

# Shock

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Shock is a common condition necessitating admission to the ICU or occurring in the course of critical care. This chapter discusses the pathophysiology of various shock states, followed by recommendations for the diagnosis and treatment of each category of shock. Lastly a brief review of commonly used vasoactive agents is presented.

## Shock Defined

Shock is defined by the presence of multisystem end-organ hypoperfusion. Clinical indicators include reduced mean blood pressure, tachycardia, tachypnea, cool skin and extremities, acute altered mental status, and oliguria. Hypotension is usually, though not always, present. The end result of multiorgan hypoperfusion is tissue hypoxia, often clinically seen as lactic acidosis.

## Clinical Evaluation of Patients in Shock

Most patients who present with shock are hypotensive. Since the mean blood pressure is the product of the cardiac output (CO) and the systemic vascular resistance (SVR), reductions in blood pressure can be categorized by decreased CO and/or decreased SVR. Accordingly, the initial evaluation of a hypotensive patient should evaluate the adequacy of the CO. Clinical evidence of diminished CO includes a narrow pulse pressure (a surrogate marker for stroke volume), and cool extremities with delayed capillary refill. Signs of increased CO include a widened pulse pressure (particularly with a reduced diastolic pressure), warm extremities with bounding pulses and rapid capillary refill. If a hypotensive patient has clinical signs of increased CO, one can infer that the reduced blood pressure is a result of decreased SVR.

In hypotensive patients with clinical evidence of reduced CO, an assessment of intravascular and cardiac volume status is appropriate. A hypotensive patient with decreased intravascular and cardiac volume status may have a history suggesting hemorrhage or other volume losses (*eg*, vomiting, diar-

rhea, polyuria). The jugular venous pulse is often reduced in such a patient. A hypotensive patient with an increased intravascular and cardiac volume status may have S3 and/or S4 gallops, increased jugular venous pressure (JVP), extremity edema, and crackles on lung auscultation. The chest radiograph may show cardiomegaly, congestion of the vascular pedicle,<sup>1</sup> Kerley B lines and pulmonary edema. Chest pain and electrocardiograph (ECG) changes consistent with ischemia may also be noted.

In hypotensive patients with clinical evidence of increased CO, a search for causes of decreased SVR is appropriate. The most common cause of high cardiac output hypotension is sepsis. Accordingly, one should search for signs of the systemic inflammatory response syndrome (SIRS), which include abnormalities in temperature ( $\geq 38^{\circ}\text{C}$  or  $\leq 36^{\circ}\text{C}$ ), heart rate ( $\geq 90$  beats/min), respiratory rate ( $\geq 20$  breaths/min), and WBC count ( $\geq 12,000/\text{mm}^3$  or  $\leq 4,000/\text{mm}^3$  or  $\geq 10$  bands).<sup>2</sup> A person with SIRS and a presumed or confirmed infectious process fulfills criteria for sepsis. A person with sepsis and one or more organ failures fulfills criteria for severe sepsis. Other causes of high cardiac output hypotension include: liver failure, severe pancreatitis, burns and other trauma which elicit the systemic inflammatory response syndrome, anaphylaxis, thyrotoxicosis and peripheral arteriovenous shunts.

In summary, the three most common categories of shock include cardiogenic, hypovolemic and high CO with decreased SVR. Certainly these categories may overlap and occur simultaneously (*eg*, hypovolemic and septic shock, septic and cardiogenic shock).

The initial assessment of a patient in shock as outlined above should take only a few minutes. It is important that aggressive, early resuscitation is instituted based on the initial assessment, particularly since there are data suggesting that early resuscitation of shock (both septic and cardiogenic) may improve survival.<sup>3,4</sup> If the initial bedside assessment yields equivocal or confounding data, more objective assessments such as echocardiography and/or central venous or pulmonary artery

catheterization may be useful. The goal of early resuscitation is to reestablish adequate perfusion to prevent or minimize end organ injury.

During the initial resuscitation of patients in shock, principles of advanced cardiac life support should be followed. Since patients in shock may be obtunded and unable to protect the airway, an early assessment of the patient's airway is mandatory during resuscitation from shock. Early intubation and mechanical ventilation are often required. Reasons for institution of endotracheal intubation and mechanical ventilation include acute hypoxemic respiratory failure as well as ventilatory failure. Acute hypoxemic respiratory failure may occur in cardiogenic shock (pulmonary edema) as well as septic shock (pneumonia or the acute respiratory distress syndrome [ARDS]). Ventilatory failure often occurs as a result of an increased load on the respiratory system. This load may present in the form of acute metabolic acidosis (often lactic acidosis) or decreased compliance of the lungs as a result of pulmonary edema. Inadequate perfusion to respiratory muscles in the setting of shock may be another reason for early intubation and mechanical ventilation. Normally, the respiratory muscles receive a very small percentage of the CO.<sup>5</sup> However, in patients who are in shock with respiratory distress for the reasons listed above, the percentage of cardiac output dedicated to respiratory muscles may increase ten fold or more.<sup>6,7</sup> Mechanical ventilation may relieve the patient of the work of breathing and permit redistribution of a limited cardiac output to other vital organs. Such patients often demonstrate signs of respiratory muscle fatigue including: inability to speak full sentences, accessory respiratory muscle use, paradoxical abdominal muscle activity, extreme tachypnea (>40 breaths/min), and decreasing respiratory rate despite an increasing drive to breathe.

Endotracheal intubation and mechanical ventilation with sedation and, if necessary, muscle paralysis will decrease oxygen demand of the respiratory muscles allowing improved oxygen delivery to other hypoperfused tissue beds.<sup>8</sup> Patients in shock should be intubated before other procedures are performed, since attention to the airway and breathing may wane during such procedures.

### *Resuscitation*

Resuscitation should focus on improving end organ perfusion, not simply raising the blood pressure. Accordingly, a patient with a reduced CO by

clinical assessment with a decreased intravascular and cardiac volume status should receive aggressive intravenous resuscitation. The type of intravenous fluid is controversial, though recent data suggest that colloid (albumin) is not better than crystalloid and indeed may be associated with increased morbidity and mortality.<sup>9</sup> Though one study reported improved outcomes in trauma patients whose volume resuscitation was delayed until definite surgical repair (average time to operation ~ 2 h),<sup>10</sup> aggressive volume resuscitation in patients with reduced intravascular and cardiac volume status is merited in virtually all but perhaps torso trauma patients who can undergo surgical repair quickly. Early administration of vasoactive drugs in hypovolemic patients in order to increase the blood pressure is not recommended. This practice may impair the assessment of the patient's circulatory status and potentially delay definitive treatment. The transfusion of packed red blood cells to anemic patients in order to improve oxygen delivery is physiologically rational; however, recent data suggest that, as long as hemoglobin levels remain greater than 7 g/dL, this practice may not improve outcomes and perhaps even worsen outcomes in select subgroups of patients.<sup>11</sup> Certainly, a conservative transfusion strategy does not apply to hemorrhaging, hypovolemic patients in shock. Blood products should be administered through a blood warmer, in order to minimize hypothermia and subsequent disturbances in coagulation. In summary, it is important to remember that oxygen delivery is the product of cardiac output, oxygen-carrying capacity of the blood, and arterial oxygen saturation. Each of these components must be considered and optimized when addressing resuscitation of patients in shock.

Early reassessment of the patient with purported hypovolemic shock after the initial resuscitation is extremely important. Concrete end points such as increased blood pressure and pulse pressure, improved capillary refill, urine output and mental status should be sought. The absence of a response suggests that the volume challenge may not be adequate. Careful and repeated searches for signs of volume overload (increased JVP, new gallop or extra heart sounds, pulmonary edema) should be done while the resuscitation is ongoing.

If the patient remains in shock despite adequate volume resuscitation, support with vasoactive drugs is appropriate. Occasionally, vasoactive

drugs must be started “prematurely” when volume resuscitation needs are large. When severe hypotension and hypovolemia are present, this approach is occasionally needed to “buy time” while volume resuscitation is ongoing. This strategy is only rarely necessary and should only be instituted temporarily until volume resuscitation is accomplished. It is important to remember that vasoactive drugs may obscure hypovolemic shock by raising blood pressure in spite of a low cardiac output state.

Once intravascular volume has been restored, patients who remain in shock may benefit from vasoactive drugs. These drugs should be titrated to end-organ perfusion, rather than an arbitrary blood pressure value. Accordingly, mental status, urine output, lactic acidosis, capillary refill and skin temperature, and venous oxygen saturation are reasonable end points to target in these patients. If evidence of hypoperfusion persists, one should consider inadequate volume resuscitation, impaired cardiac output, inadequate hemoglobin, and/or inadequate oxygen saturation as a likely explanation. If objective information obtained by physical examination is unclear or ambiguous, additional information obtained via invasive monitoring (central venous pressure, pulmonary artery catheterization or echocardiography) may be useful. Echocardiography is a useful adjunct or even replacement to invasive pressure measurements and can be used to distinguish poor ventricular pumping function from hypovolemia; a good study can exclude or confirm tamponade, pulmonary hypertension, or significant valve dysfunction, all of which influence therapy and may supplement or replace the more invasive right heart catheterization. These topics are covered separately in another chapter in the syllabus.

## Cardiogenic Shock

The model of the heart as a pump is useful in considering cardiogenic shock. By definition, pump failure is seen when cardiac output is inappropriately low despite adequate input in the form of venous return (determined by right atrial pressure). The specific cause of decreased pump function must be considered. Left and/or right ventricular dysfunction may occur due to decreased systolic contractility, impaired diastolic relaxation, increases in afterload, valvular dysfunction, or abnormal heart rate and rhythm.

## Left Ventricular Failure

*Systolic Dysfunction:* This is the classic example of cardiogenic shock. When left ventricular (LV) systolic function is impaired, the most common reason is acute coronary ischemia. The result is a reduction of cardiac output relative to increases in preload. Attempted compensation for this impaired pump function occurs via the Frank-Starling mechanism as well as by fluid retention by the kidneys and by increased venous tone mediated by the sympathetic nervous system. Patients present with reduced cardiac output and a resulting increased oxygen extraction ratio by the peripheral tissues. The low mixed venous oxygen saturation may exacerbate hypoxemia, especially in patients with pulmonary edema and intrapulmonary shunt physiology. As mentioned above, acute myocardial infarction or ischemia is the most common cause of LV failure leading to shock. Cardiogenic shock is reported to complicate up to 10% of acute myocardial infarctions.<sup>12</sup> Recent evidence supports the use of early aggressive revascularization using angioplasty or coronary artery bypass grafting in patients with cardiogenic shock.<sup>4</sup> Survival benefit was seen in patients subjected to this strategy compared to medical management of cardiogenic shock, including those given thrombolytic therapy. Treatment of cardiogenic shock due to systolic dysfunction includes the judicious administration of volume if hypovolemia is present. A more precise characterization of the circulation can be obtained with the use of pulmonary artery catheterization and/or echocardiography—topics discussed in more detail in another chapter of the syllabus. Inotropic support includes the use of agents such as dobutamine or milrinone. Intra-aortic balloon counterpulsation may be used to support the circulation as a bridge to coronary artery revascularization.

*Diastolic Dysfunction:* Increased LV diastolic chamber stiffness and impaired LV filling most commonly occur as a result of myocardial ischemia, though LV hypertrophy and restrictive myocardial diseases may also contribute. Patients usually present with increased cardiac filling pressures despite a small LV end diastolic volume as documented by echocardiography (usually best seen in the short axis view at the level of the papillary muscles). Aside from the management of acute ischemia, this condition may be difficult to treat. Volume administration can be tried, but many times only

further increases diastolic pressure with little change in diastolic volume. Inotropic agents are usually ineffective. Aggressive management of tachycardia with volume administration and cautious use of negative chronotropic agents is a rational approach to therapy. Since very little ventricular filling occurs late in diastole in these patients, a very low heart rate (eg, sinus bradycardia) may be detrimental. Often, careful titration of chronotropic agents to achieve the “optimal” heart rate which maximizes cardiac output is necessary. The maintenance of a normal sinus rhythm is important to maximize ventricular filling.

*Valvular Dysfunction:* The management of valvular disease contributing to cardiogenic shock is guided by interventions to counter the specific pathophysiology. Accordingly, aortic stenosis is managed by efforts to decrease heart rate while maintaining sinus rhythm. Preload should be maintained and afterload must not be reduced, since there is a fixed afterload imposed by the aortic stenosis which may not tolerate further reductions in afterload via arteriolar dilation. Surgical evaluation or palliative valvuloplasty are other important considerations in cardiogenic shock complicated by aortic stenosis. Cardiogenic shock due to aortic insufficiency may present acutely and may require urgent surgical repair. Medical management includes the use of chronotropic agents to decrease regurgitant filling time and afterload reducing agents to facilitate forward flow. Mitral regurgitation may occur acutely as a result of ischemic injury to papillary muscles. Medical management includes attempts to establish and maintain sinus rhythm, as well as afterload reduction to decrease the percentage of regurgitant blood flow. This may be accomplished with medications such as nitroprusside or intra-aortic balloon counterpulsation as a bridge to mitral valve repair or replacement. Mitral stenosis contributing to cardiogenic shock is managed by negative chronotropic agents, which seek to maximize diastolic filling time across the stenotic valve. Lastly, hypertrophic cardiomyopathy may contribute to cardiogenic shock. This lesion is managed by maintenance of preload with volume administration and negative inotropic and chronotropic agents, which serve to decrease the obstruction of the LV outflow tract during systole. Rarely, acute obstruction of the mitral valve by left atrial thrombus or myxoma may also result in cardiogenic shock. These conditions generally require acute surgical interventions.

*Cardiac Arrhythmias:* Dysrhythmias may exacerbate shock in critically ill patients. Detailed discussion on the management of dysrhythmias is beyond the scope of this chapter and the reader is referred to other sections of the syllabus for further discussion of this topic.

### *Right Ventricular Failure*

Right ventricular (RV) failure resulting in cardiogenic shock is typically associated with increased right atrial pressure and reduced cardiac output. Though the most common reason for RV failure is concomitant LV failure, this section will discuss management of isolated RV failure. Right ventricular infarction may result in RV failure, usually accompanied by inferior myocardial infarction. Elevated JVP in the presence of clear lungs is the classic physical finding seen in acute RV infarction. It is important to distinguish RV infarction from cardiac tamponade. Echocardiography may be helpful in making this distinction. Therapy includes volume administration, dobutamine to increase RV inotropy,<sup>13</sup> and norepinephrine which may improve RV endocardial perfusion.

Right ventricular failure as a result of increases in right heart afterload may be due to pulmonary embolism, ARDS and other causes of alveolar hypoxia, hypercapnia and metabolic acidosis. Management is focused at treating the underlying physiologic derangement, with circulatory support again centered around inotropic agents as well as norepinephrine.<sup>14,15</sup> Treatment of RV failure is complicated, since volume administration may result in worsening RV function by causing mechanical overstretch and/or by reflex mechanisms that depress contractility.<sup>16</sup> However, some investigators have found volume administration to result in favorable hemodynamics in acute RV failure due to increased RV afterload.<sup>17</sup> Optimal management is often facilitated by echocardiographic or pulmonary artery catheter directed therapy. Thrombolytic therapy for acute pulmonary embolism complicated by cardiogenic shock has been shown to improve survival<sup>18</sup> and is currently accepted as a recommended strategy.<sup>19</sup> A recent study of patients with acute pulmonary embolism and pulmonary hypertension or right ventricular dysfunction but without shock compared heparin alone to heparin plus thrombolysis (alteplase). Though no survival benefit was seen with thrombolysis, a lower inci-

dence of clinical deterioration requiring escalation of treatment (defined as: catecholamine infusion, secondary thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or emergency surgical embolectomy or thrombus fragmentation by catheter) was seen with thrombolytics and heparin combined. This benefit occurred without an increase in bleeding.<sup>20</sup> Hypoxic pulmonary vasoconstriction may be reduced by improving alveolar and mixed venous oxygenation by administering supplemental oxygen. More aggressive correction of hypercapnia and acidemia may be necessary in patients with acute right heart syndromes. Pulmonary vasodilator therapy (eg, inhaled nitric oxide and prostaglandin E<sub>1</sub>) may be considered, though outcome benefits in the acute setting are largely lacking.

### *Pericardial Tamponade and Other Syndromes Causing External Compression of the Heart*

Cardiac tamponade impairs diastolic filling, resulting in shock. The diagnosis is established by the presence of elevated jugular venous pulse with Kussmaul's sign and pulsus paradoxus. Pulmonary artery catheterization may reveal a decreased cardiac output with equalization of right atrial, left atrial (PCWP) and RV diastolic pressures. Echocardiography reveals pericardial fluid with diastolic collapse of the atria and RV, and right-to-left septal shift during inspiration. Other causes of external cardiac compression include tension pneumothorax, elevated intra-abdominal pressure (eg, tense ascites)—so called abdominal tamponade, large pleural effusions and pneumopericardium. Treatment is focused at the underlying cause and includes pericardial drainage with a catheter or surgical "window" in the case of pericardial tamponade. In unstable patients, blind drainage of the pericardial sac with a needle may be necessary. Medical management of the circulatory pathophysiology of tamponade includes the use of aggressive volume administration as well as inotropic and chronotropic support to increase heart rate and thus maintain forward flow.

## **Decreased Venous Return**

Hypovolemia is the most common cause of shock due to decreased venous return. The venous circuit has tremendous capacitance potential and venoconstriction in response to hypovolemia can

compensate for initial decreases in intravascular volume. Orthostatic changes in blood pressure and heart rate may be seen early in hypovolemic shock.<sup>21</sup> At a level of approximately 40% loss of intravascular volume, venoconstriction driven by the sympathetic nervous system can no longer maintain mean arterial blood pressure.

In hypovolemic shock, tissue injury (especially gut ischemia) and resulting systemic inflammation may lead to ongoing shock despite replacement of volume losses.<sup>22</sup> This is particularly relevant if resuscitation is delayed and underscores the importance of early aggressive resuscitation of hypovolemic shock. The phenomenon of systemic inflammation as it pertains to shock will be discussed in more detail in the section on septic shock.

Other causes of shock due to decreased venous return include severe neurologic damage or drug exposure resulting in hypotension due to loss of venous tone. The prototypical example of loss of venous tone due to drug exposure is anaphylaxis. This unregulated immunologically-mediated release of histamine can result in profound shock requiring aggressive catecholamine support (epinephrine is the drug of choice). Septic shock is a common cause of shock due to decreased venous tone and is discussed separately in the following section. All of these processes result in decreased venous tone and impaired venous return resulting in decreased cardiac output and blood pressure. Obstruction of veins due to compression (eg, pregnancy, intra-abdominal tumor), thrombus formation, or tumor invasion increases the resistance to venous return and may occasionally result in shock.

The principal therapy of hypovolemic shock and other forms of shock due to decreased venous return is aggressive volume resuscitation while attempting to reverse the underlying problem driving the pathophysiology. This has been described in more detail above. In hemorrhagic shock, resuscitation with packed red blood cells should be done through a blood warmer. The optimal hemoglobin concentration is controversial and transfusion should be paced by the extent of ongoing blood loss. After large volume red blood cell transfusions, dilutional thrombocytopenia and reduction in clotting factors should be anticipated, sought and corrected with platelet and plasma product transfusions as directed by platelet count and coagulation assays.

## High Cardiac Output Hypotension

### *Septic Shock*

Septic shock is the most extreme presentation of a spectrum of pathophysiologic responses to an infectious insult. Sepsis is defined by the presence of the systemic inflammatory response syndrome in the presence of known or suspected infection.<sup>2</sup> Severe sepsis occurs when patients with sepsis accrue one or more organ failure(s). Septic shock is seen in patients with severe sepsis who manifest shock as described above. Any infectious organism may result in sepsis and septic shock, including all bacteria, fungi, viruses and parasites. As noted above, patients typically present with evidence of high cardiac output (assuming hypovolemia has been resuscitated). These patients have a widened pulse pressure, warm extremities, brisk capillary refill, and a reduced diastolic and mean blood pressure. A subgroup of patients with septic shock may present with depressed cardiac function. Circulating myocardial depressant factors have been identified in some septic patients,<sup>23-25</sup> but the reason only a small subgroup of patients manifest cardiac depression is not well understood.

Sepsis is a significant problem in the care of critically ill patients. It is the leading cause of death in noncoronary ICUs in the United States.<sup>26</sup> Current estimates suggest that more than 750,000 patients are affected each year<sup>27</sup> and these numbers are expected to increase in the coming years as the population continues to age and a greater percentage of people vulnerable to infection will likely seek medical care.

Decades of research have focused on modifying the pathophysiologic responses of the body to severe infection. For many years, an unregulated pro inflammatory state was thought to be the driving force behind severe sepsis and septic shock. Numerous trials attempting to block a particular inflammatory pathway were conducted without any survival benefits noted.<sup>28</sup> More recently, the pathophysiology behind severe sepsis has become better understood. Currently, the pathophysiology of severe sepsis, is thought to be driven by unregulated inflammation (via cytokines such as interleukin 6 and tumor necrosis factor), coupled to a hypercoagulable state favoring microvascular coagulation and impaired fibrinolysis. Such unregulated microvascular coagulation is thought

to lead to impaired tissue perfusion and predispose patients to the multiple organ dysfunction syndrome that is commonly observed in severe sepsis.<sup>29</sup> Activated protein C has a salutary impact on all three pathophysiologic derangements noted in severe sepsis. Recently, a survival benefit was reported in patients with severe sepsis treated with recombinant activated protein C.<sup>30</sup> This study was the first to ever demonstrate a survival benefit from a therapy directed at modifying the underlying pathophysiology of severe sepsis. Because of its anticoagulant properties, there was a small but significant increase in bleeding complications associated with activated protein C.

The mainstay of therapy for septic shock is aggressive supportive care. This includes early identification of the source of infection with eradication by surgical or percutaneous drainage, if possible. Over 80% of patients with severe sepsis will require ventilatory support for respiratory failure, which should be instituted early for reasons outlined earlier in this chapter. Circulatory failure is supported with aggressive volume administration to correct any component of hypovolemia. Objective monitoring using central venous catheterization, pulmonary artery catheterization, and echocardiography should be used early to guide therapy. Vasoactive support is directed by the underlying circulatory derangement. The optimal extent of volume resuscitation is controversial. Some clinicians favor aggressive volume administration, while others favor earlier use of vasoactive drugs (keeping patients "dry"). Trials are ongoing to attempt to better answer this difficult question. Early institution of broad spectrum antibiotic therapy focused on potential pathogens has been shown to improve survival.<sup>31,32</sup> Acute renal failure in septic shock carries a poor prognosis. Recent literature supports the use of an aggressive approach to renal replacement therapy, with a survival benefit demonstrated with daily hemodialysis compared to alternate day hemodialysis.<sup>33</sup> The use of low-dose dopamine as a renal protective strategy was recently found to be of no benefit in preventing acute tubular necrosis in patients with SIRS and acute renal insufficiency.<sup>34</sup> Other therapeutic interventions in severe sepsis await further evaluation. Early trials evaluating the utility of high dose corticosteroids in septic shock failed to demonstrate a survival benefit.<sup>35,36</sup> Corticosteroid therapy remains controversial and further studies are needed before it can be recommended

for widespread use. Recent data suggest that the response to an ACTH stimulation test may have important prognostic implications.<sup>37</sup> Furthermore, a recent multicenter trial found that a combination of low dose hydrocortisone and fludrocortisone improved survival in patients with septic shock who had relative adrenal insufficiency.<sup>38</sup>

### *Other Types of Shock*

Adrenal insufficiency is often viewed as a rare occurrence in critically patients. However, a recent study reported a 54% incidence of blunted adrenal response to ACTH in patients with septic shock.<sup>37,38</sup> This number may be a generous estimate since the parameters for defining adrenal insufficiency are not universally agreed upon;<sup>39</sup> nevertheless, adrenal insufficiency may not be as rare as previously thought. It is reasonable to consider testing all patients who present with septic or other occult reasons for shock with an ACTH stimulation test. Conventionally, this test is performed in the morning with a baseline cortisol level drawn and then 250  $\mu\text{g}$  of ACTH administered intravenously. Thirty- and sixty-minute cortisol levels are then drawn. A level greater than 20  $\mu\text{g}/\text{dL}$  is viewed as an appropriate response. If adrenal insufficiency is suspected, dexamethasone (does not cross react with the cortisol laboratory assay) should be administered while the ACTH stimulation test is performed.

Neurogenic shock typically occurs as a result of severe injury to the central nervous system. The loss of sympathetic tone results in venodilation and with venous blood pooling. Mainstays of therapy include volume repletion and vasoactive support with drugs that have vasoconstricting properties

Severe hypothyroidism or hyperthyroidism may result in shock. Myxedema presenting as shock should be treated with administration of intravenous thyroid hormone. One should watch carefully for myocardial ischemia and/or infarction which may complicate aggressive thyroid replacement. Thyroid storm requires urgent therapy with Lugol's solution, propylthiouracil, steroids, propranolol, fluid resuscitation, and identification of the precipitating cause. Pheochromocytoma often present with a paradoxical hypertension despite a state of shock and impaired tissue perfusion. Intravascular volume depletion is masked by extreme vasoconstriction from endogenous catecholamines in pheochromocytoma. The increase in afterload caused by endogenous cat-

echolamines may also precipitate a shock-like state. Treatment includes aggressive volume replacement as well as alpha and beta adrenergic blockade. A search for the location of the pheochromocytoma with subsequent surgical removal is indicated.

## **Vasoactive Agents**

The choice of vasoactive medications should be based upon the underlying pathophysiology of the circulation as gleaned by the physical examination and supplemented by more sophisticated measurements. It is sobering to realize that despite widespread use of these agents for many decades, there are no outcomes studies to guide clinicians with regard to a particular agent in the management of shock.

### *Dobutamine*

Dobutamine is a powerful inotrope which stimulates both  $\beta_1$ - and  $\beta_2$ -receptors. The end result is typically an increase in cardiac output with diminished systemic vascular resistance. This reduction in afterload may benefit patients with LV systolic dysfunction.

### *Milrinone*

Milrinone is an inotropic agent that induces a positive inotropic state via phosphodiesterase inhibition. It has potent vasodilating properties that decrease both systemic and pulmonary vascular resistance. A recent study of patients with acute exacerbations of congestive heart failure did not demonstrate a benefit with regard to days hospitalized for cardiovascular causes, in-hospital mortality, 60-day mortality, or the composite incidence of death or hospital readmission. Rather, hypotension and new atrial arrhythmias were found to occur more frequently in patients who received milrinone compared to placebo.<sup>40</sup>

### *Dopamine*

Dopamine is purported to have varying physiologic effects at different doses. Classically, "low-dose" dopamine (1-3  $\mu\text{g}/\text{kg}/\text{min}$ ) is thought to stimulate dopaminergic receptors and increase renal and mesenteric blood flow. This notion has recently been disproved, however.<sup>34,41</sup> Indeed, there

is evidence that dopamine may impair mesenteric perfusion to a greater degree than norepinephrine.<sup>42</sup> As data are accumulating reporting the ill effects of dopamine in shock, this agent has recently fallen out of favor in the view of many clinicians, with other agents such as norepinephrine being more widely used (see below).<sup>43</sup>

### *Norepinephrine*

Norepinephrine stimulates  $\beta_1$ - as well as  $\alpha$ -receptors. Data are now accumulating suggesting norepinephrine may be a preferred drug in septic and other vasodilatory types of shock. It appears to have a lesser propensity to cause renal injury<sup>44</sup> and provides a more reliable increase in blood pressure compared to dopamine.<sup>45</sup> A recent prospective observational cohort study found a significant reduction in mortality when compared to dopamine and/or epinephrine in patients with septic shock.<sup>46</sup>

### *Phenylephrine*

Phenylephrine is a pure  $\alpha_1$ -agonist, which results in veno- and arteriolar constriction. It often elicits a reflex bradycardia mediated via baroreceptors. This may prove useful in patients with tachydysrhythmias accompanied by hypotension. In a prospective observational study of patients with septic shock, phenylephrine was found to increase blood pressure, SVR and cardiac index when added to low-dose dopamine or dobutamine after volume resuscitation.<sup>47</sup> There is a theoretical concern that  $\alpha$ -agonism may precipitate myocardial ischemia, though are few objective data to support or refute this concern.

### *Epinephrine*

Epinephrine has both  $\beta$ - as well as  $\alpha$ -agonist properties. It has potent inotropic as well as vasoconstricting properties. It appears to have a higher propensity toward precipitating mesenteric ischemia,<sup>48</sup> a property which limits its utility as a first-line agent for the management of shock, regardless of the underlying etiology.

### *Vasopressin*

The use of vasopressin as a vasoactive agent has increased tremendously in the last few years. Patients who present with septic shock or late-phase hemorrhagic shock have been shown to have a relative deficiency of vasopressin. A recent study found patients with septic shock to demonstrate an increase in blood pressure and urine output without evidence of impaired cardiac, mesenteric or skin perfusion when treated with "low-dose" (40 milliunits per minute) vasopressin.<sup>49</sup> The exact role of vasopressin in various shock states requires further investigation.

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## Notes

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