

FURTHER READING

- AMATO MBP et al: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 338:347, 1998
- BOZEMAN YP et al: Etomidate as a sole agent for endotracheal intubation in the prehospital air medical setting. *Air Med J* 21:32, 2002

- ESTEBAN A et al: A comparison of four methods of weaning patients from mechanical ventilation. *N Engl J Med* 332:345, 1995
- GATTINONI L et al: Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 345:568, 2001
- INGENITO EP, DRAZEN JM: Mechanical ventilators, in *Principles of Critical Care*, 2d ed, JB Hall, GA Schmidt, LDH Wood (eds). New York, McGraw-Hill, 1997, pp 142–154
- TOBIN MJ: Advances in mechanical ventilation. *N Engl J Med* 344:1986, 2001

Section 2 Shock and Cardiac Arrest

253 APPROACH TO THE PATIENT WITH SHOCK

Ronald 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 hemorrhage, 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. Au-

to-regulation, 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.

Arteriolar vascular smooth muscle has both α - and β -adrenergic receptors. The α_1 receptors mediate vasoconstriction, while the β_2 receptors mediate vasodilation. Efferent sympathetic fibers release norepinephrine, which acts primarily on α_1 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 thromboxane A_2 . Both norepinephrine and epinephrine are released by the adrenal medulla, and the concentrations of these catecholamines in the bloodstream rise. Circulating vasodilators in shock include prostacyclin [prostaglandin (PG) I_2], nitric oxide (NO), and, importantly, products of local metabolism such as adenosine that match flow to the metabolic needs of the tissue. The balance between these various vasoconstrictor and vasodilator influences acting upon the microcirculation determines local perfusion.

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 osmolarity. 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-interstitial liquid exchange (Chap. 29). Metabolic changes (including hyperglycemia and elevations in the products of glycolysis, lipolysis, and proteolysis) raise extracellular osmolarity, leading to an osmotic gradient between cells and interstitium that increases interstitial and intravascular volume at the expense of intracellular volume.

CELLULAR RESPONSES Interstitial transport of nutrients is impaired, leading to a decline of 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 vasoconstrictor 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,

TABLE 253-1 Classification of Shock

Hypovolemic	Septic
Traumatic	Hyperdynamic
Cardiogenic	Hypodynamic
Intrinsic	Neurogenic
Compressive	Hypoadrenal

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 an autonomic response that attempts to restore blood volume, maintain central perfusion, and mobilize metabolic substrates. Hypotension disinhibits the vasomotor center, resulting in increased adrenergic output and reduced vagal activity. Release of norepinephrine induces peripheral and splanchnic vasoconstriction, a major contributor 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 innate immune cells.

Severe pain and other severe stress cause the hypothalamic release of adrenocorticotropic 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. Vasopressin has a direct action 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 myocardial 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 circulating blood volume, most in the small veins, and serves as a dynamic reservoir for autoinfusion of blood. Active venoconstriction as a consequence of α -adrenergic activity is an important compensatory mechanism for the maintenance of venous return and therefore of ventricular filling during shock. On the other hand, venous dilatation, as occurs in neurogenic shock, reduces ventricular filling and hence stroke volume and cardiac output (see below).

PULMONARY 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 tachypnea reduces tidal volume and increases both dead space and minute ventilation. Relative hypoxia and the subsequent tachypnea 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, hypoxemia, 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 requirements of respiratory muscles increase.

RENAL RESPONSE Acute renal failure (Chap. 260), a serious complication of shock and hypoperfusion, occurs less frequently than heretofore 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 aminoglycosides and angiographic contrast media), and rhabdomyolysis; the latter may be particularly severe in skeletal muscle trauma. The physiologic response of the kidney to hypoperfusion 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 necrosis of tubular epithelium and tubular obstruction by cellular debris with back-leak of filtrate. The depletion of renal ATP stores that occurs with prolonged renal hypoperfusion contributes to subsequent impairment 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 converted from pyruvate in the periphery in the presence of oxygen deprivation) enhances the hepatic production of glucose. With reduced availability of oxygen, the breakdown of glucose to pyruvate and ultimately lactate represents an inefficient cycling of substrate with minimal net energy production. An elevated plasma lactate/pyruvate ratio is consistent with anaerobic 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 injury 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 subsequent lysis leading to repeated episodes of ischemia and reperfusion. Components of the coagulation system, such as thrombin, are potent proinflammatory mediators that cause expression of adhesion molecules on endothelial cells and activation of neutrophils, leading to microvascular injury. Coagulation also activates the kallikrein-kininogen cascade, contributing to hypotension.

TABLE 253-2 Normal Hemodynamic Parameters

Parameter	Calculation	Normal Values
Cardiac output (CO)	SV × HR	4–8 L/min
Cardiac index (CI)	CO/BSA	2.6–4.2 (L/min)/m ²
Stroke volume (SV)	CO/HR	50–100 mL/beat
Systemic vascular resistance (SVR)	[(MAP – RAP)/CO] × 80	700–1600 dynes · s/cm ⁵
Pulmonary vascular resistance (PVR)	[(PAP _m – PCWP)/CO] × 80	20–130 dynes · s/cm ⁵
Left ventricular stroke work (LVSW)	SV(MAP – PCWP) × 0.0136	60–80 g-m/beat
Right ventricular stroke work (RVSW)	SV(PAP _m – RAP)	10–15 g-m/beat

Note: HR, heart rate; BSA, body surface area; MAP, mean arterial pressure; RAP, right atrial pressure; PAP_m, pulmonary artery pressure—mean; PCWP, pulmonary capillary wedge pressure.

Eicosanoids are vasoactive and immunomodulatory products of arachidonic acid metabolism that include cyclooxygenase-derived prostaglandins and thromboxane A₂ as well as lipxygenase-derived leukotrienes and lipoxins. Thromboxane A₂ is a potent vasoconstrictor that contributes to the pulmonary hypertension and acute tubular necrosis of shock. PGI₂ 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. LTB₄ is a potent neutrophil chemoattractant and secretagogue that stimulates the formation of reactive oxygen species. Platelet-activating factor, an ether-linked, arachidonyl-containing phospholipid mediator, causes pulmonary vasoconstriction, bronchoconstriction, systemic vasodilation, increased capillary permeability, and the priming of macrophages and neutrophils to produce enhanced levels of inflammatory mediators.

Tumor necrosis factor (TNF) α, 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 chemoattractants 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), the inflammatory response stimulates the inducible isoform of NO synthase (iNOS), which is overexpressed and produces toxic NO and oxygen-derived free radicals which contribute to the hyperdynamic cardiovascular response in sepsis.

Multiple inflammatory cells, including neutrophils, macrophages, and platelets, are a major contributor to inflammation-induced injury. Margination of activated neutrophils in the microcirculation is a common pathologic finding in shock, causing secondary injury due to the release of toxic oxygen radicals and proteases. Tissue-fixed macrophages produce virtually all major components of the inflammatory response and orchestrate the progression and duration of the inflammatory response.

TABLE 253-3 Oxygen Transport Calculations

Parameter	Calculation	Normal Values
Oxygen-carrying capacity of hemoglobin		1.39 mL/g
Plasma O ₂ concentration		P _{O₂} × 0.0031
Arterial O ₂ concentration (Ca _{O₂})	1.39 Sa _{O₂} + 0.0031 Pa _{O₂}	20 vol%
Venous O ₂ concentration (Cv _{O₂})	1.39 Sv _{O₂} + 0.0031 Pv _{O₂}	15.5 vol%
Arteriovenous O ₂ difference (Ca _{O₂} – Cv _{O₂})	1.39 (Sa _{O₂} – Sv _{O₂}) + 0.0031 (Pa _{O₂} – Pv _{O₂})	3.5 vol%
Oxygen delivery (D _{O₂})	Ca _{O₂} × CO (L/min) × 10 (dL/L) 1.39 Sa _{O₂} × CO × 10	800–1600 mL/min
Oxygen uptake (V _{O₂})	(Ca _{O₂} – Cv _{O₂}) × CO × 10 1.39 (Sa _{O₂} – Sv _{O₂}) × CO × 10	150–400 mL/min
Oxygen delivery index (D _{O₂} I)	D _{O₂} /BSA	520–720 (mL/min)/m ²
Oxygen uptake index (V _{O₂} I)	V _{O₂} /BSA	115–165 (mL/min)/m ²
Oxygen extraction ratio (O ₂ ER)	[1 – (V _{O₂} /D _{O₂})] × 100	22–32%

Note: P_{O₂}, partial pressure of oxygen; Sa_{O₂}, saturation of hemoglobin with O₂ in arterial blood; Pa_{O₂}, partial pressure of O₂ in arterial blood; Sv_{O₂}, saturation of hemoglobin with O₂ in venous blood; Pv_{O₂}, partial pressure of O₂ in venous blood; CO, cardiac output; BSA, body surface area.

APPROACH TO THE PATIENT

Monitoring Patients in shock require care in an intensive care unit. Careful and continuous assessment of the physiologic status is necessary. Arterial pressure through an indwelling line, pulse, and respiratory rate should be monitored continuously; a Foley catheter should be inserted to follow urine flow; and mental status assessed frequently.

Although there is ongoing debate as to the indications for using the flow-directed

pulmonary artery catheter (PAC, Swan-Ganz catheter), most intensivists believe that the ability to predict the hemodynamic profiles of patients in shock accurately without a PAC is poor. The PAC is placed percutaneously via the subclavian or jugular vein through the central venous circulation and right heart into the pulmonary artery. There are ports both proximal in the right atrium and distal in the pulmonary artery to provide access for infusions and for cardiac output measurements. Right atrial and pulmonary artery pressures are measured, and the pulmonary capillary wedge pressure (PCWP) serves as an approximation of the left atrial pressure. Normal hemodynamic parameters are shown in Table 212-3 and Table 253-2.

Cardiac output is determined by the thermodilution technique, and high-resolution thermistors can also be used to determine right ventricular end-diastolic volume to monitor further the response of the right heart to fluid resuscitation. A PAC with an oximeter port offers the additional advantage of on-line monitoring of the mixed venous oxygen saturation, an important index of tissue perfusion. Systemic and pulmonary vascular resistances are calculated as the ratio of the pressure drop across these vascular beds to the cardiac output (Chap. 212). Determinations of oxygen content in arterial and venous blood, together with cardiac output and hemoglobin concentration, allow calculation of oxygen delivery, oxygen consumption, and oxygen-extraction ratio (Table 253-3). The hemodynamic patterns associated with the various forms of shock are shown in Table 253-4.

In resuscitation from shock, it is critical to restore tissue perfusion and optimize oxygen delivery, hemodynamics, and cardiac function rapidly. A reasonable goal of therapy is to achieve normal mixed venous oxygen saturation and arteriovenous oxygen-extraction ratio. To enhance oxygen delivery, red cell mass, arterial oxygen saturation, and cardiac output may be augmented singly or simultaneously. An increase in oxygen delivery not accompanied by an increase in oxygen consumption implies that oxygen availability is adequate and that oxygen consumption is not flow-dependent. Conversely, an elevation of oxygen consumption with

increased cardiac output implies that the oxygen supply was inadequate. A reduction in systemic vascular resistance accompanying an increase in cardiac output indicates that compensatory vasoconstriction is reversing due to improved tissue perfusion. The determination of stepwise expansion of blood volume on cardiac performance allows identification of the optimum preload (Starling's law). An algorithm for the resuscitation of the patient in shock is shown in Fig. 253-1.

SPECIFIC FORMS OF SHOCK

HYPOVOLEMIC 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

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

Type of Shock	CVP and PCWP	Cardiac Output	Systemic Vascular Resistance	Venous O ₂ Saturation
Hypovolemic	↓	↓	↑	↓
Cardiogenic	↑	↓	↑	↓
Septic				
Hyperdynamic	↓↑	↑	↓	↑
Hypodynamic	↓↑	↓	↑	↓
Traumatic	↓	↓↑	↓	↓
Neurogenic	↓	↓	↓	↓
Hypoadrenal	↓↑	↓	↓	↓

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

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 ($\leq 20\%$ 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 ($\geq \sim 40\%$ 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 derangements 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, hemoglobin 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 hemoconcentration, and free water loss leads to hypernatremia. 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 S₃ 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.

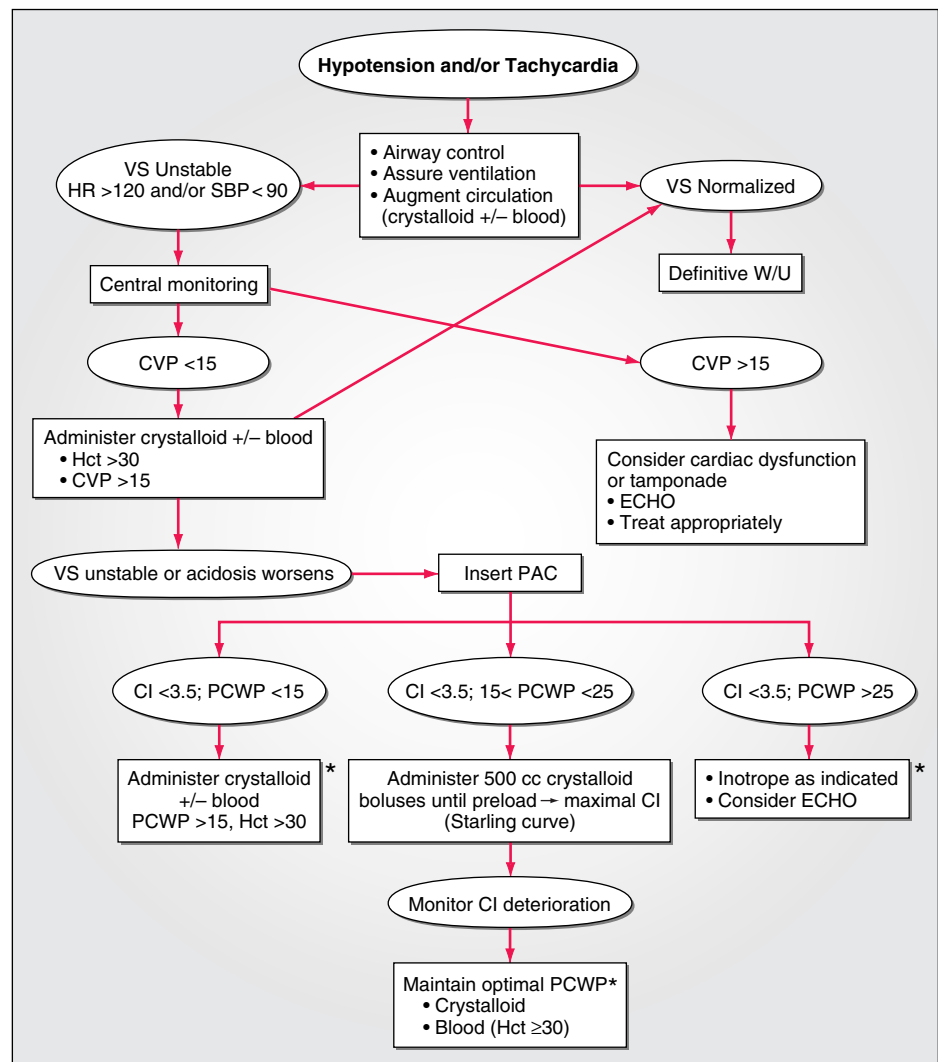


FIGURE 253-1 An algorithm for the resuscitation of the patient in shock. VS, vital signs; HR, heart rate; SBP, systolic blood pressure; W/U, work up; CVP, central venous pressure; Hct, hematocrit; ECHO, echocardiogram; PAC, pulmonary artery catheter; CI, cardiac index in (L/min)/m²; PCWP, pulmonary capillary wedge pressure in mmHg.

*Monitor SV_{O₂}, SVRI, and RVEDVI as additional markers of correction for perfusion and hypovolemia. Consider age-adjusted CI. SV_{O₂}, saturation of hemoglobin with O₂ in venous blood; SVRI, systemic vascular resistance index; RVEDVI, right-ventricular end-diastolic volume index.

TABLE 253-5 Hypovolemic Shock

Mild (<20% Blood Volume)	Moderate (20–40% Blood Volume)	Severe (>40% Blood Volume)
Cool extremities	Same, plus:	Same, plus:
Increased capillary refill time	Tachycardia	Hemodynamic instability
Diaphoresis	Tachypnea	Marked tachycardia
Collapsed veins	Oliguria	Hypotension
Anxiety	Postural changes	Mental status deterioration (coma)

Volume resuscitation is initiated with the rapid infusion of isotonic saline (although care must be taken to avoid hyperchloremic acidosis) or a balanced salt solution such as Ringer's lactate through large-bore intravenous lines. No distinct benefit from the use of colloid has been demonstrated and, in trauma patients, it is associated with a higher mortality. The infusion of 2 to 3 L over 20 to 30 min should restore normal hemodynamic parameters. Continued hemodynamic instability implies that shock has not been reversed and/or that there are significant ongoing blood or volume losses. Continuing blood loss, with hemoglobin concentrations declining to ≤ 100 g/L (10 g/dL), should initiate blood transfusion, preferably as fully cross-matched blood. In extreme emergencies, type-specific or O-negative packed red cells may be transfused. In the presence of severe and/or prolonged hypovolemia, inotropic support with dopamine, vasopressin, or dobutamine may be required to maintain adequate ventricular performance, after blood volume has been restored. Infusion of norepinephrine to increase arterial pressure by raising peripheral resistance is inappropriate, other than as a temporizing measure in severe shock while blood volume is reexpanded.

Successful resuscitation also requires support of respiratory function. Supplemental oxygen should be provided, and endotracheal intubation may be necessary to maintain arterial oxygenation. Following resuscitation from isolated hemorrhagic shock, end-organ damage is frequently less than following septic or traumatic shock. This may be due to the absence of the massive activation of inflammatory mediator response systems and the consequent nonspecific organ injury seen in the latter conditions.

TRAUMATIC SHOCK Shock following trauma is, in large measure, due to hypovolemia. However, even when hemorrhage has been controlled, patients can continue to suffer loss of plasma volume into the interstitium of injured tissues. These fluid losses are compounded by injury-induced inflammatory responses, which contribute to the secondary microcirculatory injury. This causes secondary tissue injury and maldistribution of blood flow, intensifying tissue ischemia and leading to multiple organ system failure. Trauma to the heart, chest, or head can also contribute to the shock. For example, pericardial tamponade or tension pneumothorax impairs ventricular filling, while myocardial contusion depresses myocardial contractility.

Rx TREATMENT

Inability of the patient to maintain a systolic blood pressure ≥ 90 mmHg after trauma-induced hypovolemia is associated with a mortality rate of $\sim 50\%$. To prevent decompensation of homeostatic mechanisms, therapy must be promptly administered.

The initial management of the seriously injured patient requires attention to the "ABCs" of resuscitation: assurance of an airway (A), adequate ventilation (breathing, 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 hematomata 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.

INTRINSIC 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 brady- or tachyarrhythmias, valvular heart disease, significant cardiac contusion, or in the terminal stage of chronic heart failure of any cause, including ischemic heart disease and dilated cardiomyopathy. Cardiogenic shock is characterized by a low cardiac output, diminished peripheral perfusion, pulmonary congestion, and elevation of 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. Interstitial 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 intra-alveolar fluid causes a progressive reduction in lung compliance, thereby increasing the work of ventilation while increasing perfusion of poorly ventilated alveoli.

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 abnormalities. An electrocardiogram may provide evidence of AMI or preexisting cardiac disease. The chest x-ray may show pulmonary edema and cardiomegaly. Transthoracic 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 injury. 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.

Rx TREATMENT

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, inotropic agents may provide significant reduction. The goal is to increase contractility without significant increases in heart rate. Dopamine, norepinephrine, or vasopressin exert both inotropic and vasoconstrictor 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

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 cardiac 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). Pulsus 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, viruses, 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 increased while oxygen extraction is reduced due to maldistribution of microcirculatory perfusion and impaired mitochondrial utilization. In this setting the presence of a normal mixed venous oxygen saturation is not indicative of adequate peripheral perfusion, and even though the cardiac output may be elevated, it 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, vasoconstriction occurs and the cardiac output declines. The patient usually becomes markedly tachypneic, 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 anesthesia, 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 vasoconstriction-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 hypersecrete 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.

TREATMENT

In the hemodynamically unstable patient, dexamethasone sodium phosphate, 4 mg, should be given intravenously. This agent is preferred because unlike hydrocortisone it does not interfere with the ACTH stimulation test. If the diagnosis of absolute or relative adrenal insufficiency has been established as shown by non-response to corticotropin stimulation, the patient has a reduced risk of death if treated with hydrocortisone, 100 mg every 6 to 8 h, and tapered as the patient achieves hemodynamic stability. Simultaneous volume resuscitation and pressor support are required.

ADJUNCTIVE THERAPIES

As described above, the sympathomimetic amines dobutamine, dopamine, and norepinephrine are widely used in the treatment of all forms of shock. Arginine-vasopressin (antidiuretic hormone) is also being used increasingly and may better protect vital organ blood flow and prevent pathologic vasodilation.

POSITIONING Positioning of the patient may be a valuable adjunct in the initial treatment of hypovolemic shock. Elevating the foot of the bed (i.e., placing it on “shock blocks”) and assumption of the Trendelenburg position without flexion at the knees are effective but may increase work of breathing and risk for aspiration. Simply elevating both legs may be the optimal approach.

PNEUMATIC ANTISHOCK GARMENT (PASG) The PASG and the military antishock trousers (MAST) are inflatable external compression devices that can be wrapped around the legs and abdomen and have been widely used in the prehospital setting as a means of providing temporary support of central hemodynamics in shock. They cause an increase in systemic vascular resistance and blood pressure by arterial compression, without causing a significant change in cardiac output. The most appropriate use appears to be as a means to tamponade bleeding and augment hemostasis. Inflation of the suit provides splinting of fractures of the pelvis and lower extremities and arrests hemorrhage.

REWARMING Hypothermia is a potential adverse consequence of massive volume resuscitation. The infusion of large volumes of refrigerated blood products and room-temperature crystalloid solutions can rapidly drop core temperatures if fluid is not run through warming devices. Hypothermia may depress cardiac contractility and thereby further impair cardiac output and oxygen delivery. Hypothermia, particularly temperatures $<35^{\circ}\text{C}$, directly impairs the coagulation pathway, sometimes causing a significant coagulopathy. Rapid rewarming to $>35^{\circ}\text{C}$ significantly decreases the requirement for blood products and produces an improvement in cardiac function. The most effective method for rewarming is extracorporeal countercurrent warmers through femoral artery and vein cannulation. This process does not require a pump and can rewarm from 30° to 35°C in <30 min.

FURTHER READING

- ANNANE D et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 288:862, 2002
- BERNARD GR et al: Pulmonary artery catheterization and clinical outcomes: National Heart, Lung, and Blood Institute and Food and Drug Administration Workshop Report Consensus Statement. *JAMA* 283:2568, 2000
- CHEN P: Vasopressin: New uses in critical care. *Am J Med Sci* 324:146, 2002
- CHOI PT et al: Crystalloids vs. colloids in fluid resuscitation: A systematic review. *Crit Care Med* 27:200, 1999
- MCGEE S et al: The rational clinical examination. Is this patient hypovolemic? *JAMA* 281:1022, 1999
- RIVERS E et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 345:1368, 2001

254 SEVERE SEPSIS AND SEPTIC SHOCK

Robert S. Munford

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*. When sepsis is associated with dysfunction 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 Severe 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 40 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 case 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 >50 years old and in those with a primary pulmonary, abdominal, or neuromeningeal 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 $>300,000$. 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 widespread 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 other virulence factors. In both cases, the body can fail to kill the invaders despite mounting a vigorous inflammatory reaction that can progress to severe sepsis. The septic response may also be induced by microbial exotoxins that act as superantigens (e.g., toxic shock syndrome toxin 1; Chap. 120).

Host 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 bioactive 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 polysaccharides, and fimbriae elicit responses in animals that are similar to those induced by LPS; whereas some of