Section 2 Shock and Cardiac Arrest

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APPRAOCH TO THE PATIENT WITH SHOCK

Renauld V. Maier

Shock is the clinical syndrome that results from inadequate tissue perfusion. Irrespective of cause, the hypoperfusion-induced imbalance between the delivery of and requirements for oxygen and substrate leads to cellular dysfunction. The cellular injury created by the inadequate delivery of oxygen and substrates also induces the production and release of inflammatory mediators that further compromise perfusion through functional and structural changes within the microvasculature. This leads to a vicious cycle in which impaired perfusion is responsible for cellular injury which causes maldistribution of blood flow, further compromising cellular perfusion; the latter causes multiple organ failure and, if the process is not interrupted, leads to the death of the patient. The clinical manifestations of shock are the result, in part, of sympathetic neuroendocrine responses to hypoperfusion as well as the breakdown in organ function induced by severe cellular dysfunction. When very severe and/or persistent, inadequate oxygen delivery leads to irreversible cell injury; thus, only rapid restoration of oxygen delivery can reverse the progression of the shock state. The fundamental approach to management, therefore, is to recognize overt and impending shock in a timely fashion and to intervene emergently to restore perfusion. This requires the expansion or reexpansion of blood volume. Control of any inciting pathologic process, e.g., continued hemorhage, impairment of cardiac function, or infection, must occur simultaneously.

Clinical shock is usually accompanied by hypotension, i.e., a mean arterial pressure <60 mmHg in previously normotensive persons. Multiple classification schemes have been developed in an attempt to synthesize the seemingly dissimilar processes leading to shock. Strict adherence to a classification scheme may be difficult from a clinical standpoint because of the frequent combination of two or more causes of shock in any individual patient, but the classification shown in Table 253-1 provides a useful reference point from which to discuss and further delineate the underlying processes.

PATHOGENESIS AND ORGAN RESPONSE

MICROCIRCULATION Normally when cardiac output falls, systemic vascular resistance rises to maintain a level of systemic pressure that is adequate for perfusion of the heart and brain at the expense of other tissues such as muscle, skin, and especially the gastrointestinal tract. Systemic vascular resistance is determined primarily by the luminal diameter of arterioles. The metabolic rates of the heart and brain are high, and their stores of energy substrate are low. These organs are critically dependent on a continuous supply of oxygen and nutrients, and neither tolerates severe ischemia for more than brief periods. Autoregulation, i.e., the maintenance of blood flow over a wide range of perfusion pressures, is critical in sustaining cerebral and coronary perfusion despite significant hypotension. However, when mean arterial pressure drops to ≤60 mmHg, flow to these organs falls and their function deteriorates.

A3. Vascular smooth muscle has both α- and β-adrenergic receptors. The α receptors mediate vasoconstriction, while the β receptors mediate vasodilation. Efficient sympathetic fibers release nor- epinephrine, which acts primarily on α receptors in one of the most fundamental compensatory responses to reduced perfusion pressure. Other constrictor substances that are increased in most forms of shock include angiotensin II, vasopressin, endothelin-1, and thrombosan A3. Both noradrenaline and epinephrine are released by the adrenal medulla, and the concentrations of these catecholamines in the bloodstream rise. Circulating vasoconstrictors in shock include prostaglandin (prostaglandin (PGF2)), nitric oxide (NO), and, importantly, products of local metabolism such as adenosine. The breakdown in organ function induced by severe cellular dysfunction is central to the pathophysiologic responses in the late stages of all forms of shock, results in the derangement of cellular metabolism, which is ultimately responsible for organ failure.

TABLE 253-1 Classification of Shock

<table>
<thead>
<tr>
<th>Hypovolemic</th>
<th>Septic</th>
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<tr>
<td>Traumatic</td>
<td>Hyperdynamic</td>
</tr>
<tr>
<td>Cardiogenic</td>
<td>Hypodynamic</td>
</tr>
<tr>
<td>Immune</td>
<td>Neurogenic</td>
</tr>
<tr>
<td>Compressive</td>
<td>Hypothetical</td>
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Transport to cells depends on microcirculatory flow; capillary permeability; the diffusion of oxygen, carbon dioxide, nutrients, and products of metabolism through the interstitium; and the exchange of these products across cell membranes. Impairment of the microcirculation, which is central to the pathophysiologic responses in the late stages of all forms of shock, results in the derangement of cellular metabolism, which is ultimately responsible for organ failure.

The endogenous response to mild or moderate hypovolemia is an attempt at restitution of intravascular volume through alterations in hydrostatic pressure and osmolality. Constriction of arterioles leads to reductions in both the capillary hydrostatic pressure and the number of capillary beds perfused, thereby limiting the capillary surface area across which filtration occurs. When filtration is reduced while intravascular oncotic pressure remains constant or rises, there is net reabsorption of fluid into the vascular bed, in accord with Starling’s law of capillary-venous liquid exchange (Chap. 29). Metabolic changes (including hyperglycemia and elevations in the products of glycolysis, lipolysis, and proteolysis) raise extracellular somedity, leading to an osmotic gradient between cells and interstitium that increases interstitial and intravascular volume at the expense of intravascular volume. Cellular responses Interstitial transport of nutrients is impaired, leading to a decline in intracellular high-energy phosphate stores. Mitochondrial dysfunction and uncoupling of oxidative phosphorylation are the most likely causes for decreased amounts of ATP. As a consequence, there is an accumulation of hydrogen ions, lactate, and other products of anaerobic metabolism. As shock progresses, these vaso- dilator metabolites override vasomotor tone, causing further hypotension and hypoperfusion. Dysfunction of cell membranes is thought to represent a common end-stage pathophysiologic pathway in the various forms of shock. Normal cellular transmembrane potential falls,
and there is an associated increase in intracellular sodium and water, leading to cell swelling, which interferes further with microvascular perfusion.

**NEUROENDOCRINE RESPONSE** Hypovolemia, hypotension, and hypoxia are sensed by baroreceptors and chemoreceptors, which contribute to the maintenance of central organ perfusion, while reduced vagal activity increases the heart rate and cardiac output. The effects of circulating epinephrine released by the adrenal medulla in shock are largely metabolic, causing increased glycogenolysis and gluconeogenesis and reduced pancreatic insulin release. Epinephrine also inhibits production and release of inflammatory mediators through stimulation of β-adrenergic receptors on immune cells.

Severe pain and other severe stress causes the hypothalamic release of adrenocorticotrophic hormone (ACTH). This stimulates cortisol secretion, which contributes to decreased peripheral uptake of glucose and amino acids, enhances lipolysis, and increases gluconeogenesis. Increased pancreatic secretion of glucagon during stress accelerates hepatic gluconeogenesis and further elevates blood glucose concentration. These hormonal actions act synergistically in the maintenance of blood volume. Many critically ill patients exhibit low plasma cortisol levels and an impaired response to ACTH stimulation. The importance of the cortisol response to stress is illustrated by the profound circulatory collapse that occurs in hypoadrenal patients (see below).

Renin release is increased in response to adrenergic discharge and reduced perfusion of the juxtaglomerular apparatus in the kidney. Renin induces the formation of angiotensin I, which is then converted to angiotensin II, an extremely potent vasoconstrictor and stimulator of aldosterone release by the adrenal cortex and of vasopressin by the posterior pituitary. Aldosterone contributes to the maintenance of intravascular volume by enhancing renal tubular reabsorption of sodium, resulting in the excretion of a low-volume, concentrated, sodium-free urine. Renin acts on vascular smooth muscle, contributing to vasoconstriction, and acts on the distal renal tubules to enhance water reabsorption.

**CARDIOVASCULAR RESPONSE** Three variables—ventricular filling (preload), the resistance to ventricular ejection (afterload), and myocardial contractility—are paramount in controlling stroke volume (Chap. 215). Cardiac output, the major determinant of tissue perfusion, is the product of stroke volume and heart rate. Hypovolemia leads to decreased ventricular preload, which in turn reduces the stroke volume. An increase in heart rate is a useful but limited compensatory mechanism to maintain cardiac output. A shock-induced reduction in myo-cardial compliance is frequent, reducing ventricular end-diastolic volume and hence stroke volume at any given ventricular filling pressure. Restoration of intravascular volume returns stroke volume to normal but only at elevated filling pressures. In addition, sepsis, ischemia, myocardial infarction, severe tissue trauma, hypothermia, general anesthesia, prolonged hypotension, and acidemia may all impair myocardial contractility and also reduce the stroke volume at any given ventricular end-diastolic volume. The resistance to ventricular ejection is significantly influenced by the systemic vascular resistance, which is elevated in most forms of shock. However, resistance is depressed in the early hyperdynamic stage of septic shock (see below), thereby allowing the cardiac output to be maintained or elevated.

The venous system contains nearly two-thirds of the total circulat-ing blood volume, most in the small veins, and serves as a dynamic reservoir for autoregulation of blood flow. Active vasoconstriction as a consequence of sympathetic activity is an important compensatory mechanism for the maintenance of venous return and therefore of ventricular filling. On the other hand, venous dilatation, as occurs in neurogenic shock, reduces ventricular filling and hence stroke vol-ume and cardiac output (see below).

**POULMONARY RESPONSE** The response of the pulmonary vascular bed to shock parallels that of the systemic vascular bed, and the relative increase in pulmonary vascular resistance, particularly in septic shock, may exceed that of the systemic vascular resistance. Shock-induced tachycardia reduces tidal volume and increases both dead space and minute ventilation. Relative hypoxia and the subsequent tachycardia induce a respiratory alkalosis. Recumbency and involuntary restriction of ventilation secondary to pain reduce functional residual capacity and may lead to atelectasis. Shock is recognized as a major cause of acute lung injury and subsequent acute respiratory distress syndrome (ARDS; Chap. 251). These disorders are characterized by noncardiogenic pulmonary edema secondary to diffuse pulmonary capillary endothelial and alveolar epithelial injury, hypoxia, and bilateral diffuse pulmonary infiltrates. Hypoxemia results from perfusion of underventilated and nonventilated alveoli. Loss of surfactant and lung volume in combination with increased interstitial and alveolar edema reduce lung compliance. The work of breathing and the oxygen re-quirements of respiratory muscles increase.

**RENAL RESPONSE** Acute renal failure (Chap. 260), a serious complication of shock and hyperperfusion, occurs less frequently than here-tofore because of early aggressive volume repletion. Acute tubular necrosis is now more frequently seen as a result of the interactions of shock, sepsis, the administration of nephrotoxic agents (such as amino-glycosides and aminoglycosic contrast media), and rhabdomyolysis; the latter may be particularly severe in skeletal muscle trauma. The physiologic response of the kidney to hyperperfusion is to conserve salt and water. In addition to decreased renal blood flow, increased afferent arteriolar resistance accounts for diminished glomerular filtration rate, which together with increased aldosterone and vasopressin is responsible for reduced urine formation. Toxic injury causes necro-sis of tubular epithelium and tubular obstruction by cellular debris with a leak of filtrate. The depletion of stored vasopressin with prolonged renal hypoperfusion contributes to subsequent impair-ment of renal function. There is no convincing evidence that low-dose dopamine protects against acute renal failure.

**METABOLIC DERANGEMENTS** During shock, there is disruption of the normal cycles of carbohydrate, lipid, and protein metabolism. Through the citric acid cycle, alanine in conjunction with lactate (which is con-verted from pyruvate in the periphery in the presence of oxygen depri-vation) enhances the hepatic production of glucose. With reduced availability of oxygen, the breakdowns of glucose to pyruvate and ultimately lactate represent an inefficient cycling of substrate with min-imal net energy production. An elevated plasma lactate/pyruvate ratio is consistent with anerobic metabolism and reflects inadequate tissue perfusion. Decreased clearance of exogenous triglycerides coupled with increased hepatic lipogenesis causes a significant rise in serum triglyceride concentrations. There is increased protein catabolism, a negative nitrogen balance, and, if the process is prolonged, severe muscle wasting.

**INFLAMMATORY RESPONSES** Activation of an extensive network of proinflammatory mediator systems plays a significant role in the progression of shock and contributes importantly to the development of organ in-jury and failure. Multiple humoral mediators are activated during shock and tissue injury. The complement cascade, activated through both the classic and alternate pathways, generates the anaphylatoxins C3a and C5a. Direct complement fixation to injured tissues can progress to the C5- C9 attack complex, causing further cell damage. Activation of the coagulation cascade causes microvascular thrombosis, with subse-quent lysis leading to repeated episodes of ischemia and reperfusion. Components of the coagulation system, such as tissue factor, are potent proinflammatory mediators that cause expression of adhesion mole-cules on endothelial cells and activation of neutrophils, leading to microvascular injury. Coagulation also activates the kallikrein-kininogen cascade, contributing to hypotension.
Eicosanoids are vasoactive and immunomodulatory products of arachidonic acid metabolism that include cyclooxygenase-derived prostaglandins and thromboxane A2 as well as lipoygenase-derived leukotrienes and lipoxins. Thromboxane A2 is a potent vasoconstrictor that contributes to the pulmonary hypertension and acute tubular necrosis of shock. PGD2 and PGE2 are potent vasodilators that enhance capillary permeability and edema formation. The cysteinyl leukotrienes LTC4 and LTD4 are pivotal mediators of the vascular sequelae of anaphylaxis, as well as of shock states resulting from sepsis or tissue injury. LTBr is a potent neutrophil chemotactant and secretagogue that stimulates the formation of reactive oxygen species. Platelet-activating factor, an ether-linked arachidonoyl-containing phospholipid mediator, causes pulmonary vasoconstriction, bronchoconstriction, systemic vasoconstriction, increased capillary permeability, and the priming of macrophages and neutrophils to produce enhanced levels of inflammatory mediators.

Tumor necrosis factor (TNF) α is produced by activated macrophages, reproduces many components of the shock state including hypotension, lactic acidosis, and respiratory failure. Interleukin (IL) 1, produced by tissue-fixed macrophages, is critical to the inflammatory response. Chemokines such as IL-8 are potent neutrophil chemotactants and activators that upregulate adhesion molecules on the neutrophil to enhance aggregation, adherence, and damage to the vascular endothelium. While the endothelium normally produces nitric oxide (NO) that induces vasodilation and inhibits the inducible isoform of NO synthase (iNOS), which is overexpressed and produces toxic NO. Oxygen-derived free radicals which contribute to the hyperdynamic cardiovascular response in sepsis.

Interleukins 1, 6, and 8 are critical to the inflammatory response. Chemokines such as IL-8 are potent neutrophil chemoattractant and secretagogues. LTB4 is a potent neutrophil chemotaxant and secretagogue of anaphylaxis, as well as of shock states resulting from sepsis or tissue injury. LTB4 is a potent neutrophil chemotaxant and secretagogue of anaphylaxis, as well as of shock states resulting from sepsis or tissue injury.

Cardiac output (CO) is measured in liters per minute. Stroke volume (SV) is measured in milliliters per beat. Systemic vascular resistance (SVR) is measured in dynes/cm² second per m². Pulmonary vascular resistance (PVR) is measured in dynes/cm² second per m². Left ventricular stroke work (LVSW) is measured in dynes/cm² second per m². Right ventricular stroke work (RVSW) is measured in dynes/cm² second per m². Venous oxygen saturation (SvO2) is measured in percent.

### Oxygen Transport Calculations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Calculation</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen-carrying capacity of hemoglobin</td>
<td>1.39 mL/L</td>
<td></td>
</tr>
<tr>
<td>Plasma O2 concentration (PaO2)</td>
<td>(SaO2 − 0.031 PaO2) × 1.39 SaO2</td>
<td>90–100 mmHg</td>
</tr>
<tr>
<td>Venous O2 concentration (CvO2)</td>
<td>(SaO2 − 0.031 PaO2) × 1.39 SaO2</td>
<td>70–90 mmHg</td>
</tr>
<tr>
<td>Arterial–venous O2 difference (Ca–CvO2)</td>
<td>(PaO2 − CvO2) × 1.39 SaO2</td>
<td>15–25 mL/dL</td>
</tr>
<tr>
<td>Oxygen delivery (DO2)</td>
<td>(CaO2 − CvO2) × 1.39 SaO2</td>
<td>400–600 mL/min</td>
</tr>
<tr>
<td>Oxygen uptake (VO2)</td>
<td>(CaO2 − CvO2) × 1.39 SaO2</td>
<td>200–400 mL/min</td>
</tr>
<tr>
<td>Oxygen extraction ratio (OER)</td>
<td>(VO2/DO2) × 100</td>
<td>20–30%</td>
</tr>
</tbody>
</table>

### Specific Forms of Shock

#### Hemorrhagic Shock

This most common form of shock results either from the loss of red blood cell mass and plasma from hemorrhage or from the loss of plasma volume alone arising...
from extravascular fluid sequestration or gastrointestinal, urinary, and insensible losses. The signs and symptoms of nonhemorrhagic hypovolemic shock are the same as those of hemorrhagic shock, although they may have a more insidious onset. The normal physiologic response to hypovolemia is to maintain perfusion of the brain and heart while restoring an effective circulating blood volume. There is an increase in sympathetic activity, hyperventilation, collapse of venous capacitance vessels, release of stress hormones, and expansion of intravascular volume through the recruitment of interstitial and intracellular fluid and reduction of urine output.

Mild hypovolemia (<20% of the blood volume) generates mild tachycardia but relatively few external signs, especially in a supine resting young patient (Table 253-5). With moderate hypovolemia (~20 to 40% of the blood volume) the patient becomes increasingly anxious and tachycardic; although normal blood pressure may be maintained in the supine position, there may be significant postural hypotension and tachycardia. If hypovolemia is severe (~>40% of the blood volume), the classic signs of shock appear; the blood pressure declines and becomes unstable even in the supine position, and the patient develops marked tachycardia, oliguria, and agitation or confusion. Perfusion of the central nervous system is well maintained until shock becomes severe. Hence, mental obtundation is an ominous clinical sign. The transition from mild to severe hypovolemic shock can be insidious or extremely rapid. If severe shock is not reversed rapidly, especially in elderly patients and those with comorbid illnesses, death is imminent. A very narrow time frame separates the degradations found in severe shock that can be reversed with aggressive resuscitation from those of progressive decompensation and irreversible cell injury.

Diagnosis Hypovolemic shock is readily diagnosed when there are signs of hemodynamic instability and the source of volume loss is obvious. The diagnosis is more difficult when the source of blood loss is occult, as into the gastrointestinal tract, or when plasma volume alone is depleted. After acute hemorrhage, hemorrhagic and hematocrit values do not change until compensatory fluid shifts have occurred or exogenous fluid is administered. Thus, an initial normal hematocrit does not disprove the presence of significant blood loss. Plasma losses cause hemococoncentration, and free water loss leads to hypotension. These findings should suggest the presence of hypovolemia.

It is essential to distinguish between hypovolemic and cardiogenic shock (see below) because definitive therapy differs significantly. Both forms are associated with a reduced cardiac output and a compensatory sympathetic mediated response characterized by tachycardia and elevated systemic vascular resistance. However, the findings in cardiogenic shock of jugular venous distention, rales, and an S_3 gallop distinguish it from hypovolemic shock and signify that ongoing volume expansion is undesirable.

TREATMENT

Initial resuscitation requires rapid reexpansion of the circulating blood volume along with interventions to control ongoing losses. In accordance with Starling’s law (Chap. 215), stroke volume and cardiac output rise with the increase in preload. After resuscitation, the compliance of the ventricles may remain reduced due to increased interstitial fluid in the myocardium. Therefore, elevated filling pressures are required to maintain adequate ventricular performance.

**TABLE 253-4** Physiologic Characteristics of the Various Forms of Shock

<table>
<thead>
<tr>
<th>Type of Shock</th>
<th>CVP and PCWP</th>
<th>Cardiac Output</th>
<th>Systemic Vascular Resistance</th>
<th>Venous O_2 Saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
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<tr>
<td>Cardiogenic</td>
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<tr>
<td>Septic</td>
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<tr>
<td>Traumatic</td>
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</tr>
<tr>
<td>Neurogenic</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypovolemic</td>
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</tbody>
</table>

Note: CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure.

FIGURE 253-1 An algorithm for the resuscitation of the patient in shock. VS, vital signs; HR, heart rate; SBP, systolic blood pressure; R/R, work up; CVP, central venous pressure; Hct, hematocrit; ECHO, echocardiogram; PAC, pulmonary artery catheter; CI, cardiac index (in liters/min/m^2); PCWP, pulmonary capillary wedge pressure in mmHg.

*Monitor CI, Hct, and PCWP or PCWP on PICU as additional markers of correction for perfusion and hypovolemia. Consider age-adjusted CI; _T_ _a_ and saturation of hemoglobin with O_2 in venous blood; _T_ _a_ O_2, oxygen uptake resistance index, Hct(0.4), right-ventricular end-diastolic volume index.
The initial management of the seriously injured patient requires attention to the “ABCS” of resuscitation: assurance of an airway (A), adequate ventilation (B), and establishment of an adequate blood volume to support the circulation (C). Control of hemorrhage requires immediate attention. Early stabilization of fractures, debridement of devitalized or contaminated tissues, and evacuation of hematoma all reduce the subsequent inflammatory response to the initial insult and minimize subsequent organ injury. Supplementation of depleted endogenous antioxidants also reduces subsequent organ failure and mortality.

**Intrinsically Cardiogenic Shock**

This form of shock is caused by failure, often sudden, of the heart as an effective pump. It occurs most commonly as a complication of acute myocardial infarction (AMI, Chaps. 228 and 255), but it may also be seen in patients with severe bradycardia or tachyarrhythmias, valvular heart disease, significant cardiac conduction system dysfunction, or in the terminal stage of chronic heart failure. Other causes include ischemic heart disease and dilated cardiomyopathy. Cardiogenic shock is characterized by a low cardiac output, diminished peripheral perfusion, pulmonary congestion, and elevated systemic vascular resistance and pulmonary vascular pressures. Acute right heart failure can arise as the result of right ventricular infarction or may complicate ARDS and severe pulmonary hypertension of any etiology. As a consequence of right ventricular failure, left ventricular preload falls, and this, in turn, reduces systemic perfusion. In contrast to other forms of shock, absolute or relative hypovolemia is usually not present in cardiogenic shock.

The ineffective contractile activity of either the right or left side of the heart leads to the accumulation of blood in the venous circulation upstream to the failing ventricle. Cardiogenic shock with left-sided heart failure increases fluid in the lungs that can overwhelm the capacity of the pulmonary lymphatics and causes interstitial and eventually alveolar edema. Intestinal lung edema usually occurs at pulmonary capillary pressures >18 mmHg, and overt pulmonary alveolar edema develops at pressures >24 mmHg (Chap. 29). Pulmonary edema impacts cardiac function further by impairing diffusion of oxygen, setting up a vicious cycle. The increase in interstitial and intralum-

**TREATMENT**

In establishing the diagnosis of cardiogenic shock, a history of cardiac disease or of AMI is of value. Associated physical findings include those of hemodynamic instability, peripheral vasoconstriction, and pulmonary and/or systemic venous congestion, as well as findings specific to the underlying cardiac abnormality that may provide evidence of AMI or preexisting cardiac disease. The chest x-ray may show pulmonary edema and cardiomegaly. Troponin I or anionized albumin, or transesophageal echocardiograms assist in the diagnosis of structural abnormalities and/or functional impairment of contractility. Serum cardiac markers will support the diagnosis of acute cardiac ischemia or infarction. Hemodynamic monitoring is usually necessary in the presence of shock. Placement of a PAC is helpful and will show a reduced cardiac output and an elevated PCWP, and direct measurement of right atrial pressure allows calculation of systemic vascular resistance which is elevated.

For all forms of cardiogenic shock, preload, afterload, and contractility should be modified using the information provided by the PAC. A PCWP of 15 to 20 mmHg should be the initial goal. If the PCWP is excessively elevated, isotropic agents may provide significant reduction. The goal is to increase contractility without significant increases in heart rate. Dopamine, norepinephrine, or vasopressin evert both isotropic and vasodilator actions that are useful in the presence of persistent hypotension. Dobutamine, a positive inotropic agent with vasodilator properties, or vasodilators may be substituted when arterial pressure has been restored. Pulmonary congestion may be responsive to intravenous furosemide. Patients with an inadequate response to these measures can be supported by using intraaortic balloon counterpulsation to permit recovery of myocardial function. Additional measures to consider in cases of refractory cardiogenic shock include urgent myocardial revascularization in patients with AMI, correction of anatomic cardiac defects such as rupture of the papillary muscles of the interventricular septum, the placement of ventricular assist devices, and even urgent cardiac transplantation.

**COMPRESSIVE CARDIOGENIC SHOCK**

With compression, the heart and surrounding structures are less compliant and, thus, normal filling pressures generate inadequate diastolic filling. Blood or fluid within the
In septic shock, in contrast to other types of shock, total oxygen delivery may be reduced because unlike hydrocortisone it does not interfere with the adrenocortical insufficiency. Inflammatory mediator–induced processes include increased capillary permeability and continued loss of intravascular volume. In septic shock, in contrast to other types of shock, total oxygen delivery may be increased while oxygen extraction is reduced due to maldistribution of microcirculatory perfusion and impaired mitochondrial function. In this setting the presence of a normal mixed venous oxygen tension suggests inadequate peripheral perfusion. Inadequate peripheral perfusion, even though the cardiac output may be elevated, is still inadequate to meet the total metabolic needs. The toxicity of the infectious poorly distensible pericardial sac may cause tamponade (Chap. 222). Any cause of increased intrathoracic pressure, such as tension pneumothorax, herniation of abdominal viscera through a diaphragmatic hernia, or excessive positive pressure ventilation to support pulmonary function, can also cause compressive cardiogenic shock while simultaneously impeding venous return. Acute right heart failure with a sudden decline in cardiac output can be caused by pulmonary embolism obstructing right ventricular outflow and impairing left ventricular filling. Although initially responsive to increased filling pressures produced by volume expansion, as compression increases, cardiogenic shock recurs.

The diagnosis of compressive cardiogenic shock is most frequently based on clinical findings, the chest radiograph, and an echocardiogram. The diagnosis of compressive cardiogenic shock may be more difficult to establish in the setting of trauma when hypovolemia and cardiac compression are present simultaneously. The classic findings of pericardial tamponade include the triad of hypotension, neck vein distention, and muffled heart sounds (Chap. 222). Pulmonary paradoxus, i.e., an inspiratory reduction in systolic pressure >10 mmHg, may also be noted. The diagnosis is confirmed by echocardiography, and treatment consists of immediate pericardiocentesis. A tension pneumothorax produces ipsilateral decreased breath sounds, tracheal deviation away from the affected thorax, and jugular venous distention. Radiographic findings include increased intrathoracic volume, depression of the diaphragm of the affected hemithorax, and shifting of the mediastinum to the contralateral side. Chest decompression must be carried out immediately. Release of air and restoration of normal cardiovascular dynamics are both diagnostic and therapeutic.

**Septic Shock** (See also Chap. 254) This form of shock is caused by the systemic response to a severe infection. It occurs most frequently in elderly or immunocompromised patients and in those who have undergone an invasive procedure in which bacterial contamination has occurred. Infections of the lung, abdomen, or urinary tract are most common, and approximately half of the patients have bacteremia. Gram-positive and -negative bacteria, fungi, rickettsiae, and protozoa have all been reported to produce the clinical picture of septic shock, and the overall response is generally independent of the specific type of invading organism. The clinical findings in septic shock are a consequence of the combination of metabolic and circulatory derangements driven by the systemic infection and the release of toxic components of the infectious organisms, e.g., the endotoxin of gram-negative bacteria or the exotoxins and enterotoxins of gram-positive bacteria. Organism toxins lead to the release of cytokines, including IL-1 and TNF-α, from tissue macrophages. Tissue factor expression and fibrin deposition are increased, and disseminated intravascular coagulation may develop. The inducible form of NO synthase is stimulated, and NO, a powerful vasodilator, is released. Hemodynamic changes in septic shock occur in two characteristic patterns: early, or hyperdynamic, and late, or hypodynamic, septic shock.

**Hyperdynamic Response** In hyperdynamic septic shock, tachycardia is present, the cardiac output is normal or elevated, and the systemic vascular resistance is reduced while the pulmonary vascular resistance is elevated. The extremities are usually warm. However, splanchnic vasoconstriction with decreased visceral flow is present. The venous capacitance is increased, which decreases venous return. With volume expansion cardiac output becomes supranormal. Myocardial contractility is depressed in septic shock by mediators including NO, IL-1, and/or TNF-α. Inflammatory mediator–induced processes include increased capillary permeability and continued loss of intravascular volume.

In septic shock, in contrast to other types of shock, total oxygen delivery may be decreased while oxygen extraction is reduced due to maldistribution of microcirculatory perfusion and impaired mitochondrial function. In this setting the presence of a normal mixed venous oxygen tension suggests inadequate peripheral perfusion. Inadequate peripheral perfusion, even though the cardiac output may be elevated, is still inadequate to meet the total metabolic needs. The toxicity of the infectious agents and their byproducts and the subsequent metabolic dysfunction drive the progressive deterioration of cellular and organ function. ARDS, thrombocytopenia, and neutropenia are common complications.

**Hypodynamic Response** As sepsis progresses, vasosconstriction occurs and the cardiac output declines. The patient usually becomes markedly tachycardic, febrile, diaphoretic, and obtunded, with cool, mottled, and often cyanotic extremities. Oliguria, renal failure, and hypothermia develop; there may be striking increases in serum lactate.

**Treatment** Aggressive volume expansion with a crystalloid solution to a PCWP of ~15 mmHg and the restoration of arterial oxygenation with inspired oxygen and frequently with mechanical ventilation are the highest priorities. In the presence of sepsis, augmentation of cardiac output may require inotropic support with dopamine, norepinephrine, or vasopressin in the presence of hypotension or with dobutamine if arterial pressure is normal. High-dose, activated protein C (APC) provides a survival benefit in patients with severe sepsis and septic shock. Antibiotics should be administered, either appropriate for the results of cultures or empirical therapy based on the likely source of infection. Surgical debridement or drainage may also be necessary to control the infection.

**Neurogenic Shock** Interruption of sympathetic vasomotor input after a high cervical spinal cord injury, inadvertent cephalad migration of spinal anesthetics, or severe head injury may result in neurogenic shock. In addition to arteriolar dilatation, venodilation causes pooling in the venous system, which decreases venous return and cardiac output. The extremities are often warm, in contrast to the usual vasocostriction-induced coolness in hypovolemic or cardiogenic shock. Treatment involves a simultaneous approach to the relative hypovolemia and to the loss of vasomotor tone. Excessive volumes of fluid may be required to restore normal hemodynamics. Once hemorrhage has been ruled out, norepinephrine may be necessary to augment vascular resistance.

**Hypoadrenal Shock** (See also Chap. 321) The normal host response to the stress of illness, operation, or trauma requires that the adrenal glands hyposecrete cortisol in excess of that normally required. Hypoadrenal shock occurs in settings in which unrecognized adrenal insufficiency complicates the host response to the stress induced by acute illness or major surgery. Adrenocortical insufficiency may occur as a consequence of the chronic administration of high doses of exogenous glucocorticoids. Recent studies have shown that critical illness, including trauma and sepsis, may also induce a relative hypoadrenal state. Other less common causes include adrenal insufficiency secondary to idiopathic atrophy, tuberculosis, metastatic disease, bilateral hemorrhage, and amyloidosis. The shock produced by adrenal insufficiency is characterized by reductions in systemic vascular resistance, hypovolemia, and reduced cardiac output. The diagnosis of adrenal insufficiency may be established by means of an ACTH stimulation test.
SEVERE SEPSIS AND SEPTIC SHOCK
Robert S. Manford

DEFINITIONS (See Table 254-1) Animals mount both local and systemic responses to microbes that traverse epithelial barriers and invade underlying tissues. Fever or hypothermia, leukocytosis or leukopenia, tachypnea, and tachycardia are the cardinal signs of the systemic response often called the systemic inflammatory response syndrome (SIRS). SIRS may have an infectious or a noninfectious etiology. If infection is suspected or proven, a patient with SIRS is said to have sepsis. Severe sepsis occurs when dysfunctions of organs distant from the site of infection, the patient has severe sepsis. Severe sepsis may be accompanied by hypotension or evidence of hypoperfusion. When hypotension cannot be corrected by infusing fluids, the diagnosis is septic shock. These definitions were proposed by a consensus conference committee in 1992 and are now widely used; there is evidence that the different stages form a continuum. As sepsis progresses to septic shock, the risk of dying increases substantially. Sepsis is usually reversible, whereas patients with septic shock often succumb despite aggressive therapy.

Etiology Sepsis can be a response to any class of microorganism. Microbial invasion of the bloodstream is not essential for the development of severe sepsis, since local inflammation can also elicit distant organ dysfunction and hypotension. In fact, blood cultures yield bacteria or fungi in only ~20 to 40% of cases of severe sepsis and 60 to 70% of cases of septic shock. Individual gram-negative or gram-positive bacteria account for ~70% of these isolates; the remainder are fungi or a mixture of microorganisms (Table 254-2). In patients whose blood cultures are negative, the etiologic agent is often established by culture or microscopic examination of infected material from a local site. In some series, a majority of patients with a clinical picture of severe sepsis or septic shock have had negative microbiologic data. Factors that predispose to infections with positive blood cultures are listed in (Table 254-3). Among patients who have positive blood cultures, the risk of developing severe sepsis is greater in persons >60 years old and in those with a primary pulmonary, abdominal, or neurosurgical site of infection.

Epidemiology The septic response is a contributing factor in >200,000 deaths per year in the United States. The incidence of severe sepsis and septic shock has increased over the past 20 years, and the annual number of cases is now ~3,000. Approximately two-thirds of cases occur in patients hospitalized for other illnesses. The increasing incidence of severe sepsis in the United States is attributable to the aging of the population, the increasing longevity of patients with chronic diseases, and the relatively high frequency with which sepsis develops in patients with AIDS. The increasing use of antimicrobial agents, glucocorticoids, indwelling catheters and mechanical devices, and mechanical ventilation also plays a role.

Pathophysiology Most cases of severe sepsis are triggered by bacteria or fungi that do not ordinarily cause systemic disease in immunocompetent hosts (Table 254-2). These microbes probably exploit deficiencies in innate host defenses (e.g., phagocytes, complement, and natural antibodies) to survive within the body. Microbial pathogens, in contrast, are able to circumvent innate defenses by elaborating toxins or antibodies to survive within the body. Microbial pathogens, in contrast, are able to circumvent innate defenses by elaborating toxins or antibodies to survive within the body. Microbial pathogens, in contrast, are able to circumvent innate defenses by elaborating toxins or antibodies to survive within the body. Microbial pathogens, in contrast, are able to circumvent innate defenses by elaborating toxins or antibodies to survive within the body. Microbial pathogens, in contrast, are able to circumvent innate defenses by elaborating toxins or antibodies to survive within the body.

Rest Mechanisms for Sensing Microbes Animals have exquisitely sensitive mechanisms for recognizing and responding to conserved microbial molecules. The lipid A moiety of lipopolysaccharide (LPS, also called endotoxin; Chap. 105) is the best-studied example. Lipid A is the biocomplex center of the LPS of all gram-negative bacteria found in nature. A host protein (LPS-binding protein, or LBP) binds lipid A and transfers LPS to CD14 on the surfaces of monocytes, macrophages, and neutrophils. LPS and CD14 then interact with toll-like receptor (TLR) 4 and MD-2 to form a molecular complex that transduces the LPS signal to the interior of the cell. This signal rapidly triggers the production and release of mediators, such as tumor necrosis factor (TNF) α (see below), that amplify the LPS signal and transmit it to other cells and tissues. Bacterial peptidoglycan, lipoteichoic acids, DNA, certain polycarboxylic acids, and fibrinect responses in animals that are similar to those induced by LPS; whereas some of