are not seen.[1] A pericardial friction rub, if pericarditis is involved, may be heard. Except in severe tamponade, the pericardium around the apex of the heart may contain relatively little fluid, and left ventricular contraction typically is vigorous unless underlying left ventricular dysfunction also is present. Hence, a palpable point of maximal impulse may be felt.

A particular feature that differentiates tamponade from decompensated congestive heart failure is the typical presence of clear lungs in the case of the former. Although both right and left atrial pressures are markedly elevated, flow into the pulmonary circulation is limited, and the pressure-volume curve for the pulmonary vascular system is not affected.

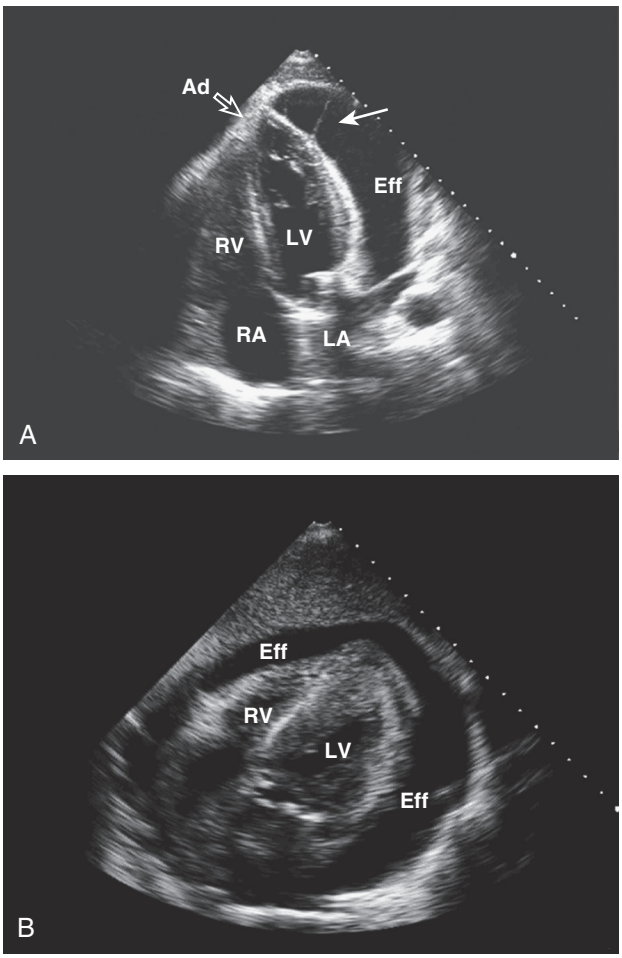

Figure 24.6 Echocardiographic images of two types of pericardial effusions. **A,** A large posterior pericardial effusion, with relatively little fluid anterior to the heart or at the apex. The apex is adherent to the pericardial surface. The *arrow* points to a fibrous strand. This is a fairly typical appearance of a chronic postcardiotomy effusion. Needle access would be problematic. **B,** By contrast, this effusion is circumferential, with somewhat more fluid behind the left ventricle, a largely gravitational effect. Leaning the patient forward 20 to 30 degrees would facilitate pericardiocentesis, although the patient was not significantly hemodynamically compromised. Ad, adhesion; Eff, effusion; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

DIAGNOSTIC TESTS

ECHOCARDIOGRAPHY

Echocardiography is the most easily accessible and accurate means for the timely diagnosis of tamponade and remains the diagnostic modality of choice.[28] Besides evaluating presence and degree of chamber collapse, the echocardiogram is useful for assessing the amount and location of effusion in the pericardial space, for characterizing the fluid, and for judging the hemodynamic effect. Cardiac tamponade represents an echocardiographic continuum, from a small accumulation of fluid with at most subtle clinical findings, to large, usually circumferential[29] accumulations with resultant cardiogenic shock. Until effusions are at least moderate in size, fluid may be shifted by gravity to a location primarily posterior to the heart, because most patients are recumbent during echocardiography (Fig. 24.6).

Several echocardiographic features have been described in tamponade that result from an increase in intrapericardial pressure. These include exaggerated late diastolic right atrial collapse, early diastolic right ventricular collapse, significant respiratory variation in Doppler inflow velocities across the tricuspid and mitral valves, a plethora of the inferior vena cava, exaggerated expiratory flow reversal of the hepatic veins, and blunted diastolic flow of the inferior vena cava (IVC) during expiration.[30] Because the right-sided cardiac chambers are more compliant, thin walled, and at relatively low pressure, the increase in intrapericardial pressure results in the collapse of these chambers first.

Immediately after atrial contraction, the right atrial volume is at its lowest, whereas right ventricular volume is at its maximum; total pericardial volume in cardiac tamponade is relatively fixed. The increase in ventricular filling during diastole increases pericardial pressure, which prevents expansion of the right atrium during atrial relaxation (late ventricular diastole).[31] Persistence of right atrial collapse for more than one third of the cardiac cycle is a useful marker for early tamponade physiology. This phenomenon

is best appreciated from the apical or subcostal four-chamber views (see Fig. 8.43 in Chapter 8).

The right ventricle, conversely, is more vulnerable to collapse during early diastole, when its pressure is at its lowest as it expands following closure of the pulmonic valve. The right ventricular outflow tract is the more compressible area of the right ventricle and hence tends to collapse first.[30] With increasing intrapericardial pressure, the collapse extends to the right ventricular free wall, which is best appreciated on parasternal long or short axis views (see Figure 8.44 in Chapter 8). This is a more specific finding for tamponade than right atrial collapse, as the latter can occur in the setting of hypovolemia alone. However, right ventricular diastolic collapse may not be seen in conditions that result in significantly elevated right ventricular diastolic pressure or in right ventricular hypertrophy. Collapse of the higher-pressure left-sided chambers, particularly the left ventricle, is uncommon, but, when seen, is highly specific for tamponade. Collapse of the left atrium is not uncommon in the immediate postcardiac surgery period, frequently a result of loculated effusion causing regional tamponade.[32]

Although cardiac chamber collapse is a highly sensitive marker and typically seen before clinical manifestations of tamponade, a number of other findings are more specific. As discussed previously, pulsus paradoxus results from exaggerated ventricular coupling. The ventricular interdependence (Fig. 24.7) can be appreciated on echocardiography by demonstration of marked respiratory variation of Doppler flow across the atrioventricular or semilunar valves (see also Figs. 8.43 and 8.44 in Chapter 8). During inspiration, the drop in intrathoracic pressure results in increased right ventricular (RV) filling. As right ventricular cavity size increases during diastole, the increased intrapericardial pressure impairs expansion of the right ventricular free wall, and continued RV filling is accomplished only by diastolic expansion of the interventricular septum. The consequent bulging of the interventricular septum into the left ventricular (LV) cavity during diastole results in marked reduction in LV compliance and inspiratory filling.[12,33] These filling changes are reflected in a marked inspiratory increase in tricuspid valve Doppler inflow velocities with simultaneous inspiratory decrease in mitral valve inflow velocities.

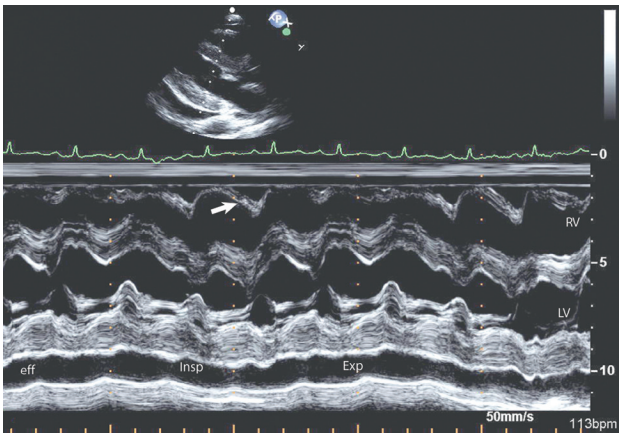

Figure 24.7 Classic findings for ventricular interdependence in cardiac tamponade. See the legend for Figure 8.45 in Chapter 8.

Reciprocal changes are noted during expiration. A corollary to these respiratory changes is noted in the hepatic vein and vena cava flow patterns. Normal vena cava flow into right atrium occurs during both ventricular systole and diastole. In tamponade, already impaired diastolic flow is further compromised in expiration by the exaggerated ventricular interdependence. This hemodynamic effect manifests on Doppler as blunted diastolic caval flow during expiration with increased expiratory flow reversal in the Doppler flow pattern of hepatic veins[34] (Fig. 24.8). Although it is expected that in tamponade the IVC will be dilated and nonreactive,[35] a plethora of the IVC can be seen in any condition causing elevation of right atrial pressure, including positive pressure ventilation in an intubated patient.

Portable echocardiography, performed at the bedside, in the emergency room, or in critical care units, is highly reliable in cardiac tamponade.[36,37] However, adequate training in basic technique and fundamental anatomy is essential to avoid misdiagnosis. Epicardial fat can be confused with effusion,[38] and isolated or coexistent pleural effusions, mediastinal masses, and atelectasis can confound the diagnosis as well.[39] It is important to assess the heart from as many echo windows as possible for small but opportunistic loculated accumulations of fluid, for the presence of clot, fibrinous "strandlike" material or masses, and for compression from processes outside the pericardium, such as a mediastinal hematoma and pleural effusion, all of which will significantly impact management.

X-RAY STUDIES

The classic "water bottle" configuration of the heart is due to a large pericardial effusion and therefore occurs only if the pressure-volume curve has altered sufficiently through chronic accumulation to allow significant increase in pericardial volume. It is a misconception that a normal-sized heart excludes tamponade; in acute tamponade the heart size can be expected to appear normal or minimally enlarged.[12] With marked enlargement of the cardiac silhouette, the finding is nonspecific and not readily distinguishable from cardiomegaly, although in tamponade pulmonary vascular congestion is usually not seen, whereas prominence of the vena cava may be noted. Other modalities such as computed tomography (CT) scanning and magnetic resonance imaging (MRI) show large effusions and can demonstrate chamber collapse. In addition, characterization of pericardial thickness and of the pericardial fluid to differentiate between blood and fluid of different densities can be useful. Although CT and MRI show primarily anatomy rather than physiology, they can identify chamber collapse, characterize soft tissue, and demonstrate reflux into the azygous vein, a useful sign of tamponade.[40] CT scanning can provide information supplemental to that seen on echocardiography, including identification of extracardiac disease lesions,[41] and can provide additional sensitivity for the detection of loculated effusions.[42] Coronary sinus compression on CT is an early and specific indicator of tamponade.[43]

ELECTROCARDIOGRAPHY

The classic electrocardiographic features include low voltage, a result of poor transmission of electrical activity

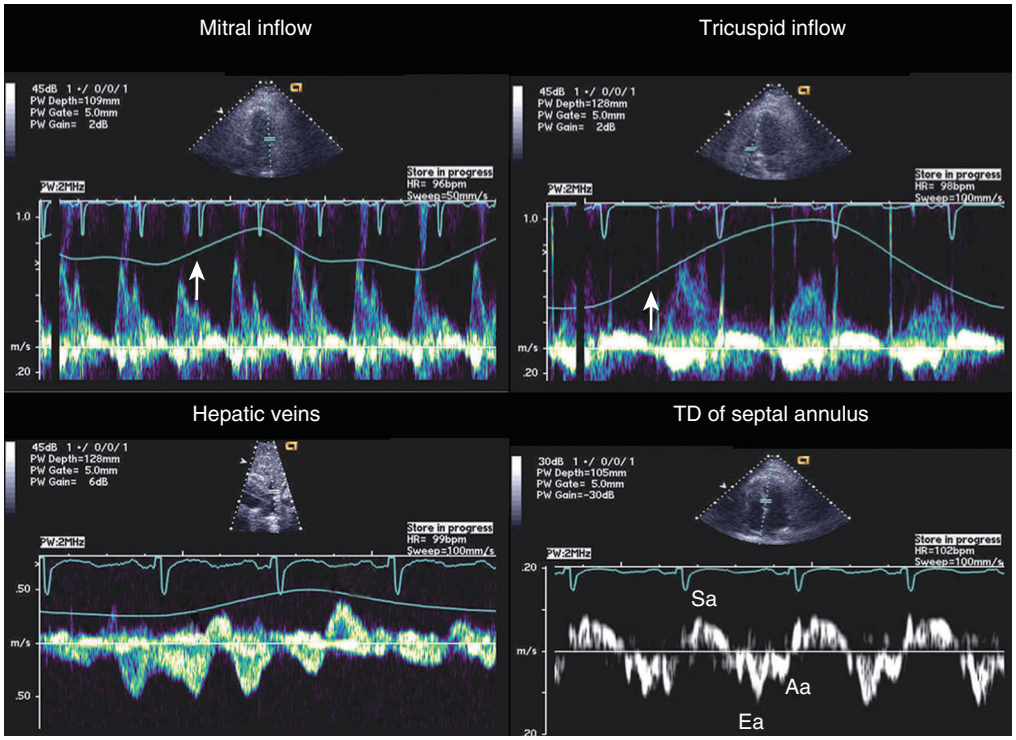

Figure 24.8 Pulsed Doppler signal of hepatic vein showing reduced forward flow *(arrows)* and increased diastolic flow reversal during expiration (E) in tamponade. I, inspiration.

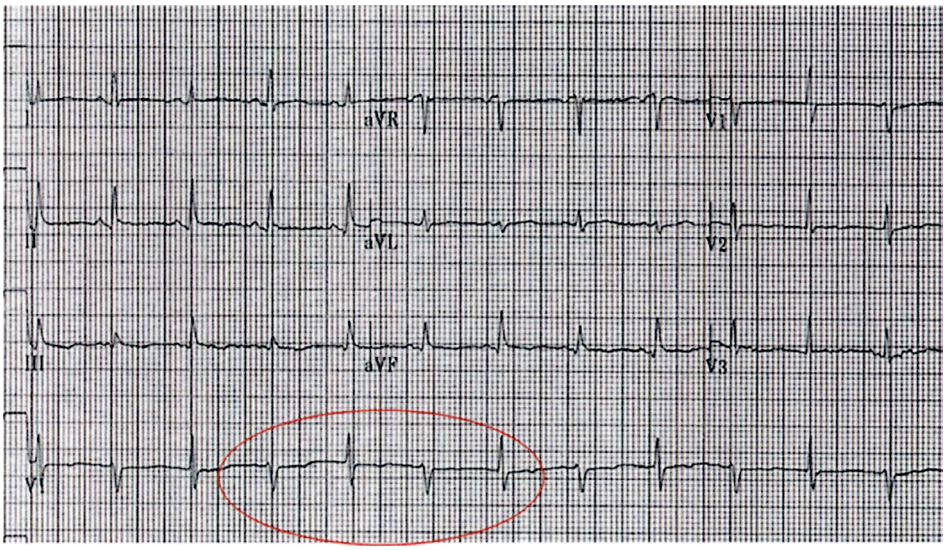

Figure 24.9 Electrocardiogram demonstrating classic electrical alternans in a patient with pericardial tamponade. Note the change in amplitude of the R wave in lead V1 *(red oval).* Similar findings are seen throughout the limb and precordial leads shown.

across the fluid in the pericardial space, and electrical alternans, an insensitive but relatively specific finding for tamponade generated by swinging of the heart in the fluid-filled chamber (Fig. 24.9). Electrical alternans typically is seen only with large effusions in the later stages of tamponade, although the finding is related more to fluid volume and the ability of the heart to swing within the pericardial space. It may involve alternans of both QRS complexes and P waves. Thus, tamponade with adhesions (Fig. 24.10), loculation, or masses that restrict heart motion may not manifest the alternans phenomenon.

OVERALL ASSESSMENT

In general, the severity of tamponade can be judged by the extent of hypotension, tachycardia, and pulsus paradoxus on physical examination and confirmed by findings on echocardiography.[44] Mild tamponade features no hypotension or tachycardia, and no pulsus, with mild RV collapse by echo. Patients with moderate tamponade have preservation of systemic pressure, but have tachycardia, some degree of pulsus paradoxus, and clear RV collapse on echo. Severe

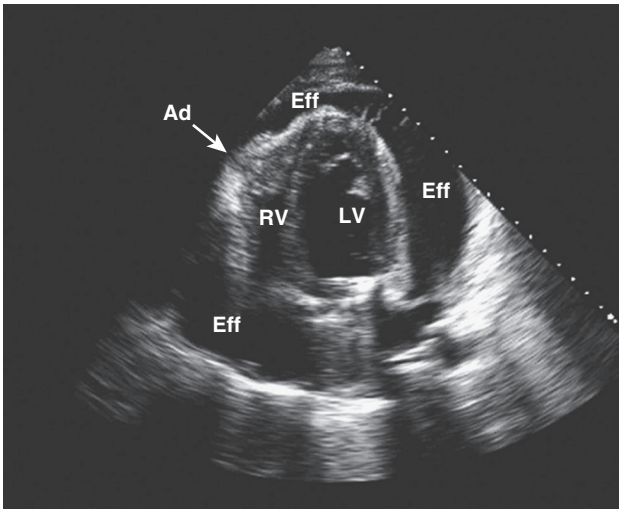

Figure 24.10 Echocardiogram showing pericardial tamponade with right-sided collapse, adhesion of the right ventricle to the pericardium *(arrow),* and fibrous strands of early adhesions seen at the 1 o'clock position near the apex of the left ventricle. Even if the effusion accumulates further, electrical alternans would be less likely because of lack of mobility of the heart. Ad, adhesion; Eff, effusion; LV, left ventricle; RV, right ventricle.

tamponade is associated with tachycardia, shock, profound pulsus paradoxus, and chamber collapse with a swinging heart on ultrasound.[21] Hemodynamic findings correlate with increasing pericardial pressure at each stage of tamponade,[45] initially less than right atrial or pulmonary wedge pressure, then equilibrating with right but less than left atrial pressure, and in severe tamponade equilibrating with both.

SPECIAL SYNDROMES IN TAMPONADE

Although most cases of tamponade have at least some of the classic features, there are several important variants. Loculated effusions that compress the heart primarily in one region are typically postsurgical, although they may be due to neoplasms or a number of other etiologies; they are discussed in the section on postcardiac surgery cases that follows. There are also a number of conditions where pulsus paradoxus does not occur or is masked, summarized in Box 24.1.

EFFUSIVE CONSTRICTIVE DISEASE

This phenomenon is an important-to-recognize condition occurring in less than 10% of patients with tamponade,[46] but up to 40% in some series. Hospitals with disproportionately high populations of oncology patients, because of tumor metastases or postradiation pericardial involvement, or tuberculosis, will have a higher percentage of tamponade patients with this diagnosis. The syndrome can occur after acute pericarditis of multiple etiologies and may even be transient.[47] The classic features of tamponade are seen on presentation, and a history of malignancy should increase the suspicion of prepericardiocentesis.

Effusive constrictive disease is a setting in which careful hemodynamic monitoring is very helpful for accurate diagnosis. Monitoring of intrapericardial and right atrial or wedge pressure during pericardiocentesis demonstrates findings as seen in Figure 24.11. In general, with relief of tamponade intrapericardial hypertension resolves, and classic respiratory variation is seen in most patients, whereas right atrial pressure remains elevated though lower than prior to the pericardiocentesis. The Y descent becomes prominent because of the elimination of high transmural pressures that restrict filling during early diastole in tamponade, unmasking classic constrictive physiology. Figure 24.12 shows echocardiographic images in a typical patient with this syndrome.

LOW- AND HIGH-PRESSURE TAMPONADE

Low-pressure tamponade has been defined as featuring hypotension secondary to pericardial effusion but with low venous and intrapericardial pressures, most commonly in the setting of hypovolemia resulting from dehydration or blood loss. A more formal definition, based on a single site experience, was described by Sagrista-Sauleda and colleagues[48] as an intrapericardial pressure less than 7 mm Hg, with a post-pericardiocentesis right atrial pressure less than 4 mm Hg and equalization of intrapericardial and right atrial pressures before pericardiocentesis. Importantly, 20% of their patients with cardiac tamponade met these criteria (and 10% of their patients with large pericardial effusions), suggesting that low-pressure tamponade, previously the subject primarily of case reports and small series, may be more common than previously appreciated. Because of low pressures, there is a lack of features such as pulsus paradoxus or jugular venous distention, with only 24% demonstrating these classic findings, making the diagnosis significantly more difficult. Fluid challenge may result in more typical findings.

Patients with chronic hypertension in whom tamponade develops occasionally have high blood pressure despite tamponade physiology, presumably because of an exaggerated systemic pressure response to the catecholamine storm associated with tamponade.[49] In this setting, injudicious use of the usual medications to lower blood pressure can result in profound hemodynamic compromise.

SETTINGS IN WHICH TAMPONADE IS SEEN

THE EMERGENCY ROOM

The primary cause of tamponade in the emergency room relates to hemopericardium, although the complete range of medical etiologies can be seen in this setting. Trauma[50] includes gunshot and stab wounds, as well as penetrating and crush wounds to the chest, including those related to automobile accidents. Penetrating wounds are significantly more likely to result in tamponade than crush injuries.[51] Medical presentations with acute hemopericardium include aortic dissection with tamponade, postmyocardial infarction rupture, or leaking thoracic aneurysm, situations in which pericardiocentesis may lead to further hemodynamic

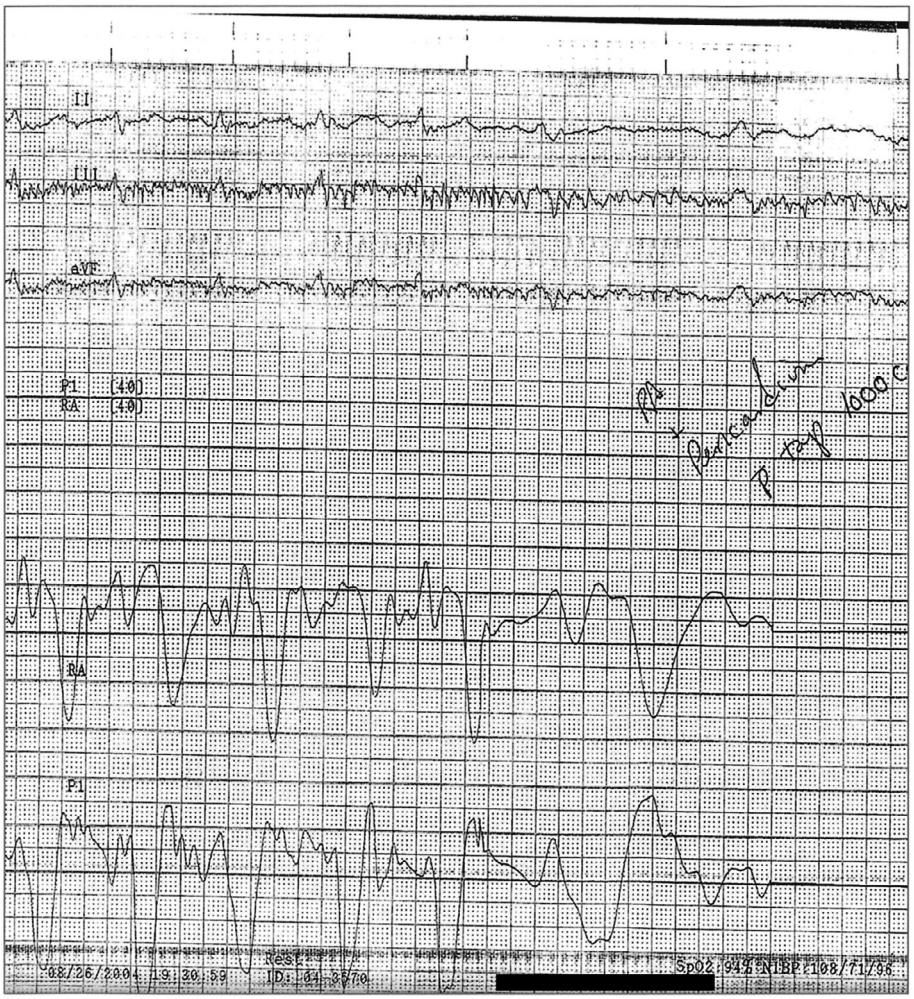

Figure 24.11 Hemodynamic tracings (40–mm Hg scale) obtained 1 hour after those seen in Figure 24.5. After pericardiocentesis of 1 L of fluid, the pericardial pressure has achieved a mean equivalent to atmospheric pressure (0 mm Hg by convention), while right atrial pressure remains elevated near 22 mm Hg. This is physiology consistent with effusive-constrictive disease. On removal of the effusion, the hemodynamics, including the newly seen steep Y descent, are classic for constriction. This patient had a malignant pericardial effusion. P, intrapericardial pressure; RA, right atrium.

decompensation,[52,53] as well as hemopericardium secondary to overanticoagulation. In general, acute hemopericardium may be associated with continued hemorrhage as well as clot in the pericardium; the latter makes complete drainage difficult. Clot alone can compress the heart and cause tamponade-like physiology. The clinical presentation of acute intrapericardial hemorrhage is typically shock, and jugular venous distention may or may not be present because of venoconstriction and hypovolemia as previously described. Use of echocardiography in the emergency room in patients with unexplained dyspnea is an important diagnostic tool.[54]

THE CARDIAC CATHETERIZATION AND ELECTROPHYSIOLOGY LABORATORIES

Perforation of the heart, including coronary arteries and cardiac chambers, during invasive cardiac procedures has become an increasingly important cause of pericardial tamponade.[55] Common scenarios include electrophysiology procedures, where relatively stiff catheters are placed in the relatively thin-walled structures of the right heart, including the right atrium, right ventricle, and the coronary venous system including the coronary sinus. Anticoagulation, when required for electrophysiology procedures, such as those involving left atrial ablation, raises the risk substantially. Perforation of coronary arteries occurs in particular with atheroablation devices such as those used for rotational atherectomy, directional atherectomy and lasers, with guidewires used in chronic total occlusions or injudiciously manipulated distal to the target lesion, and with oversized balloons and stents.[56] Even with normal sizing, settings such as myocardial bridges or ruptured balloons are associated with vessel perforation or rupture. A third setting is transseptal puncture, a resurgent technique because of burgeoning technologies requiring left atrial access[57] but associated with a significant risk of tamponade.[58] Besides left-sided ablations, mitral valvuloplasties, and percutaneous circulatory bypass (with its intake source in the left atrium), transseptal puncture is required for a number of techniques under development, including left atrial appendage occlusion and percutaneous mitral valve repair. The risk of pericardial effusion and tamponade with these interventions

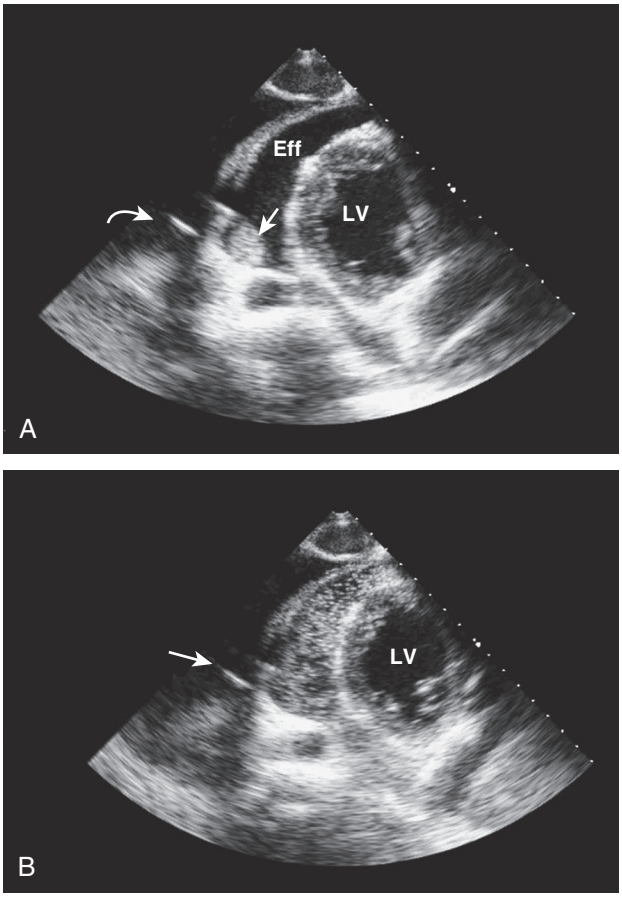

Figure 24.12 Echocardiographic images from a patient with effusive-constrictive disease. **A,** Tamponade. *Curved arrow* points to needle in pericardial space; *straight arrow* points to tumor mass. The pericardium is thickened. **B,** Agitated saline has been injected through the needle *(arrow)* to confirm entry into the pericardial space. Eff, effusion; LV, left ventricle.

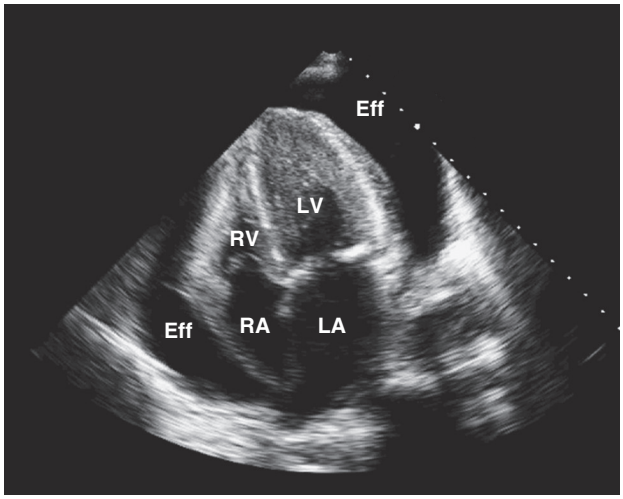

Figure 24.13 Echocardiogram showing large circumferential pericardial effusion in myxedema. Severe tamponade is rare. Eff, effusion; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

contributes significantly to their overall morbidity and mortality.[55] However, and somewhat counterintuitively, electrophysiologists now frequently anticoagulate prior to transseptal puncture or perform the procedure in patients already on full oral anticoagulation.[59] This practice is driven by fear of thromboembolism rather than tamponade, the former an important complication of left-sided ablations in particular, which can be long procedures, and associated with clot inducing char formation. Other endovascular procedures associated with tamponade include myocardial biopsy and central venous line placement, pacemaker lead extraction, as well as erosion of devices implanted across the atrial septum or in the left atrial appendage.[60]

The potentially catastrophic setting of free perforation during coronary interventions is usually readily diagnosable during the procedure, with free flow in the pericardium seen during coronary injection, sometimes before the patient shows any signs of hemodynamic deterioration. This is readily treatable with balloon occlusion of the coronary artery at the perforation site, pericardiocentesis if necessary, and excluding the fenestration with a covered stent. However, lower-grade perforations that result in pooling of contrast or small adventitial craters can be more subtle. It is essential to discontinue anticoagulation on such patients and consider heparin reversal, and to ensure that personnel responsible for postprocedure management monitor the patient closely for hypotension and tachycardia. With transseptal punctures, hypotension at any time during the case, but especially after anticoagulation is administered, should raise the possibility of tamponade. A quick and relatively specific finding in the catheterization laboratory is straightening and lack of motion of the left heart border on anteroposterior fluoroscopy associated with hypotension (and sometimes reflex bradycardia); rapid intervention is essential in these patients. Hypotension after the procedure should raise the possibility that left atrial access involved a "stitch perforation" whereby the needle exited the right atrium and then entered the left atrium through the pericardial space; this mishap is possible with low punctures and frequently manifests only when catheters are removed from the fenestration at the end of the procedure. In patients who have had pacemaker placement, tamponade can develop acutely or after considerable delay as in the case of lead erosion.[61]

CRITICAL CARE UNITS AND MEDICAL WARDS

Tamponade in the critical care unit typically is due to complications of myocardial infarction, concomitant sepsis with purulent pericarditis, or hemorrhage into the pericardium because of anticoagulation (either iatrogenic or endogenous) or, most commonly, is secondary to neoplasms. In myocardial infarction, tamponade can be acute, secondary to massive or limited rupture, or somewhat more insidious in onset as part of Dressler's syndrome, with hemodynamic compromise sometimes exacerbated by anticoagulation. Tamponade also can be iatrogenic, in particular, secondary to placement of various lines through the venous or arterial circulation. Uncommon causes of tamponade, even with pericardial effusions of sometimes significant size, are viral pericarditis, congestive heart failure, uremia, myxedema (Fig. 24.13), and connective tissue disorders.

In patients with malignancy, several possible causes of tamponade are seen, including tumor involvement in the pericardium, postradiation pericarditis, graft-versus-host disease, and direct or indirect complications of therapy.[62] Patients with malignancies also are at increased risk for infectious pericarditis, coagulopathies or thrombocytopenia with secondary hemorrhage, and hypothyroid- and hypoalbuminemia-related effusions. AIDS and other immunosuppressed patients similarly are predisposed to infectious tamponade, as well as pericardial tumor involvement, including that from lymphoma. The mechanisms of pericardial effusion in cancer are varied but include direct spread to the pericardium from primary tumors such as lung, mediastinal, and esophageal cancer; hematogenous spread such as with lymphomas; and obstruction of the lymphatic drainage of the heart by tumors in the mediastinum.

Tamponade after cardiac surgery is an important phenomenon, usually occurring as a result of hemorrhagic effusion. Early postoperative tamponade is not uncommon and is important to recognize as a cause of hypotension because it has been reported to occur with a frequency of 5% to 10%, although this generally is thought to be in the 1% range in the modern era.[63] Moderate to large pericardial effusions that do not cause hemodynamic compromise have been much more common.[64] Delayed tamponade after heart surgery, with onset on average at 2 to 3 weeks postoperatively but as late as 6 months or more, occurs in less than 1% of patients but is disproportionately more common in patients undergoing valve surgery, probably related to postoperative anticoagulation in this cohort.[65,66] Delayed tamponade probably is a variant of the more common postcardiotomy syndrome.

Late tamponade typically is due to loculated effusion resulting from formation of adhesions (see Figs. 24.6 and 24.10) during recovery from surgery. Such adhesions can cause decreased cardiac output if they compress the left side of the heart, and in some cases pulmonary edema occurs if obstruction to inflow results. A variety of clinical problems related to increased right-sided heart pressure occur when tamponade involves the right side, including a clinical picture that resembles superior vena cava syndrome; several case reports have described right-to-left shunting across a patent foramen ovale as well.[67] Pericardiectomy to prevent postoperative tamponade has an uncertain risk-benefit ratio but does appear to decrease the incidence of hemodynamic compromise.[68]

Patients on dialysis present a special diagnostic and management problem. With underdialysis, volume overload can exacerbate chronic fluid accumulation in the pericardial space. Hypotension during or after dialysis may be secondary to inadequate intravascular volume and diminished venous pressure and needs to be avoided as well.

MANAGEMENT

Pericardial tamponade is life threatening, requiring difficult diagnostic and, in particular, management decisions. When hemodynamics do not suggest significant compromise and effusion is small to moderate in volume, intervention frequently is not necessary and may involve increased risk to the patient, whereas late intervention may be fatal. Typically, the risk associated with pericardiocentesis is inversely related to the volume of accumulated fluid and also is related to the location of the effusion. Thus, relatively small effusions, early in the course of tamponade, usually are located primarily posteriorly because of gravity-dependent accumulation. Waiting until the effusion is large and occupies significant volume anteriorly decreases the risk of percutaneous drainage but increases the possibility of decompensation and death before intervention. Frequent monitoring of hemodynamics and the application of sound clinical judgment are essential, but an optimal algorithm does not exist. Comorbid conditions such as endogenous or extrinsic anticoagulation may substantially confound the situation.[69] The clinical decision to drain the effusion percutaneously or to send the patient for thoracotomy will be a function of the clinician's assessment of risk of the former versus the potential advantages of surgery in obtaining pericardial tissue and providing a pericardial window as well. If the percutaneous approach is chosen, performing pericardiocentesis in the cardiac catheterization laboratory has significant advantages. However, the benefit of positioning the pericardial effusion anteriorly, for increased safety during needle entry into the pericardial space, requires that the patient's chest be elevated during the procedure, which typically can be accomplished only to a 20- or 30-degree angle on most catheterization tables because of the image intensifier unless the table has tilt capabilities. A moribund patient frequently needs pericardiocentesis performed at the bedside without fluoroscopic guidance, sometimes without adequate hemodynamic monitoring, and at times without echocardiographic monitoring—all of which are associated with increased risk of failed pericardiocentesis and adverse cardiac events. Patients with severe tamponade are often anxious and hypoxic; sedation is hazardous as is intubation, though the latter is at times necessary. As a result of associated positive intrathoracic pressure, intubation may cause abrupt hemodynamic deterioration because it decreases venous return to the heart.[2] Cardiopulmonary resuscitation using chest compression is unlikely to be effective; immediate pericardiocentesis or thoracotomy are ordinarily the only possibilities for survival. Further discussion of percutaneous interventions for tamponade can be found in Chapter 6.

Little in the way of medical treatment is clearly therapeutic for tamponade. Volume expansion in relatively acute tamponade will support right-sided filling in patients with low circulatory volumes, such as are seen in trauma.[70] Patients with chronic tamponade typically have considerable fluid retention, and additional hydration is unlikely to be of benefit. Pressors may be modestly helpful, but for patients with preserved cardiac function, catecholaminergic drugs provide only modest augmentation of cardiac output; patients with hemodynamically important tamponade are usually already maximally catecholamine stimulated. Vasodilator therapy is less clearly beneficial, and drugs that decrease preload, such as nitrates and nitroprusside, should be avoided if the patient is hypotensive. Reversal of anticoagulation is essential, both to stop bleeding into the pericardial space and to decrease the risk of trauma to the heart or major blood vessels during pericardiocentesis (e.g., coronary arteries, hepatic vessels). The introduction of direct thrombin inhibitors may affect this portion of the

management algorithm because they are not reversible with vitamin K, and there are anecdotal reports of tamponade occurring after the introduction of oral versions of these agents[71] as well as failed pericardiocentesis during percutaneous coronary intervention associated with bivalirudin administration.[72] Antibiotic therapy in the setting of purulent pericarditis and tamponade is not expected to acutely relieve hemodynamic decompensation in most settings; postdrainage treatment, including local infusion of drugs, is discussed in Chapter 6. A targeted approach for patients with malignant pericardial disease includes the use of sclerosing agents combined with antineoplastic drugs infused into the pericardial space, sometimes combined with radiation; a variety of such management strategies continue to be applicable for some cancer patients.[73] Leaving an indwelling drain is controversial because of the associated risk of infection, although there is some evidence that it can decrease the risk of recurrent tamponade.[74] An excellent review of the clinical approach to pericardial disease in general has been published by the European Society of Cardiology.[75]

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KEY POINTS

- Pericardial tamponade represents a continuum, ranging from effusions associated with little or no hemodynamic compromise to hemodynamic collapse.
- The primary physiologic feature of tamponade is impairment of cardiac chamber filling due to high intrapericardial pressure, with a resultant decrease in cardiac output.
- Acute tamponade occurs after a relatively limited accumulation of fluid in the setting of a nondistensible pericardium.
- Chronic tamponade may involve a pericardial effusion of 1 L or more; because hemodynamic decompensation occurs in the steep part of the pressure-volume curve, accumulation of a small amount of additional fluid can result in substantial hemodynamic deterioration.
- Pulsus paradoxus is seen in a variety of conditions besides cardiac tamponade and is absent despite tamponade in a number of settings. A large pericardial effusion and right ventricular collapse, a 10 to 20 mm Hg or larger decrease in systolic pressure with inspiration, and a significant decline in pulse pressure combined are specific for tamponade.
- Right atrial pressure, except in settings such as hypovolemia, usually is significantly elevated, but jugular venous distention may not be seen with acute tamponade.
- Despite markedly elevated right and left atrial pressures, pulmonary vascular congestion usually is not seen.
- Persistent high right atrial pressure after fluid drainage suggests effusive-constrictive disease, most commonly associated with malignancy but also seen with infection and acute pericarditis.
- Management of pericardial tamponade involves determining the optimal timing and method of intervention. Fluid and drug therapy constitute modest adjunctive care only.

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