INTRODUCTION

Despite significant technologic advances and improved understanding of shock, it remains a diagnosis associated with significant morbidity and mortality. Hippocrates and Galen were the first to describe a “posttraumatic syndrome,” then, in 1737, LeDran, a French surgeon, used the term shock to characterize a severe impact or jolt (1). However, it was not until 1867 that Edwin Morris popularized the term (2), defining shock as “a peculiar effect on the animal system, produced by violent injuries from any cause, or from violent mental emotions.”

In the late 1800s, Fischer and Mapother further delineated the pathophysiology of shock (3,4), with Fischer proposing a generalized “vasomotor paralysis” resulting in splanchic blood pooling as the underlying mechanism, while Mapother suggested that the clinical manifestations appreciated in shock were the result of the extravascular leakage of fluids. A variation of Fischer’s theory was supported by Crile in 1899 (5).

In the early 1900s, Walter B. Cannon (6) proposed a toxin as the source of this altered capillary permeability and intravascular volume loss. Blalock (7) challenged this theory in 1930, charging that significant hemorrhage alone could account for insufficient cardiac output (CO) in shock states and that a circulating toxin was not needed. In the 1940s, Carl Wiggers (8) demonstrated that, following prolonged shock, irreversible circulatory failure could occur. At that time, hypotension was synonymous with shock, as blood pressure was the primary end point of resuscitation in shock. As such, volume resuscitation was the primary management strategy.

It was not until the turn of the 19th century that etiologies other than trauma were thought to cause shock; sepsis was first depicted as causing shock during the Spanish-American War (9). This was followed in 1906 with the description of anaphylactic shock. Subsequently, Tennant and Wiggers documented, in 1935, decreased myocardial contractility following coronary perfusion deprivation (10).

DEFINITION OF SHOCK

The definition of shock has historically been a moving target. Initially equated with hypotension (11,12), shock is now defined as an acute clinical syndrome resulting from cellular dysoxia, ultimately leading to organ dysfunction and failure (13). Cellular dysoxia or inadequate tissue perfusion is critical in diagnosing shock, as there are many other causes of organ dysfunction and failure that are not resultant from shock.

Note the emphasis on shock as a syndrome, as this constellation of signs and symptoms predictably follows a well-described series of pathophysiologic events (14). Its clinical presentation varies widely based on the underlying etiology, the degree of organ perfusion, and prior organ dysfunction.

CLASSIFICATION OF SHOCK

The incidence and prevalence of shock are poorly characterized for a multitude of reasons. First and foremost—even today—the definition of shock continues to lack consensus. As such, screening for shock tends to be inadequate, and thus it is underreported. Additionally, patients presumably die from shock in the prehospital setting. Taking these facts into account, one can readily appreciate why the reported incidence and mortality of shock varies widely.

Blalock’s 1937 classification of shock (15) defined four categories: hematogenic or oligemic (hypovolemic), cardiogenic, neurogenic, and vasogenic. Subsequently, Weil and Shubin (16) characterized shock based on cardiovascular parameters. The categories included hypovolemic, cardiogenic, extracardiac obstructive, and distributive; Table 44.1 represents an adaptation of this system (17). It is important to appreciate that most shock states incorporate different components of each of the aforementioned shock categories.

Hypovolemic Shock

Hypovolemic shock represents a state of decreased intravascular volume. Inciting events include internal or external hemorrhage, significant fluid losses from the gastrointestinal tract (emesis, high-output fistulae, or diarrhea) or urinary tract (hyperosmolar states), and “third spacing” (“capillary leakage” into the interstitial tissues or the corporeal cavities) (see Table 44.1). Additional etiologies include malnutrition and large open wounds (burns and the open abdomen) (16,18).

The pathophysiology of shock is dependent upon its classification. Hypovolemic shock is characterized by a decrease in intravascular volume with resultant decreases in pulmonary capillary wedge pressure (PCWP) and CO (Table 44.2). There is a subsequent increased sympathetic drive in an attempt to increase peripheral vasculature tone, cardiac contractility, and heart rate. These, initially, beneficial measures ultimately turn detrimental, as their resultant hypermetabolic state predisposes tissues to localized hypoxia (14). Furthermore, the aforementioned increased peripheral vascular tone (systemic vascular resistance; SVR) may result in tissue ischemia via an inconsistent microcirculatory flow. In cases of severe hypovolemic shock, a significant inflammatory component coexists.

Cardiogenic Shock

Cardiogenic shock is defined as inadequate tissue perfusion due to primary ventricular failure. Its incidence has remained fairly stable, ranging from 6% to 8% (19–23). In the United States, it is the most common cause of mortality from coronary artery disease (CAD) (19). Despite medical advances, cardiogenic shock remains the number one cause of in-hospital
mortality in patients experiencing a transmural myocardial infarction (MI), with rates ranging between 70% and 90% (21,24). Other causes include myocarditis, cardiomyopathies, valvular heart diseases, and dysrhythmias (Table 44.1).

The most common inciting event in cardiogenic shock is an acute MI. Historically, once 40% of the myocardium has been irreversibly damaged, cardiogenic shock may result. From a mechanical perspective, decreased cardiac contractility diminishes both stroke volume (SV) and CO (see Table 44.2). These lead to increased ventricular filling pressures, cardiac chamber dilatation, and ultimately univentricular or biventricular failure with resultant systemic hypotension; this further reduces myocardial perfusion and exacerbates ongoing ischemia. The end result is a vicious cycle with severe cardiovascular decompensation. Similar to hypovolemic shock, a significant systemic inflammatory response has been implicated in the pathophysiology of cardiogenic shock.

**Obstructive Shock**

In obstructive shock, external forces compress the thin-walled chambers of the heart, the great vessels, or any combination thereof. These forces impair either the diastolic filling or the systolic contraction of the heart (see Table 44.1). Large obstructive intrathoracic tumors, tension pneumothoraces, pericardial tamponade, and constrictive pericarditis limit ventricular filling, while pulmonary emboli (PE) and aortic dissection impede cardiac contractility.

The hemodynamic parameters witnessed in obstructive shock include increases in central venous pressure (CVP) and SVR, and decreases in CO and mixed venous oxygen saturation (SvO₂) (see Table 44.2). The PCWP and other hemodynamic indices are dependent on the obstructive cause. In pericardial tamponade, there is equalization of the right and left ventricular diastolic pressures, the CVP, and the PCWP (increased). However, following a massive PE, right ventricular failure leads to increased right heart pressures and a normal or decreased PCWP.

**Distributive Shock**

Distributive shock is characterized by a decrease in SVR. Septic shock is the most common form although, additionally, distributive shock includes the other oft-quoted classes of shock including anaphylactic, neurogenic, and adrenal shock (see Table 44.1). Physiologically, all forms of distributive shock exhibit a decreased SVR (see Table 44.2). Subsequently, these patients experience relative hypovolemia as evidenced by a decreased (or normal) CVP and PCWP. The CO is initially diminished; however, following appropriate volume loading, the CO increases.

**CELLULAR ALTERATIONS**

All forms of shock, especially hemorrhagic and septic, induce a host response that is characterized by local and systemic release of proinflammatory cytokines, arachidonic acid metabolites, and activation of complement factors, kinins, and...
coagulation as well as hormonal mediators. Clinically, this is the systemic inflammatory response syndrome (SIRS). Parallelizing this response is an anti-inflammatory response referred to as the compensatory anti-inflammatory response syndrome (sometimes abbreviated CARS). An imbalance between these responses appears to be responsible for increased susceptibility to infection and organ dysfunction (25–29).

**Systemic Inflammatory Response Syndrome**

In 1991, a consensus conference of the American College of Chest Physicians and the American Society of Critical Care Medicine defined SIRS as a generalized inflammatory response triggered by a variety of infectious and noninfectious events (30). They arbitrarily established clinical parameters through a consensus process; Table 44.3 summarizes the SIRS diagnostic criteria. At least two of the four criteria must be present to fulfill the diagnosis of SIRS. Note, this definition emphasizes the inflammatory process regardless of its etiology. Subsequent studies have validated these criteria as predictive of increased ICU mortality, and indicated that this risk increases concurrent with the number of criteria present. SIRS is characterized by the local and systemic production, and release, of multiple protein responses appears to be responsible for increased susceptibility to infection and organ dysfunction (25–29).

**Compensatory Anti-Inflammatory Response Syndrome**

Shock stimulates not only the release of proinflammatory mediators, but also the parallel release of anti-inflammatory mediators (26). This compensatory anti-inflammatory response is present concurrently with SIRS (Fig. 44.1) (32). When these two opposing responses are appropriately balanced, the patient is able to effectively recover without incurring secondary injury from the autoimmune inflammatory response (25). However, overwhelming CARS appears responsible for post-shock immunosuppression, which leads to increased susceptibility to infections and sepsis (26,31,33). With time, SIRS ceases to exist and CARS is the predominant force.

**Cytokine Response**

Proinflammatory cytokines, tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β) are key to the resultant inflammation (34,35). Secondary proinflammatory cytokines are released in a subacute fashion and include IL-2, IL-6, IL-8, platelet-activating factor (PAF), interferon-γ (IFN-γ), endothelin-1, leukotrienes, thromboxanes, prostaglandins, and the complement cascade (34,36).

IL-6 also acts as an immunoregulatory cytokine by stimulating the release of anti-inflammatory mediators such as IL-1 receptor antagonists and TNF receptors, which bind circulatory proinflammatory cytokines (35). IL-6 also triggers the release of prostaglandin E2 (PGE2) from macrophages (35); PGE2 is potentially the most potent endogenous immunosuppressant (35). Not only does it suppress T-cell and macrophage responsiveness, but it also induces the release of IL-10, a potent anti-inflammatory cytokine that deactivates monocytes (35). A listing of pro- and anti-inflammatory mediators may be found in Tables 44.4 and 44.5.

**Cell-Mediated Response**

Shock alters the ability of splenic, peritoneal, and alveolar macrophages to release IL-1, IL-6, and TNF-α, leading to decreased levels of these proinflammatory cytokines (35). Kupffer cells, however, have an enhanced capacity for production of proinflammatory cytokines. Cell-mediated immunity requires not only functional macrophage and T cells, but also intact macrophage–T-cell interaction (35). Following injury, human leukocyte antigen (HLA-DR) receptor expression is decreased, leading to a loss of antigen-presenting capacity and decreased TNF-α production. PGE2, IL-10, and TGF-β all contribute to this “immunoparalysis” (25,35).

T-helper cells differentiate into either T_{H}1 or T_{H}2 lymphocytes; T_{H}1 cells promote the proinflammatory cascade through the release of IL-2, IFN-γ, and TNF-β, while T_{H}2 cells...
### TABLE 44.4 Proinflammatory Mediators

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>IL-1 is pleiotropic. Locally, it stimulates cytokine and cytokine receptor production by T cells as well as stimulating B-cell proliferation. Systemically, IL-1 modulates endocrine responses and induces the acute phase response.</td>
</tr>
<tr>
<td>IL-6</td>
<td>IL-6 induces acute phase reactants in hepatocytes and plays an essential role in the final differentiation of B cells into Ig-secreting cells. Additionally, IL-6 has anti-inflammatory properties.</td>
</tr>
<tr>
<td>IL-8</td>
<td>IL-8 is one of the major mediators of the inflammatory response. It functions as a chemoattractant and is also a potent angiogenic factor.</td>
</tr>
<tr>
<td>IL-12</td>
<td>IL-12 regulates the differentiation of naive T cells into T(_{H1}) cells. It stimulates the growth and function of T cells and alters the normal cycle of apoptotic cell death.</td>
</tr>
<tr>
<td>TGF-β</td>
<td>TGF-β is pleiotropic. It and IL-1 act alone or together to induce systemic inflammation as above. TGF-β is also chemotactic for neutrophils and monocytes, as well as increasing neutrophil activity.</td>
</tr>
<tr>
<td>MIF</td>
<td>MIF forms a crucial link between the immune and neuroendocrine systems. It acts systemically to enhance the secretion of IL-1 and TNF-α.</td>
</tr>
</tbody>
</table>

### TABLE 44.5 Anti-Inflammatory Mediators

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-10</td>
<td>IL-10 has pleiotropic effects in immunoregulation and inflammation. It downregulates the expression of T(_{H1}) cytokines, MHC class II antigens, and costimulatory molecules on macrophages. It also enhances B-cell survival, proliferation, and antibody production. In addition, it can block NF-κB activity, and is involved in the regulation of the JAK-STAT signaling pathway.</td>
</tr>
<tr>
<td>IL-11</td>
<td>IL-11 stimulates the T-cell-dependent development of immunoglobulin-producing B cells. It is also found to support the proliferation of hematopoietic stem cells and megakaryocyte progenitor cells.</td>
</tr>
<tr>
<td>IL-13</td>
<td>IL-13 is involved in several stages of B-cell maturation and differentiation. It upregulates CD23 and MHC class II expression, and promotes IgE isotype switching of B cells. It downregulates macrophage activity, thereby inhibiting the production of proinflammatory cytokines and chemokines.</td>
</tr>
<tr>
<td>IFN-α</td>
<td>IFN-α enhances and modifies the immune response.</td>
</tr>
<tr>
<td>TGF-β</td>
<td>TGF-β regulates the proliferation and differentiation of cells, wound healing, and angiogenesis.</td>
</tr>
<tr>
<td>α-MSH</td>
<td>α-MSH modulates inflammation by way of three mechanisms: direct action on peripheral inflammatory cells; actions on brain inflammatory cells to modulate local reactions; and indirect activation of descending neural anti-inflammatory pathways that control peripheral tissue inflammation.</td>
</tr>
</tbody>
</table>

Proinflammatory cytokines enhance PMNL recruitment, phagocytic activity, and the release of proteases and oxygen-free radicals by PMNLs. This recruitment of leukocytes represents a key element for host defense following trauma, although it allows for the development of secondary tissue damage (38–41). Recruitment involves a complex cascade of events culminating in transmigration of the leukocyte, whereby the cell exerts its effects (42). The first step is capture and tethering, mediated via constitutively expressed leukocyte selectin denoted L selectin; L selectin functions by identifying glycoprotein ligands on leukocytes and those upregulated on cytokine-activated endothelium (42). Following capture and tethering, endothelial E selectin and P selectin assist in leukocyte rolling or slowing (37,43–48). P selectin is found in the membranes of endothelial storage granules, termed Weibel-Palade bodies (45). Following granule secretion, P selectin binds to carbohydrates presented by P selectin glycoprotein ligand (PSGL-1) on the leukocytes (25). In contrast, E selectin is not stored, yet it is synthesized de novo in the presence of inflammatory cytokines (43,44). These selectins cause the leukocytes to roll along the activated endothelium, whereby secondary capturing of leukocytes occurs via homotypic interactions. The third step in leukocyte recruitment is firm adhesion, which is mediated by membrane-expressed β\(_{1}\) and β\(_{2}\)-integrins (49–51). The integrins bind to ICAM, resulting in cell–cell interactions and ultimately signal transduction. This step is critical to the formation of stable shear-resistant adhesion, which stabilizes the leukocyte for transmigration (49–51).

Transmigration is the final step in leukocyte recruitment following the formation of bonds between the aforementioned integrins and immunoglobulin (Ig)-superfamily members (42). The arrested leukocytes cross the endothelial layer via bicanular and tricellular endothelial junctions in a process coined diapedesis (52). This is mediated by platelet endothelial cell adhesion molecules (PECAMs), proteins expressed on both the leukocytes and intercellular junctions of endothelial cells (42).
Proteases and Reactive Oxygen Species

Polymorphonuclear lymphocytes and macrophages are not only responsible for phagocytosis of microorganisms and cellular debris, but can also cause secondary tissue and organ damage through degranulation and release of extracellular proteases and formation of reactive oxygen species (ROS) or respiratory burst (25,39,40,41,53–55). Elastases and metalloproteinases, which degrade both structural and extracellular matrix proteins, are present in increased concentrations following trauma (25). Neutrophil elastases also induce the release of proinflammatory cytokines (25).

ROS are generated by membrane-associated nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase, which is activated by proinflammatory cytokines, arachidonic acid metabolites, complement factors, and bacterial products (56,57). Superoxide anions are reduced in the Haber–Weiss reaction to hydrogen peroxide by superoxide dismutase located in the cytosol, mitochondria, and cell membrane (25). Hydrochloric acid is formed from H2O2 by myeloperoxidase, while the Fenton reaction transforms H2O2 into hydroxyl ions (25). These free ROS cause lipid peroxidation, cell membrane disintegration, and DNA damage of endothelial and parenchymal cells (58–60). Oxygen radicals also induce PMNLs to release proteases and collagenase as well as inactivating protease inhibitors (61).

Reactive oxygen species cause additional tissue damage following trauma (62). Nitric oxide (NO), which induces vasodilation, is generated from L-arginine by inducible nitric oxide synthase (iNOS) in PMNLs or vascular muscle cells and is associated with the initiation of the hepatic acute phase reaction, and release of proinflammatory cytokines (i.e., monocytes, polymorphonuclear cells, and macrophages), enhancement of the hepatic acute phase reaction, and release of vasoactive mediators (i.e., histamine) (52,65). They also enhance the adhesion of leukocytes to endothelial cells, which results in increased vascular permeability and edema. C5a induces apoptosis and cell lysis through the interaction of its receptor and the MAC (52,65,66); additionally, C3a and C5a activate reperative mechanisms (65). C1 inhibitor inactivates C1s and C1r, thereby regulating the classic complement pathway. However, during inflammation, serum levels of C1 inhibitor are decreased via its degradation by PMNL elastases (65).

The plasma kallikrein–kinin system is a contact system of plasma proteases related to the complement and coagulation cascades. It consists of the plasma proteins FXII, prekallikrein, kininogen, and factor XI (FXI) (67). Activation of FXII and prekallikrein is via contact, when endothelial damage occurs and exposes the basement membrane (67). Factor XII activation forms factor XIIa (FXIIa), which initiates the complement cascade through the classic pathway, whereas prekallikrein activation forms kallikrein, which stimulates fibrinolysis through the conversion of plasminogen to plasmin or the activation of urokinase-like plasminogen activator (tPA) (67); tissue plasminogen activator (tPA) functions as a cofactor. Additionally, kallikrein supports the conversion of kininogen to bradykinin (67). The formation of bradykinin also occurs through the activation of the tissue kallikrein–kinin system, most likely through organ damage, as the tissue kallikrein–kinin system is found in many organs and tissues including the pancreas, kidney, intestine, and salivary glands. The kinins are potent vasodilators, increase vascular permeability and inhibit the function of platelets (67).

The intrinsic coagulation cascade is linked to the contact activation system via the formation of factor Xa (FXa) from factor Xa (FXa) (25). Its formation leads to the consumption of FXII, prekallikrein, and FXI while plasma levels of enzyme–inhibitor complexes are increased (25). These include FXIIa-C1 inhibitor and kallikrein-C1 inhibitor. C1 inhibitor and α1-protease inhibitor are both inhibitors of the intrinsic coagulation pathway (68,69).

Although the intrinsic pathway provides a stimulus for activation of the coagulation cascade, the major activation following trauma is via the extrinsic pathway. Increased expression of tissue factor (TF) on endothelial cells and monocytes is induced by the proinflammatory cytokines TNF-α and IL-1β (69–71). The factor VII (FVII)–TF complex stimulates the formation of factor Xa (FXa) and ultimately thrombin (FIIa) (25). Thrombin-activated factor V (FV), factor VIII (FVIII), and FXI result in enhanced thrombin formation (25). Following cleavage of fibrinogen by thrombin, the fibrin monomers polymerize to form stable fibrin clots. The consumption of coagulation factors is controlled by the hepatocytic formation of antithrombin (AT) III (25). The thrombin–antithrombin complex inhibits thrombin, FXa, FXa, FXa, and FXIIa (72); other inhibitors include TF pathway inhibitor (TFPI) and activated protein C in combination with free protein S (72). Free protein S is decreased during inflammation due to its binding with the C4b-binding protein (68,72).

Disseminated intravascular coagulation (DIC) may occur following shock. After the initial phase, intra- and extravascular fibrin clots are observed. Hypoxia-induced cellular damage is the ultimate result of intravascular fibrin clots. Likewise, there is an increase in the interactions between endothelial cells and leukocytes (68–70,73). Clinically, coagulation factor consumption and platelet dysfunction are responsible for the diffuse hemorrhage (68,71). Consumption of coagulation factors is further enhanced via the proteolysis of fibrin clots to fibrin fragments (68,71). The consumption of coagulation factors is further enhanced through the proteolysis of fibrin clots to fibrin fragments by the protease plasmin (25,69,74).
Acute Phase Reaction

The acute phase reaction describes the early systemic response following shock and other insult states. During this phase, the biosynthetic profile of the liver is significantly altered. Under normal circumstances, the liver synthesizes a range of plasma proteins at steady-state concentrations. However, during the acute phase reaction, hepatocytes increase the synthesis of positive acute phase proteins (i.e., C-reactive protein [CRP], serum amyloid A [SAA], complement proteins, coagulation proteins, proteinase inhibitors, metal-binding proteins, and other proteins) essential to the inflammatory process at the expense of the negative acute phase proteins. The list of acute phase proteins, both positive and negative, is shown in Table 44.6 (75,76).

The acute phase response is initiated by hepatic Kupffer cells and the systemic release of proinflammatory cytokines IL-1, IL-6, IL-8, and TNF-α (77,78). The acute phase reaction typically lasts for 24 to 48 hours prior to its downregulation (35). IL-4, IL-10, glucocorticoids, and various other hormonal stimuli function to downregulate the proinflammatory mediators of the acute phase response (35); this modulation is critical. In instances of chronic or recurring inflammation, an aberrant acute phase response may result in exacerbated tissue damage (35).

The major acute phase proteins include CRP and SAA, the activities of which are both poorly understood (79,80). CRP was so named secondary to its ability to bind the C-polysaccharide of Pneumococcus. During inflammation CRP levels may increase by up to 1,000-fold over several hours depending on the insult and its severity (35). It acts as an opsonin for bacteria, parasites, and immune complexes; activates complement via the classic pathway; and binds chromatin (35). Binding chromatin may minimize autoimmune responses by disposing of nuclear antigens from sites of tissue debris (35). Clinically, CRP levels are relatively nonspecific and not predictive of posttraumatic complications. Despite this fact, serial measurements are helpful in trending a patient’s clinical course (35).

SAA interacts with the third fraction of high-density lipoprotein (HDL3), thus becoming the dominant apolipoprotein during acute inflammation (81). This association enhances the binding of HDL3 to macrophages, which may engulf cholesterol and lipid debris. Excess cholesterol is then utilized in tissue repair or excreted (35). Additionally, SAA inhibits thrombin-induced platelet activation and the oxidative burst of neutrophils, potentially preventing oxidative tissue destruction (35).

### DIAGNOSIS OF SHOCK

Early diagnosis of shock affords the patient the best possible outcome. The patient in overt shock with hypotension and tachycardia is relatively easy to diagnose. However, more often than not, shock presents in more insidious forms, whereby underrecognition and delay in treatment can lead to a poor outcome. Moreover, the concurrent presence of mixed shock states can confuse the picture. Diagnosis of shock relies on both basic history and physical examination skills, as well as more advanced technology available to the clinician.

Numerous clues in a patient’s history may help alert the physician to the possibility of impending shock. Large fluid losses via traumatic or gastrointestinal hemorrhage, third spacing from intra-abdominal surgery or pancreatitis, prolonged dehydration from vomiting or diarrhea, or insensible losses from burns may very easily tip the patient into hypovolemic shock. A history of infection, presence of indwelling catheters, or recent surgery may be implicated in septic shock. Neurogenic shock occurs almost exclusively after trauma, although limited forms are seen with spinal anesthesia. History of prolonged steroid use, particularly in the elderly, may indicate adrenal shock in the patient with hypotension postoperatively. Exposures to drugs, transfusions, or other allergens should be sought to rule out anaphylactic shock. Recent MI or cardiac intervention can lead to pump failure and cardiogenic shock. A detailed history is especially important for obstructive forms of shock, in which any intervention involving the chest can lead to either immediate or delayed compromise via cardiac tamponade or tension pneumothorax. Likewise, a history of deep venous thrombosis (DVT) or risk factors for thrombosis should alert the physician to the possibility of acute massive PE in the hypotensive patient.

Physical examination can provide more clues than just basic blood pressure measurements. As noted previously, hypotension alone is neither exclusive to shock nor absolute for a diagnosis, and therefore is only a small component of the physical examination. Certain findings may vary based on the type and timing of shock. The end result of any form of shock, however, is diminished end-organ perfusion. Therefore, any signs or symptoms of organ dysfunction should be considered as possible indicators of shock (Table 44.7). Often, the first sign of shock manifests as mental status changes, whether excitatory or somnolent in nature. The patient may appear diaphoretic and clammy in cardiogenic shock or warm and dry in early distributive shock. Heart rate may also be variable with

<table>
<thead>
<tr>
<th>TABLE 44.6 Acute Phase Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td><strong>Positive acute phase proteins</strong></td>
</tr>
<tr>
<td><strong>Major acute phase proteins</strong></td>
</tr>
<tr>
<td><strong>Coagulation proteins</strong></td>
</tr>
<tr>
<td><strong>Proteinase proteins</strong></td>
</tr>
<tr>
<td><strong>Metal-binding proteins</strong></td>
</tr>
<tr>
<td><strong>Other proteins</strong></td>
</tr>
<tr>
<td><strong>Negative acute phase proteins</strong></td>
</tr>
</tbody>
</table>

Positive acute phase proteins increase production during an acute phase response. Negative acute phase proteins are those that have decreased production during an acute phase response.
tachycardia compensating for diminished CO in the patient with intact sympathetic drive. Vasoplegic shock, such as neurogenic or adrenal (or in the β-blocked patient), may not have the compensatory increase in heart rate normally seen, and may itself provide a clue as to the type of shock. Tachypnea is almost universally seen, as the body tries to buffer the lactate produced in a state of tissue hypoxia. The kidneys provide a sensitive measure of adequate end-organ perfusion, as manifested by low urinary output. Cardiogenic shock has its own specific physical findings including increased venous jugular distention, acute pulmonary edema, and new murmurs or dysrhythmias.

Various modalities for evaluating shock may be used either alone or in combination. Pooling data from multiple sources, however, is often required to get an adequate picture of shock resuscitation. Basic laboratory studies such as lactate level, base deficit, hemoglobin (Hgb), creatinine, and cortisol may help provide evidence of or reason for shock. Likewise, a more advanced evaluation of shock may include echocardiogram, CVP monitoring, tissue oxygenation and capnography, or advanced methods of determining CO. Advantages and disadvantages of these more advanced modalities will be discussed later within the context of shock monitoring.

**Management of Shock**

Optimal management of shock depends first and foremost on early recognition of the syndrome, determination of its etiology, and correction of the underlying source while supporting the patient hemodynamically. Rapidity and adequacy of shock resolution will help prevent secondary reperfusion injury and prolonged morbidity. Variables of shock resuscitation must be frequently reassessed and therapy adjusted accordingly.

The underlying goal of shock management is to improve tissue oxygen perfusion. This may be accomplished by manipulating one or multiple physiologic parameters involved in oxygen delivery (DO₂) and extraction. Forms of obstructive shock require the most prompt diagnosis, as continued mechanical impairment can be rapidly fatal. Adequate treatment of these etiologies can be just as rapid in the form of needle decompression for a tension pneumothorax or pericardiocentesis for cardiac tamponade. Management of distributive and hypovolemic forms of shock likewise involves source control early in the diagnosis. This may be in the form of hemorrhage control, removal of infected tissue (source control), or removal of an anaphylactic source. Once the inflammatory cascade has initiated, vasoactive medications are often used in addition to fluid provision to increase perfusion. Treatment of cardiogenic shock employs multimodality treatment including volume optimization, vasopressors, control of dysrhythmias, use of inotropes and the mechanical-assist devices, and early revascularization in primary myocardial ischemia (82).

Classically, all forms of shock are primarily treated with a combination of fluids and vasoactive agents. Deliberation is ongoing regarding the dosing and selection of these modalities for resuscitation, and will be examined here in greater detail.

**Fluid Resuscitation**

The initial treatment for all forms of shock is fluid administration. Provision of fluid helps restore perfusion and replace intravascular volume lost via hemorrhage, capillary leak, or redistribution. Intravenous fluid is readily available, inexpensive, easy to administer, and has low intrinsic morbidity. The etiology of shock and response to fluid will further dictate continued use of volume as primary therapy; however, all forms of shock potentially benefit from an initial fluid challenge (83). Deliberation should be given to the method of delivery, timing of administration, type of fluid, and volume of administration.

**Route of Administration**

The setting of shock dictates administration of fluid primarily via the intravenous route, which may be in the form of a peripheral or central venous catheter. Although the type of shock may guide the choice of catheter (i.e., an introducer catheter for a rapid infusion system or a triple lumen catheter for anticipated vasopressor therapy), the dictum of “two large-bore peripheral IVs” cannot be overstated (84). As per Poiseuille’s Law, width and length of the catheter dictates flow; therefore, a long, narrow, peripherally inserted central catheter will be of little utility when infusing a large bolus of fluid quickly. In the severely volume-depleted patient with collapsed veins, obtaining percutaneous venous access can prove difficult; saphenous vein cut-downs or interosseous access, particularly in the trauma or pediatric patient, can provide means of fluid administration in these extreme situations.

**Timing and Volume of Administration**

For forms of hypovolemic shock in particular, the concept of early restoration of intravascular volume to prevent circulatory collapse has long been recognized. In the hemorrhagic patient,
volume resuscitation combined with source control may limit or prevent a state of irreversible shock, or the “lethal triad” of hypothermia, coagulopathy, and acidosis (85,86). The importance of the timing of volume loading is also paramount in all forms of shock, particularly in sepsis (87). Amplification of the previously described immune response can potentially be avoided if perfusion is restored early in the pathophysiologic process (88). Often the resuscitation process begins in the prehospital phase, with ambulance personnel administering crystalloid en route. Standard fluid boluses in the patient with shock typically amounts to 20 to 30 mL/kg at a time.

Overly aggressive fluid resuscitation both early and late in the course can be harmful in some circumstances. The concept of hypotensive resuscitation in the patient in whom mechanical control of bleeding has not been achieved—whether in traumatic injury, aortic aneurysm rupture, or gastrointestinal bleed—advocates for limited early aggressive fluid administration. Measures to raise blood pressure, particularly with fluid administration, may be counterproductive in this setting. In the penetrating thoracic trauma patient, early administration of large volumes of crystalloid has been shown to increase bleeding and subsequent mortality. Pushing fluid and intravascular volume beyond the initial phases of ischemia may propagate reperfusion injury and can be detrimental to further recovery. Restrictive fluid therapies for resuscitation have emerged in an effort to reduce the cardiac, wound healing, and pulmonary complications associated with large crystalloid infusions. Once patients have been stabilized, a more restrictive strategy of fluid administration can prevent subsequent morbidity.

Continued fluid administration beyond an initial bolus relies more on the patient's pathology and response to treatment rather than on arbitrary numbers. Physical examination characteristics such as jugular venous distension, skin turgor, urine output, and basic vital signs may give clues to volume state, but are notoriously subject to interpretation. The examiner is often misled by the appearance of gross edema, insomuch as it has no bearing on effective extracellular fluid volume in the patient with capillary leak. New tools for approximating intravascular volume status are emerging to provide dynamic variables for the clinician to use when estimating appropriateness for further volume resuscitation. Measures such as stroke volume variation (SVV) and pulse pressure variation (PPV) can provide more accurate assessment of volume status and are replacing CVP and pulmonary artery pressures as primary tools in the ICU (89–92); these will be discussed further below.

Types of Fluid

Considerable debate abounds regarding the types of fluid to be administered for shock resuscitation. Often the determination to use crystalloid versus colloid depends on fluid availability, clinical scenario, and regional practice differences. The fact that there is so much debate over the preferred fluid type indicates the lack of conclusive evidence for the superiority of one fluid over another.

Crystalloids. Composed of varying amounts of electrolytes and sugar, crystalloids are inexpensive, require no special tubing or preparation, and pose little to no risk of adverse reaction. Crystalloids used in shock resuscitation are generically categorized as isotonic or hypertonic, describing the in vivo toxicity of the fluid. Typical isotonic crystalloids used are normal saline, lactated Ringer solution, or other commercially available combinations of electrolytes with sodium as the primary ion. Lacking protein components, the isotonic crystalloids readily distribute to the extracellular fluid compartment and will require larger volumes of infusion to maintain intravascular filling. Traditional philosophy dictates that a threefold volume of crystalloid to colloid is required for intravascular expansion; this ratio has recently been debated, however, and may actually be closer to a ratio of 1.5:1 when comparing crystalloid to 5% albumin (93).

Normal saline (0.9% saline solution) and lactated Ringer solution compromise the majority of isotonic crystalloid used for shock. Normal saline provides sodium with an equal amount of chloride for buffer; hypernatremia and hyperchloremic metabolic acidosis are therefore potential consequences of continued normal saline administration (94). Because of this, normal saline should be used for resuscitation typically only for head trauma patients, as hypernatremia can increase morbidity in this patient population.

While the tonicity is essentially the same, the electrolyte composition of lactated Ringer solution is physiologically closer to plasma, with inclusion of potassium and calcium, and reduction in chloride concentrations. Lactated Ringer is considered one of the “balanced” crystalloids as a different anion is used besides chloride to balance the cations in solution (95). A chloride restrictive strategy is associated with less acute kidney injury in the critical care setting, and therefore these types of balanced solutions are favorable.

Hypertonic Crystalloids. Combining the convenience of crystalloid with the tonicity of colloids, hypertonic saline (HTS) has emerged as an important tool in shock resuscitation. Hypertonicity of the sodium concentration promotes influx of fluid from the interstitial space. As such, HTS is advantageous for rapid, low-volume resuscitation for hypovolemic shock, particularly in situations where resources and space are limited, such as a combat setting. Hypertonic solutions also favorably impact immune modulatory function. Studies investigating hemorrhagic shock have found a decrease in neutrophil activation, and upregulation of anti-inflammatory cytokine production with use of HTS. Additional data suggest that HTS positively affects cardiac function in addition to volume expansion in septic shock (96,97).

While relatively safe compared to colloid infusion, the administration of high concentrations of sodium for volume resuscitation carries the concern for hypernatremia and hyperosmolality. Compromise of renal function is likewise feared with high sodium and osmolar loads (98,99). Reports of hypokalemia, metabolic acidosis, and impaired platelet aggregation have also been documented with HTS use (100). Primary use of HTS is in the traumatic brain injury patient; small volumes should be used and electrolytes, creatinine, and serum osmolality should be checked frequently to avoid the abovementioned complications.

Colloids. In reference to volume resuscitation, colloids generally consist of fluids that have a higher molecular weight based on composition consisting of protein or starches. These components increase the cost of colloids, make them susceptible to shortage, and mandate specialized tubing for delivery. The possibility of transfusion reaction is increased, as some of these compounds are derived from blood products. Likewise, allergic reactions can be noted with some of the synthetic formulations.
Conceptually, colloids more rapidly expand intravascular volume owing to their higher oncotic pressure. This effect may not necessarily persist beyond a few hours, especially in the critically ill patient in which capillary permeability is altered (101). In addition to more rapid volume expansion with less fluid infusion, this same increase in intravascular oncotic pressure has prompted the employment of colloids with the intent to reduce or prevent secondary edema; this effect has not been appreciated clinically, however. Studies reveal that edema formation is more dependent on fluid volume than on fluid type per se (102).

**Albumin.** First used for fluid resuscitation during World War II, albumin is a colloid derived from pooled human plasma and diluted with sodium. Preparations consist of 5% or 25% solution in quantities of 250 to 500 mL or 50 mL, respectively. As a blood product derivative, albumin is subject to disadvantages faced by other donated products—namely, periodic shortages, high acquisition costs, and refusal based on religious grounds. While transmission of viruses or other bloodborne diseases is theoretically a risk, only a few cases have been reported. Like any resuscitation fluid, patients are subject to sequelae of volume overload if infusion amounts are not monitored.

While indications for albumin use are broad, proven benefit to particular therapies is increasingly narrow. Numerous studies detailing poor prognosis with low serum albumin levels in critically ill patients prompted attempts to improve survival with intravenous supplementation (103–105). Compared with other colloid administration, albumin itself has no benefit in this patient population (106, 107).

Albumin as a resuscitation fluid likewise has come under scrutiny. Previously, studies investigating albumin as a volume expander have been underpowered, prompting meta-analysis as the primary statistical measure of its worth. An initial Cochrane review comparing albumin to crystalloid examined 24 studies and found a 6% increase in absolute risk of death with albumin infusion (108). To confuse matters, subsequent meta-analysis of 55 studies showed no difference in mortality between albumin and crystalloid for resuscitation (109, 110). In 2004, the Saline versus Albumin Fluid Evaluation (SAFE) trial prospectively compared albumin to isotonic crystalloid for fluid resuscitation in a mixed ICU population (93); results showed no difference in morbidity or mortality overall with either fluid choice, although traumatic brain injury patients did show increased morbidity with albumin use. Subsequent multicenter studies demonstrated no difference in morbidity or mortality for albumin versus crystalloid in septic shock resuscitation.

**Starches.** Synthetic colloid polymers were developed for use in volume resuscitation in an attempt to retain the oncotic properties of albumin while decreasing cost and transfusion risk. Initial formulations of hydroxyethyl starch (HES) included high-molecular-weight moieties, accounting for an increased risk of coagulation and renal disturbances associated with their use (111–113). Lower-molecular-weight HES solutions were subsequently developed, with resultant fewer negative effects on bleeding, but concern for dose-dependent impaired renal function persisted (114).

While numerous studies have illustrated downregulation of proinflammatory cytokines with HES use, some of these results may be an effect of the efficiency of volume resuscitation, and not necessarily the fluid itself (115–117). Ongoing concerns about increase in renal failure and mortality in septic and mixed ICU populations prompted the U.S. Food and Drug Administration to add a warning regarding use of HES products in 2013. As such, HES use is not supported at this time.

Despite the theoretical advantage of colloids over crystalloids for shock resuscitation, there is no evidence from randomized controlled trials to demonstrate mortality difference. Studies demonstrating improved short-term gains with colloids use a heterogeneous population and/or fluid composition, making interpretation and application difficult. In larger studies, short-term physiologic gains made from colloid use do not translate to longer-term improvement. As colloids are not associated with improvement in survival, and are considerably more expensive, it is hard to justify their use (118).

**Special Fluid Considerations**

**Hemorrhagic Shock Resuscitation**

Aggressive use of crystalloids during the Vietnam conflict resulted in improved mortality and reduction in renal failure, but also led to the emergence of acute lung injury and acute respiratory distress syndrome in the trauma population. Extensive use of crystalloids for trauma followed, with the popular concept of pushing fluids beyond supranormal resuscitation goals (119). Consequences of this large-volume approach are becoming more evident, with adverse cardiac, pulmonary, coagulation, and immunologic effects documented with massive crystalloid infusion (120).

With the recognition of the “blood lethal triad” of coagulopathy, acidosis, and hypothermia in the bleeding trauma patient, methods to physiologically break this cycle have come into play. Pushing crystalloids for shock resuscitation merely aggravates this pathway. Appropriate resuscitation in hemorrhagic shock includes measures such as damage control surgery and hemostatic resuscitation. The goals of damage control surgery are to stop ongoing hemorrhage and provide control of any visceral injury in a truncated manner such that the patient can return to the ICU for warming and resuscitation. Key to this approach is a massive transfusion strategy in which blood is provided in a balanced manner and in preference to crystalloid or other colloid during this time period. Since the patient bleeds whole blood, it makes physiologic sense to provide blood products in a manner that resembles that of whole blood. Major studies including PROMMTT and PROPPPR have demonstrated survival benefits for hemorrhagic shock when providing platelets:FFP:RBC in as close to a 1:1:1 ratio as possible (121,122). The combination of early mechanical bleeding control with this hemostatic resuscitation is the current standard for hemorrhagic shock resuscitation.

**Pharmacotherapy in Shock**

Primary therapy for shock involves treating the cause and supplementation with fluids. When these modalities fail, vasoressors are typically employed as supplementation. Shock is not hypotension alone, however, and other agents can be used to compensate for the diminished tissue perfusion defined by this syndrome. Drugs used for shock will be examined here by the classifications of vasoressor, inotrope, and miscellaneous, although these categories may overlap to a degree.
Vasopressors

Vasopressors are generally given after an initial fluid bolus has failed or had marginal effect. Within the context of avoiding the consequences of excessive fluid administration, vasopressors may help limit volumes of fluid given; however, peripheral and end-organ vasoconstriction have their own adverse effects. Striking the balance between volume and vasopressors in the context of timing and type of shock is therefore a key component to resuscitation. With early recognition of shock, vasopressors can often be avoided by restoration of volume (123).

End-organ arterial autoregulation generally compensates for decreased MAP within a certain range; however, local vasoconstriction and vasodilatation may be unable to overcome extremes of perfusion. Administering catecholamines may help improve MAP and therefore improve tissue perfusion by redistributing CO. The venous compartment also benefits from vasopressor therapy by decreasing compliance and therefore improving effective volume. Classifications of vasopressors consist of natural and synthetic versions of catecholamines (Table 44.8).

Norepinephrine. A naturally occurring vasopressor, norepinephrine is released by the postganglionic adrenergic nerves in response to stress. It has potent α-adrenergic effects, with less potent β-stimulation. The α-adrenergic effects lead to increased systolic and diastolic blood pressure, with the addition of increased venous return via decreasing venous capacitance; this subsequently leads to increased cardiac filling pressure. Effect on the coronary arterial flow is enhanced via the increase in diastolic blood pressure. The β-adrenergic effects lead to increased chronotropic function, although this is limited by the baroreflex of vasoconstriction, resulting in zero net change in heart rate. Enhanced inotrope stimulation and stroke volume are likewise negated by an increase in left ventricular afterload, leading to a limited increase in CO.

Historically, the exaggerated peripheral vasoconstrictive properties of the drug have promoted a level of distrust leading to the often quoted “leave ‘em dead.” These fears are largely unfounded at indicated dosing ranges, and use of the drug may actually enhance renal function (124). The drug is safe and easily titratable, and lacks the tachyarrhythmic properties of other frequently used agents for shock. Resurgence in the use of norepinephrine has occurred with the recognition of its beneficial properties, and is now recommended as the first-line vasopressor in the treatment of shock (125).

Epinephrine. Epinephrine is the major physiologic adrenergic hormone of the adrenal medulla and represents the maximum in catecholamine stimulation. The agent potently stimulates α-receptors with resultant marked venous and arterial vasoconstriction. These changes may lead to detrimental effects on regional blood flow, particularly on mesenteric and renal vascular beds. β-Effects lead to increased heart rate and inotropism. Due to counter effects of β-vasodilation, the diastolic blood pressure is only slightly affected, with a lesser degree of increase in MAP than seen with norepinephrine. Stimulation of β-receptors and blunting of mast cell response also makes epinephrine highly effective for anaphylaxis. Epinephrine has dose-dependent effects, with very low doses stimulating primarily β-receptors. This property makes epinephrine attractive as a primary inotrope; however, the range of that particular low dose

### Table 44.8 Sympathomimetic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual IV dose</th>
<th>Adrenergic Effects</th>
<th>Ananthromogenic Potential</th>
<th>Dopa Setting</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>1–2 μg/kg/min²</td>
<td>1+</td>
<td>1+</td>
<td>3+</td>
<td>Oliguria despite “normal” blood pressure</td>
</tr>
<tr>
<td></td>
<td>2–10 μg/kg/min</td>
<td>2+</td>
<td>2+</td>
<td>3+</td>
<td>Initial emergency treatment of hypotension</td>
</tr>
<tr>
<td></td>
<td>10–30 μg/kg/min</td>
<td>3+</td>
<td>2+</td>
<td>3+</td>
<td>(any cause)</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2–30 μg/kg/min</td>
<td>1+</td>
<td>3+</td>
<td>0</td>
<td>Cardiac shock</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.01–0.1 μg/kg/min (0.5–80 μg/min)</td>
<td>3+</td>
<td>2+</td>
<td>0</td>
<td>Pulmonary edema with marginal blood pressure</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.5–1 mg (1:10,000)</td>
<td>1+</td>
<td>2+</td>
<td>0</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td></td>
<td>0.01–0.3 μg/kg/min (1–200 μg/min)</td>
<td>3+</td>
<td>3+</td>
<td>0</td>
<td>Severe hypotension and bradycardia</td>
</tr>
<tr>
<td></td>
<td>0.3–0.6 mg SQ (1:1,000)</td>
<td>2+</td>
<td>3+</td>
<td>0</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>0.1–1 μg/kg/min (20–200 μg/min)</td>
<td>3+</td>
<td>0</td>
<td>0</td>
<td>Distributive shock when no cardiac effect is desired</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>0.03–0.3 μg/kg/min (2–20 μg/min)</td>
<td>0</td>
<td>3+</td>
<td>0</td>
<td>Refractory bradycardia</td>
</tr>
<tr>
<td>Mirinone²</td>
<td>Load: 50 μg/kg over 10 min</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Denervated hearts</td>
</tr>
</tbody>
</table>

Dopa, dopamine.

²Increase renal and splanchnic blood flow. No impact on AKI.

³Milligram doses are in bold to differentiate from micrograms.

²SQ: Subcutaneous dosing, may be repeated every 15–20 min.

³Phosphodiesterase inhibitors; require loading dose.
varies with each patient and titration may prove dangerous. Epinephrine is advocated as a secondary pressor for septic shock, and as the primary pressor for cardiac arrest resuscitation.

**Dopamine.** As the hormone precursor of norepinephrine and epinephrine, dopamine stimulates α-, β-, and dopaminergic receptors in a dose-dependent fashion. This results in mixed vasoconstrictive, inotropic, chronotropic, and vasodilatory effects.

Classically, “renal-dose” dopamine ranges from 0 to 5 μg/kg/min and results in vasodilatation of renal and mesenteric vascular beds via dopamine receptors. Although this stimulation results in diuresis, the overall effect on renal function and need for renal replacement therapy is unchanged and may actually be worsened (126). Conversely, at high doses of 10 to 20 μg/kg/min, α-effects predominate, resulting in almost pure vasoconstriction. β-Receptor stimulation at middle doses of 5 to 10 μg/kg/min results in increased inotropic and chronotropic function leading to increased MAP similar to norepinephrine. However, without simultaneous activation of α-receptors at this dose, vasodilatation by dopamine receptors is unopposed and reflex tachycardia may predominate.

In the past, dopamine has been postulated as the first inotrope of choice in cardiogenic failure with hypotension (127). More recent recommendations, however, identify sympathetic inotropes such as dopamine as increasing mortality when used for primary left heart failure (128). Likewise, in septic shock, norepinephrine has a more reliable dosing profile and has demonstrated more beneficial outcomes compared to dopamine (129). Tachyhydryshythmias are the predominant concern with dopamine, conversely making it potentially useful in shock with associated bradycardia.

**Phenylephrine.** Phenylephrine is a rapidly acting vasopressor with a short duration of action and pure α1-receptor stimulation. As such, it increases MAP primarily by increasing SVR. Reflex bradycardia may develop; therefore, it is occasionally used for distributive shock in the face of tachyhydryshythmias. This same unopposed increase in SVR also impairs CO in the patient with impaired pump function. The use of phenylephrine has since fallen out of favor, and is generally reserved for the pregnant patient with shock for whom other vasopressors may be detrimental or as rescue therapy in patients with a high CO and low SVR. Its rapid onset and short duration of action also makes it useful in the context of low intraoperative blood pressure due to vasodilatory inhaled anesthetics.

**Inotropes**

As a group, inotropic agents augment CO by increasing contractility. Sources of left ventricular failure are many, including exacerbation of congestive heart failure (CHF), acute infarction, or sepsis-related cardiomyopathy. The inflammatory state that accompanies some forms of cardiogenic shock may result in vasodilatation instead of vasoconstriction, making particular inotropes less useful for restoration of tissue perfusion (130). As with other forms of pharmacotherapy for shock, inotropes should be used only in a short-term situation until underlying pathology can be corrected. Prolonged use can increase myocardial work and exacerbate ischemia.

**Dobutamine.** Dobutamine is a synthetic adrenergic agent derived from dopamine. Current formulation of the drug is as a racemic mixture, with the L-isomer stimulating α,- and the D-isomer stimulating β,- and β2-receptors. This combined stimulation results in a net increase in inotropic and chronotropic parameters. In theory, vasodilatory (β) effects are limited, making dobutamine useful in increasing pump function without lowering blood pressure. In practice, some degree of vasodilatation is encountered, resulting in decreased blood pressure and tachycardia acutely. With increase in CO, however, the BP generally corrects to normal. For this reason, adequate volume loading prior to initiation of dobutamine is emphasized. Likewise, the lack of increase in BP makes dobutamine a poor selection as monotherapy in primary cardiogenic shock. At higher doses, vasoconstriction may dominate leading to increased myocardial O2 consumption (VO2), so it should be used with caution in states where ischemia is present. Currently, dobutamine is the standard inotrope used in noncardiogenic shock (such as sepsis) when cardiac contractility is compromised (131).

**Isoproterenol.** With practically no α-adrenergic stimulation, isoproterenol functions as a pure β-agonist. β-Stimulation results in increased SV and heart rate, while β-stimulation induces vasodilatation. The net result is that of enhanced CO without the benefit of redistribution of blood flow. Increased myocardial VO2 exacerbated by lack of coronary perfusion due to decreased diastolic pressures may lead to cardiac ischemia. Use of isoproterenol is generally limited to β-blocker overdose or in the atropine-resistant transplanted heart.

**Phosphodiesterase Inhibitors.** A novel agent in vasoactive treatment, milrinone is the most common synthetic phosphodiesterase III inhibitor. Reduction in this enzyme results in an increase in cyclic adenosine monophosphate (cAMP), a modulator of myocardial contractility. Additional increase in cAMP results in vasodilatation, with the net effect of increasing CO and, at higher doses, tachycardia. This vasodilatory effect may decrease effective left ventricular preload, but may also benefit afterload reduction, reducing cardiac work. In the hypotensive patient, acute vasodilatation may not be tolerated, thus, while not recommended in vasodilatory shock for this reason, milrinone may be used in specific situations for cardiogenic shock. These include advanced heart failure in patients awaiting heart transplant, in acute decompensation of CHF on standard medications, and in patients in cardiogenic shock with long-term β-blocker use (132). Amrinone is an additional agent in this class, but its use is limited by its side effect profile.

**Levosimendan.** Levosimendan is the singular drug in a new class of inotropic agents. Primary mechanism of action is by increasing the sensitivity of troponin C for calcium without enhancing influx of calcium itself. It also opens ATP-dependent potassium channels, leading to enhanced ventricular contractility without compromising diastolic function. This vasodilatory effect makes it particularly useful for myocardial protection. The drug is primarily used for acute and chronic heart failure; dosing is 0.05 to 0.2 μg/kg/min. It performs similarly to dobutamine for acute heart failure.

**Vasopressin.** Vasopressin is an attractive hormone for use in shock states not only for its vasoconstrictive properties but also for its antidiuretic effects. As a noncatecholamine vasopressor, it acts via V1 receptors to restore vascular tone. Catecholamine responsiveness may decrease over time during severe sepsis, possibly due to an increase in NO-induced vasodilatation. Likewise, studies of hemorrhagic and vasodilatory
shock have demonstrated a relative deficiency of vasopressin. For this reason, vasopressin is often used at a low dose without titration, in the manner of hormone replacement. Potentiation of adrenergic agents makes vasopressin particularly useful in combination with norepinephrine, and has been recommended for the treatment of septic shock to reduce catecholamine administration (133). Although evidence from meta-analysis demonstrates decreased mortality with vasopressin administration versus norepinephrine in septic shock, a recent randomized control trial demonstrates no difference (134).

END POINTS OF RESUSCITATION

The primary goal in the management of shock is a return to normal tissue perfusion. If shock is recognized promptly, and timely, appropriate treatment strategies are implemented, reversal of its clinical signs may be appreciated. These include improvement in mental status, normalization of vital signs, and restoration of urine output. However, despite these findings, many patients remain in a state of occult hypoperfusion and ongoing tissue acidosis with resultant multiple organ failure and death (12,135). Consequently, better end points of resuscitation are needed to guide resuscitation efforts.

The holy grail of shock resuscitation in recent years has been that of achieving adequate end-organ DO2. DO2 is a function of cardiac index (CI), Hgb, and oxygen saturation (SaO2), as seen in the Fick’s equation. The use of DO2 as a resuscitation end point has had varying results. In the 1970s, Shoemaker et al. (136) reviewed the physiologic patterns in surviving and nonsurviving shock patients, observing that survivors had significantly increased DO2, VO2, and CO values (DO2 ≥600 mL/min/m2, VO2 ≥170 mL/min/m2, and CI ≥4.5 L/min/m2). In a subsequent prospective study, they documented decreased complications, lengths of stay, and hospital costs when employing these parameters as goals of resuscitation in high-risk surgical patients. Further work by Shoemaker’s group and others have shown that utilization of this “supranormal resuscitation” strategy decreases morbidity and mortality in critically ill patients (137).

More recently, however, supranormal resuscitation has been associated with significant morbidity—ongoing tissue ischemia, abdominal compartment syndrome, coagulopathy, and CHF—and mortality. Velmahos et al. (138) documented improved survival in patients who achieved supranormal DO2; however, they concluded that “this was not a function of the supranormal resuscitation, but rather the patient’s own ability to achieve these parameters”. As demonstrated here, the utilization of DO2 and, more specifically, “supranormal resuscitation” in the management of shock has had varying degrees of success. Different strategies to monitor end-organ perfusion, as well as methods to assess volume responsiveness, are more commonly used.

Basic Hemodynamic Monitoring

Basic monitoring in patients with shock includes noninvasive vital sign measurements, cardiac rhythm, and urinary output and other clinical variables of end-organ perfusion. The hemodynamic profiles of shock are depicted in Table 44.2. It is these parameters that often guide the management of shock and, in that context, meticulous equipment calibration and documentation are essential (139,140). These measurements are subject to many potential artifacts as seen in Table 44.9 (14). Therefore, it is critical for the clinician to evaluate these variables in concert with the patient’s clinical picture.

Invasive Hemodynamic Monitoring

Central venous catheters are commonly used in this patient population. As such, CVP measurements are readily available and were, in the past, often used as a rough guideline in the resuscitation of shock. It is increasingly recognized that there is actually very little correlation between intravascular volume status and CVP. As a consequence, utilization of CVP during shock resuscitation has fallen out of favor. Similarly, PACs can provide numerous additional hemodynamic parameters; however, it is not clear that the appropriate end point is the normalization of these values, nor is it clear how these end points should be achieved (141–144). Observational studies and meta-analysis have suggested that PACs may actually increase mortality, ICU length of stay, hospital costs, and resource utilization (145).

Blood and Serum Markers

Numerous laboratory values can provide some clues to degree and correction of shock. SvO2 can be obtained from a PAC and provides an indication of the end result of DO2 and VO2; an approximation of this can also be obtained from a central venous catheter (ScvO2), although the value will be higher. While both SvO2 and ScvO2 can be obtained continuously, and while initially considered essential to goal-directed resuscitation, both methods have fallen out of favor, both due to need for invasive monitoring, and due to equivalency of lactate clearance as a surrogate.

Base deficit is defined as the amount of base, in millimoles, required to increase 1 L of whole blood to the predicted pH based on the PaCO2 (146). In shock states, the base deficit may serve as a surrogate marker for anaerobic metabolism and subsequent lactic acidosis if metabolic acidosis is the primary disorder and not a compensatory response (147). In this sense, it is superior to pH secondary to the many compensatory mechanisms in place to normalize pH (148). Base deficit has numerous confounders, so it should be used as a method to trend resuscitation and not as a stand-alone measure.

Serum lactate levels are used extensively in monitoring shock resuscitation. In patients suffering from noncardiogenic shock, Vincent et al. documented a correlation between initial serum lactate levels and patient outcomes (149). However, in shock resuscitation it is the lactate trend that is most predictive of mortality. Patients whose lactate levels normalized (serum levels <2 mmol/L) within 24 hours had less than 10% mortality, those who normalized between 24 and 48 hours had a 25% mortality, while those who did not normalize by 48 hours had over 80% mortality. Lactate measurement is now an integral part of the Surviving Sepsis Guidelines for monitoring resuscitation (125).

Esophageal Doppler

Esophageal Doppler measurement uses estimation of aortic velocity as a surrogate for CO. It also provides a reasonably accurate measure of SVV. Despite variable degrees of artifact with this method, it is well studied and provides the most accurate estimation of CO when compared to PAC measurements.
SVV is also extremely valuable from this method, with data supporting its use during perioperative resuscitation. Use is limited by discomfort to the patient and possible complications from insertion.

**Near-Infrared Spectroscopy**

Near-infrared spectroscopy (NIRS) is the measurement of the wavelength and intensity of the absorption of near-infrared light by a sample. In medicine, it uses chromophores such as Hgb to do so and allows for the measurement of tissue oxygenation, PO₂, PCO₂, and pH (150). Taylor et al. (151) documented a close correlation between tissue oxygenation measurements and hemodynamic parameters in a model of hemorrhagic shock. In this study, NIRS was also better able to differentiate “responder” from “nonresponder” animals in comparison to lactate levels or global DO₂. This technology is limited by cost and waveform interference.

**Photoplethysmography**

Similar to NIRS, photoplethysmography (PPG) uses measurement of intensity of light as it relates to a waveform produced peripherally. Essentially, PPG technology uses pulse oximeter data to calculate a variability index similar to PPV which is then used to predict fluid responsiveness. Although it does not correlate as

<table>
<thead>
<tr>
<th>Variable</th>
<th>Artifact</th>
<th>Causes</th>
<th>Comments/Corrective Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular pressures</td>
<td>Preload overestimation</td>
<td>Technical: Improper leveling of transducer</td>
<td>Avoid with rigid nursing protocols</td>
</tr>
<tr>
<td>(including PCWP)</td>
<td></td>
<td>Improper calibration</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improper system frequency response</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Respiratory: Not recording pressures at end-expiration during mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active expiratory effort</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive end-expiratory pressure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improper positioning of catheter tip</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preload underestimation</td>
<td>Technical: as for overestimation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Respiratory: Not recording pressures at end-expiration during spontaneous breathing</td>
<td></td>
</tr>
<tr>
<td>Cardiac output</td>
<td>Inaccuracies</td>
<td>Technical: Incorrect injectable volume; thermistor contact with vessel wall; incorrect computational constant</td>
<td>Inspect temperature curves; suspect if pulmonary artery waveform is damped; follow rigid nursing protocol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac: Tricuspid regurgitation</td>
<td>Do not use in presence of significant tricuspid regurgitation</td>
</tr>
<tr>
<td></td>
<td>Wide variation</td>
<td>Technical: as for inaccuracies</td>
<td>Delete measurements with &gt;20% variation from the mean</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Respiratory: Variable respiratory rate during mechanical ventilation</td>
<td>Average measurements throughout respiratory cycle</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation</td>
<td>Inaccuracies</td>
<td>Technical: Light reflecting against vessel wall, catheter kinking</td>
<td>Note computer error messages</td>
</tr>
<tr>
<td></td>
<td>Misinterpretation</td>
<td>Presence of significant HgbCO</td>
<td>Measure HgbCO directly at least once</td>
</tr>
<tr>
<td></td>
<td>Extravascular lung water</td>
<td>Inaccurate measurement of cardiac output (as above)</td>
<td>Correlate cardiac output with regular thermodilution measurements</td>
</tr>
<tr>
<td></td>
<td>Underestimation</td>
<td>Presence of significant areas of nonperfused lung</td>
<td>Measurements suspect in presence of significant regional disease (i.e., lobar pneumonia) or known vascular obstruction</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>Inaccuracies</td>
<td>Inaccurate measurement of cardiac output (as above)</td>
<td>Measure directly (see above)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inaccurate measurement of blood pressure</td>
<td></td>
</tr>
</tbody>
</table>

PCWP: pulmonary capillary wedge pressure; PEEP: positive end-expiratory pressure; PAD: pulmonary artery diastolic; HgbCO: carboxyhemoglobin; Pvo₂: mixed venous oxygen partial pressure.
well to intravascular measurements of PPV, it has the advantage of being noninvasive, less expensive, and easy to use.

**Bioimpedance**

Bioimpedance and bioimpedance devices assess thoracic volume status based on noninvasive measurement of electrical current via Ohm’s law. In theory, they can be used to roughly assess SV and, therefore, when multiplied times the heart rate, yield CO. Typically, they are most useful for measuring volume responsiveness. Although these are noninvasive and easy to use, they are limited by a large amount of artifact.

**Arterial Waveform Analysis**

Increasingly popular for assessing fluid responsiveness, arterial waveform analyzers estimate SV and CO. This can be done either with an arterial catheter or with both an arterial and venous catheter to improve accuracy in some devices. Measuring the variation in stroke volume during the respiratory cycle can estimate the SVV, which is a rough estimate of where the heart is on the Starling curve. These devices can be extremely useful when determining need for further fluid administration in patients who are mechanically ventilated. Use of SVV, instead of CVP, has favorable outcomes on perioperative patients in particular, as these individuals receive, in general, less fluid.

**Key Points**

- **Shock** is likely the most common life-threatening diagnosis made in the ICU.
- Despite technological advances, it remains a significant source of morbidity and mortality.
- As the etiologies of shock are vast, the diagnosis of shock and its inciting source can be difficult to identify. Aggressive diagnostic testing is required to avoid irreversible cellular injury, multiple organ failure and, potentially, death.
- The primary goal in the management of shock is a return to normal tissue perfusion. This is attained via various volume resuscitation modalities, pharmacologic agents, and resuscitation strategies.
- Past and current research efforts continue in hopes of optimizing the diagnosis and management of shock with the ultimate goal of improving patient outcomes.

**References**


