KEY POINTS

- Shock is present when there is evidence of multisystem organ hypoperfusion; it often presents as reduced mean blood pressure.
- Initial resuscitation aims to establish an adequate airway, breathing, and circulation; a working diagnosis or clinical hypothesis of the cause of inadequate circulation should always be made immediately by physical examination and clinical presentation before treatment is initiated.
- The most common causes of shock are high cardiac output hypotension, or septic shock, reduced pump function of the heart, or cardiogenic shock, and reduced venous return despite normal pump function, or hypovolemic shock. Overlapping etiologies can confuse the diagnosis, as can a short list of other less common etiologies, which are often separated by echocardiography and right heart catheterization.
- Initial cardiovascular therapeutic interventions are volume infusion for hypovolemic shock or inotropic and vasodilating drugs for cardiogenic shock; each should be regarded as testing the clinical hypothesis concerning the etiology of shock and therefore requires careful evaluation before and soon after implementation.
- Identify and correct early all factors aggravating shock; these include suboptimal ventilator therapy, infections, arrhythmias, acidosis, electrolyte abnormalities, and hypothermia.
- Shock has a hemodynamic component, which is the focus of the initial resuscitation, but shock also has a systemic inflammatory component that leads to adverse sequelae including subsequent organ system dysfunction.
- Urgent discontinuation of excessive invasive measurements and therapy should follow hemodynamic stabilization of the patient.

Shock is a common critical illness necessitating admission to the ICU or occurring in the course of critical care. To present rational therapy, an adequate discussion must include a broad differential diagnosis of the many etiologies of shock, each requiring separate discussion of how the condition proceeds to a hypoperfusion state. Yet effective initial diagnosis and treatment follow a less detailed path at a rapid pace at the bedside of the patient in shock, based in large part on understanding cardiovascular pathophysiology. This chapter discusses shock in the way that problem should be approached in each patient: first with an early working diagnosis, then an approach to urgent resuscitation, which confirms or changes the working diagnosis, followed by a pause to ponder the broader differential diagnosis of the types of shock and the pathophysiology of shock leading to potential adverse sequelae.
Establishing a Working Diagnosis of the Cause of Shock

DEFINITION OF SHOCK
Shock is present if evidence of multisystem organ hypoperfusion is apparent. Evidence of hypoperfusion obtained during the rapid initial clinical evaluation of a patient in shock may include tachycardia, tachypnea, low mean blood pressure, diaphoresis, poorly perfused skin and extremities, altered mental status, and decreased urine output. Hypotension has special importance because it commonly occurs during shock, because blood pressure is easily measured, and because extreme hypotension always results in shock. Important caveats are that even modest hypotension (mean < 60 mm Hg, systolic < 90 mm Hg) is not always associated with shock, and shock can occur despite elevated blood pressure, as illustrated in the case presentation at the end of the chapter. Furthermore, cuff blood pressure measurements may markedly underestimate central blood pressure in low flow states. One important early manifestation of hypoperfusion is tissue hypoxia, often indicated by lactic acidosis. A second manifestation of shock that must be considered is the associated systemic inflammatory response. Hypoperfusion and resuscitation (ischemia-reperfusion) initiate a systemic inflammatory response, and, conversely, severe systemic inflammatory responses lead to shock. The inflammatory component may be relatively small (rapidly resuscitated cardiogenic shock), large (septic shock), or intermediate (trauma) and dictates much of the subsequent course, since the inflammatory component of shock leads to further metabolic abnormalities and organ dysfunction.

A QUESTIONING APPROACH TO THE INITIAL CLINICAL EXAMINATION
A simple working definition of shock is helpful in the initial diagnosis and management of the hypotensive patient. This approach acknowledges that shock is identified in most patients by hypotension and that mean blood pressure is the product of cardiac output and the systemic vascular resistance (SVR). Accordingly, hypotension may be caused by reduced cardiac output or reduced SVR. Initial examination of the hypotensive patient seeks to answer the question; is cardiac output reduced? High cardiac output hypotension is most often signaled by a large pulse pressure, a low diastolic pressure, warm extremities with good nailbed return, fever (or hypothermia), and leukocytosis (or leukopenia); these clinical findings strongly suggest a working diagnosis of septic shock (Table 20-1), the initial treatment for which is thoughtful antibiosis combined with adequate but not excessive expansion of the vascular volume (see Chap. 42).

By contrast, low cardiac output is signaled by a small pulse pressure and cool extremities with poor nailbed return. In this case, clinical examination turns to a second question; is the heart too full? A heart which is too full in a hypotensive patient is signaled by elevated jugular venous pressure (JVP), peripheral edema, crepitations on lung auscultation, a large heart with extra heart sounds (83, 84), chest pain, ischemic changes on the electrocardiogram (ECG), and a chest radiograph showing a large heart with dilated upper lobe vessels and pulmonary edema. These findings suggest
TABLE 20-1 Rapid Formulation of an Early Working Diagnosis of the Etiology of Shock

Defining Features of Shock

Blood pressure \( \downarrow \)

Heart rate \( \uparrow \)

Respiratory rate \( \uparrow \)

Mentation \( \downarrow \)

Urine output \( \downarrow \)

Arterial pH \( \downarrow \)


<table>
<thead>
<tr>
<th>High-Output Hypotension</th>
<th>Low-Cardiac-Output</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Septic Shock</strong></td>
<td><strong>Cardiogenic and Hypovolemic Shock</strong></td>
</tr>
<tr>
<td>Is cardiac output reduced?</td>
<td>No</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>( \uparrow )</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>( \uparrow \uparrow )</td>
</tr>
<tr>
<td>Extremities digits</td>
<td>Warm</td>
</tr>
<tr>
<td>Nailbed return</td>
<td>Rapid</td>
</tr>
<tr>
<td>Heart sounds</td>
<td>Crisp</td>
</tr>
<tr>
<td>Temperature</td>
<td>( \uparrow ) or ( \downarrow )</td>
</tr>
<tr>
<td>White cell count</td>
<td>( \uparrow ) or ( \downarrow )</td>
</tr>
<tr>
<td>Site of infection</td>
<td>+ + +</td>
</tr>
</tbody>
</table>

**Reduced Pump Function, Cardiogenic Shock**

- Is the heart too full? Yes
- Symptoms clinical context: Angina ECG
- Jugular venous pressure: \( \uparrow \)
- \( S_3, S_4, \) gallop rhythm: + + +
- Respiratory crepitations: + + +
- Chest radiograph: Large heart
- Pulmonary edema

**Reduced Venous Return, Hypovolemic Shock**

- Is the heart too full? No
- Symptoms clinical context: Hemorrhage dehydration
- Pulmonary hypertension (most often pulmonary embolus)
- Adrenal insufficiency
- Right ventricular infarction
- Anaphylaxis
- Cardiac tamponade
- Spinal shock

What Does Not Fit?

<table>
<thead>
<tr>
<th>High output hypotension</th>
<th>High right atrial pressure hypotension</th>
<th>Nonresponsive hypovolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver failure</td>
<td>Pulmonary hypertension (most often pulmonary embolus)</td>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>Severe pancreatitis</td>
<td>Right ventricular infarction</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Trauma with significant systemic inflammatory response</td>
<td>Cardiac tamponade</td>
<td>Spinal shock</td>
</tr>
<tr>
<td>Thyroid storm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriovenous fistula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paget’s disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Get more information</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echocardiography, right heart catheterization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cardiogenic shock, most often caused by ischemic heart disease, and are generally absent when the low cardiac output results from hypovolemia (see Table 20-1). Then, clinical examination reveals manifestations of blood loss (hemateme-sis, tarry stools, abdominal distention, reduced hematocrit, trauma) or manifestations of dehydration (reduced tissue turgor, vomiting or diarrhea, negative fluid balance). This distinction between cardiogenic and hypovolemic shock allows initial therapy to focus on vasoactive drugs or on volume infusions,
Whenever the clinical formulation is not obvious after answering the first two questions, the intensivist may find it helpful to ask a third—what does not fit? Most often, the an
swer is that the hypotension is owed to two or more of these common etiologies of shock: septic shock complicated by myocardial ischemia or hypovolemia, cardiogenic shock complicated by hypovolemia or sepsis, and hypovolemic shock masking sepsis or ischemia heart disease. At this time, more data are frequently needed, especially aided by echocardiography and right heart catheterization. Interpretation of the data and response to initial therapy frequently confirm the multiple etiologies or lead to a broader differential diagnosis of the etiologies of shock (see below). A short list of common etiologies other than septic, cardiogenic, or hypovolemic shock can be grouped as they present (see Table 20-1)—high cardiac output hypotension which
Urgent Initial Resuscitation

During the first hour the urgent initial resuscitation aims to avoid later sequelae of organ system hypoperfusion by rapidly restoring an adequate circulation. Effective therapy is based on the working diagnosis established by a systematic survey and confirmed or changed by the response to therapy. During this time, additional data are obtained from catheterization and special tests to titrate therapy toward the goal of correcting the hypoperfusion state with minimal complications. This stage ends with a careful reconsideration of what happened to set the goals of longer-term therapy or to obtain additional diagnostic tests appropriate to evaluate further the type of shock.

PRIMARY SURVEY

If shock is untreated, irreversible organ system damage often develops rapidly and leads to death. Therefore, early institution of aggressive resuscitation will improve a patient’s chances of survival. To improve efficiency at the necessarily rapid tempo, a systematic approach to initial evaluation and resuscitation is useful as it is during cardiac emergencies (ACLS) and trauma (ATLS). In analogy to these systematic “ABC” approaches, a primary survey of a critically ill patient in shock should include assessing and, if necessary, establishing an airway; evaluating breathing and considering mechanical ventilator support; and resuscitating the inadequate circulation.

AIRWAY AND BREATHING

Most patients in shock have one or more indications for airway intubation and mechanical ventilation (Table 20-2), which should therefore be instituted early. Significant hypoxemia (even if suspected before the results of a blood-gas analysis are available) is one indication for airway intubation and mechanical ventilation because external masks and other devices may not reliably deliver an adequate fraction of inspired oxygen (Fio2). Initially a high Fio2 (100%) is used until blood-gas analysis allows titration of the Fio2 down, toward less toxic concentrations. In the setting of significant arterial hypoxemia, increased Fio2 is used in combination with positive end-expiratory pressure (PEEP) in the venti

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>WHY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxemia</td>
<td>High Fio2 is not guaranteed by oxygen masks. PEEP can be added.</td>
</tr>
<tr>
<td>(inappropriately high Pco2 signs of ventilatory muscle fatigue)</td>
<td></td>
</tr>
<tr>
<td>Vital organ hypoperfusion</td>
<td>Rest ventilatory muscles (and divert cardiac output to hypoperfused vital organs).</td>
</tr>
<tr>
<td>Obtundation</td>
<td>Protect and ensure an adequate airway.</td>
</tr>
</tbody>
</table>

Ventilatory failure is another indication for airway intubation and mechanical ventilation. Elevated and rising Paco2 reliably establishes the diagnosis of ventilatory failure, but this is often a late finding. Young, previously healthy patients, in particular, are able to defend Paco2 and pH up until a precipitous respiratory arrest. Therefore, clinical signs of respiratory muscle fatigue or subtle evidence of inadequate ventilation are more important early indicators. For example, a patient in shock with a Paco2 of 30 and a pH of 7.2 has inadequate respiratory compensation for the metabolic acidosis indicating ventilatory failure. Such a patient may be much more acidic at the tissue level, as evidenced by a much greater mixed venous Paco2 associated with the large arteriovenous difference in CO2 which occurs in low cardiac output states. Evidence of respiratory muscle fatigue, including labored breathing precluding more than rudimentary verbal responses, tachypnea > 40/min or an inappropriately low and decreasing respiratory rate despite evidence of high drive to breath, abdominal paradoxical respiratory motion, accessory muscle use, or other manifestations of ventilatory failure should lead to early elective intubation and ventilation of the patient in shock (see Chap. 32).

Airway 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. This is important in shock, where the respiratory muscles consume a disproportionate share of the whole body oxygen delivery, particularly because patients are frequently hyperventilating in response to acidosis, sepsis, or pain. Airway intubation may benefit obtunded patients who may inadequately protect their airways at this time of increased ventilatory drive and anxiety. In shock, airway intubation and mechanical ventilation should precede other complicated procedures, such as central venous catheterization, or complicated tests that require transportation of the patient, because these procedures and tests restrict the medical staff’s ability to continuously assess the airway and ensure adequacy of ventilation.
Effective cardiovascular resuscitation aims to reverse the cause of shock; hence, the emphasis on establishing a working diagnosis before urgent resuscitation. From the clinical hypothesis concerning the etiology, it follows that a patient in hypovolemic shock should receive aggressive intravascular volume expansion until the hypoperfusion state is corrected without vasoactive drugs, whereas the patient with cardiogenic shock and a gallop rhythm or elevated JVP needs vasoactive drug therapy without volume expansion. Yet diagnostic uncertainty and the need for urgent resuscitation often combines these therapies during this first hour—a practice which inadvertently delays correct diagnosis and subsequent effective resuscitation for the apparent gain of raising blood pressure sooner. Increasing blood pressure by itself is insufficient since the goal of cardiovascular resuscitation is to attain an adequate cardiac output and oxygen delivery to correct organ system hypoperfusion. Oxygen delivery is the product of cardiac output, oxygen-carrying capacity of the blood, and arterial oxygen saturation. It follows that the product of the three components is more important than any one in isolation. Therefore, cardiovascular resuscitation is closely tied to correcting hemoglobin concentration and oxygen saturation. Based on the initial assessment of the patient in shock (Table 20-1), the clinician formulates a working diagnosis as to the cause of hypoperfusion. If the heart is not too full, the indicated intervention is a volume challenge. Therapy is quickly instituted, and the clinical evaluation of intravascular hypovolemia is tested, leading to the next clinical evaluation. The rate and composition of volume expanders must be adjusted in accord with the working diagnosis (Table 20-3), but for all diagnostic categories the infusion must be sufficient to test the clinical hypothesis by effecting a short-term end point indicating benefit (increased blood pressure and pulse pressure) or complication (increased JVP, new gallop or extra heart sounds, pulmonary edema). Absence of either response indicates an inadequate challenge, so the volume administered in the next interval must be greater than the last. In obvious hemorrhagic shock, immediate hemostasis is essential, blood must be obtained early, warmed and filtered; blood substitutes are administered in large amounts (plasma, albumin, hetastarch, dextran, and saline) until the blood pressure rises or the heart becomes too full. At the other extreme, a working diagnosis of cardiogenic shock without obvious fluid overload requires a smaller volume challenge (250 mL NaCl in 20 min). In each case, and in all other types of shock, the next volume challenge depends on the response to the first; it should proceed soon after the first so that the physician does not miss the diagnostic clues evident only to the examining critical care team at the bedside during this urgent resuscitation. After the shock state is improved with adequate vascular volume expansion, the lowest left ventricular filling pressure...

### TABLE 20-3 Urgent Resuscitation of the Patient with Shock—Intravenous Volume and Vasoactive Drug Therapy

<table>
<thead>
<tr>
<th>Hemorrhagic shock including trauma, ruptured aneurysms</th>
<th>Nonhemorrhagic hypovolemia including septic shock</th>
<th>Cardiogenic shock owing to myocardial ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevate legs, MAST</td>
<td>Elevate legs</td>
<td>When heart is too full, reduce blood volume (rotating tourniquets, phlebotomy, nitroglycerin, morphine, diuretics). If the heart is not too full, or blood pressure falls with above interventions, saline 250 mL/20 min Repeat if blood pressure rises until heart too full</td>
</tr>
<tr>
<td>Access infuse emergency blood</td>
<td>3 L/20 min warmed saline</td>
<td>Continue aggressive volume infusion until blood pressure normal</td>
</tr>
<tr>
<td>Group match, administer warmed blood components &gt; 3 L/20 min warmed saline</td>
<td>Group match packed RBCs and plasma re dilutional anemia</td>
<td>Detect and treat tamponade with pericardiocentesis, thoracostomy, peritoneal drainage, or reduced PEEP</td>
</tr>
<tr>
<td>Equal volumes of colloid or substitutes (albumin, dextran, hetastarch)</td>
<td>Continue aggressive volume infusion until blood pressure normal</td>
<td></td>
</tr>
<tr>
<td>Continue aggressive volume infusion until blood pressure normal</td>
<td></td>
<td>Consider early surgical hemostasis</td>
</tr>
<tr>
<td>Consider early surgical hemostasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasoactive drug therapy</td>
<td>Available multipurpose agent (dopamine or epinephrine) and increase dose from 1 to 10 (μg/kg/min for dopamine; μg/min for epinephrine) as needed to maintain blood pressure. If higher doses are needed, add norepinephrine (2-20 μg/min).</td>
<td>Discontinue these drugs as urgently as volume repletion and hemostasis allow (see second column).</td>
</tr>
</tbody>
</table>
Avoid vasoactive drugs until heart too full except dopamine (2-5 mcg/kg per minute) for renal perfusion in low flow states. Nitroglycerin and nitroprusside are contraindicated. Vasoconstrictors delay adequate volume resuscitation (see left column). In right heart overload with shock, norepinephrine (2-20 mcg/min) may help by maintaining RV perfusion. In septic shock, vasoconstrictors may help when adequate volume replacement provides inadequate perfusion pressure (see text).
Dohutamme (5-15 μg/kg per minute) to enhance contractility without excess tachycardia, arrhythmia, or vasoconstriction; higher doses dilate skeletal vascular bed.

Dopamine (2-5 μg/kg per minute) to preserve renal cortical blood flow; at higher dose (4-12 μg/kg per minute), increases heart rate, contractility, venous tone, and preload, like epinephrine.

Nitroglycerin (25-250 μg/min) for venodilation with minimal arterial dilation except for the coronary circulation.

Sodium nitroprusside (0.1-5 μg/kg per minute) for arterial dilation to reduce afterload and allow greater ejection from a depressed left ventricle or regurgitant aortic mitral valve.
sure needed to maintain adequate cardiac output and oxygen delivery is sought. This approach minimizes the complications of pulmonary edema or ventricular dysfunction (or both) caused by excessive ventricular preload. This rationale does not target specific values of pulmonary vascular pressures or cardiac output; rather it implies that management of the patient in shock involves repeated assessment to answer the question—is the heart too full?

If shock is not corrected by adequate circulating volume, then inotropic agents are indicated and will be more effective when the circulation is full. Therapy does not begin with inotropic or other vasoactive agents when the circulatory volume is inadequate, because these drugs often obscure shock by raising blood pressure without correcting the low cardiac output state.

**RATIONALE FOR VOLUME EXPANSION, THEN VASOACTIVE DRUG THERAPY**

It is important to label some preconceptions in approaching the initial cardiovascular management of shock. For the cardiologist-intensivist, hypovolemia is considered cautiously as an occasional contributor to shock because volume resuscitation has adverse effects, since the heart in cardiogenic shock is often too full. Consequently, the early resuscitation of hypotensive patients by physicians trained by cardiologist-intensivists (often this includes internal medicine residents and in-hospital cardiopulmonary resuscitation teams) includes one 18-gauge intravenous line with dextrose 0.5 N saline running to keep the vein open while central lines are inserted for appropriate vasoactive drugs needed to enhance contractility, to adjust preload and afterload, or to control arrhythmias. Not infrequently, volume infusion awaits right heart catheterization after an array of vasoactive drugs fails to restore normal blood pressure. By contrast, surgical and anesthesiology intensivists often treat hypotension in traumatized or hemorrhaging perioperative patients, where the initial resuscitation focuses appropriately on correcting hypovolemia, by rapid infusion of blood products through two 14-gauge central lines accompanied by "pressor agents" to raise blood pressure more quickly, and thus a confusing array of pharmacologic agents confounds evaluation of the end point of volume resuscitation.

Although both approaches are appropriate "preconceptions" in such "specialized" circumstances, they each leave too many hypotensive patients with inadequate circulating volume long after the first hour of urgent resuscitation. We encourage an early check on the assumed cause of shock for all patients, in part because many hypoperfusion states fall between these extremes. That is, all hypotensive patients require an adequate circulating volume, so volume infusion should be pushed until a discernable "too much" as evidenced by clinical examination revealing a heart which is too full; then positive inotropic drugs (dobutamine) can be effective in increasing output from the heart with adequate preload but poor pump function.

Too often, the blanket coverage of "pressor agents" is used early in all types of shock. Because some positive inotropic drugs can cause vasoconstriction to increase cardiac output by endogenous volume shifts (dopamine, epinephrine), there is a rationale [like that of raising the patient's legs or apply-mg military antishock trousers (MAST)] for the common practice of starting these agents in some hypotensive pa
tients while the volume resuscitation proceeds. Yet, this strategy often confounds the determination of an adequate circu-
lating volume as well as the diagnosis of the etiology of shock. This diagnostic confusion is even greater when arte-
riolar constricting agents are used to raise the blood pressure (norepinephrine, phenylephrine, metaraminol, methox-
amine), for the clinical signs that separate a too low cardiac output from a high output are obscured; furthermore, the end points of volume
infusion up to a heart too full are lost by the induced increase in SVR, which rarely improves the hypoperfusion state.
Accordingly, we encourage early aggressive volume resuscitation to a heart which is too full, followed by rapid titration of a
positive inotropic agent (dobutamine 2 to 10 μg/kg per minute) to enhance myocardial contractility, and a mesenteric
vasodilator (dopamine 2 to 5 μg/kg per minute) to preserve renal function—arteriolar vasoconstrictors are rarely indicated
in the early resuscitation (see Table 20-3). The use of a vasodilator drug to enhance mesenteric blood flow follows from a
notion that renal and gut perfusion are particularly threatened during hypoperfused states and that recognition of adequate
perfusion of these tissue beds is often obscure or delayed; even when the blood pressure rises and perfusion to the extremities
seems adequate, a concern of ongoing hypoperfusion to the viscera is probably appropriate. It is not entirely clear that
selective vasodilators do improve visceral blood flow, however. Dopamine probably enhances renal perfusion in the setting
of low flow shock accompanying left ventricular function. However, in the very common forms of high output hypotension,
such as sepsis, recent studies suggest that low-dose dopamine does not increase renal perfusion (although it may increase
urine volume by its natriuretic effects) and may actually divert blood flow away from the gastric mucosa. Thus, at the
present time low-dose dopamine can be recommended for the treatment of congestive heart failure and cardiogenic shock.
Whether other catecholamines with selective vasodilating properties (such as dopexamine) will prove useful requires further
study.

This approach of aggressive volume resuscitation avoids persistent hypovolemia as the cause for prolonged hypotension, at the risk of
causing pulmonary edema or aggravating the pumping dysfunction of the ischemic myocardium. We are not cavalier about fluid overload—
indeed, just as soon as the heart becomes evaluated as too full, we shift goals to aim for the lowest circulating volume which Still provides
adequate perfusion and O₂ delivery—but we emphasize that rational diagnosis and early resuscitation from shock requires an adequate
circulating volume before vasoactive drugs can be effective. Of course, the discerning intensivist is aware that the initial evaluation of some
hypotensive patients reveals a heart too full, so vasoactive therapy starts immediately, but this should not translate into a "shock protocol"
that initiates vasoactive drugs before ensuring adequate volume resuscitation.

Volume resuscitated septic shock stands out as a challenging hemodynamic problem. Here the inflammatory component of shock is
prominent so that after a vigorous volume resuscitation right atrial pressure may be high (for example, 18 mm Hg), cardiac output may be
spectacular (14 L/min), but mean arterial pressure may be distressingly low (45 mm Hg), and evidence of organ system hypoperfusion
PART III CARDIOVASCULAR DISORDERS

may persist (oliguria, impaired mentation, lactic acidosis). Here there is a role for pressor agents (Fig. 20-1). Whereas adequate cardiac output is more important than blood pressure (because adequate tissue oxygen delivery is the underlying issue), effective distribution of flow by the vascular system depends on an adequate pressure head. At pressures below an autoregulatory limit, normal flow distribution mechanisms are lost so that significant organ system hypoperfusion may persist in the face of elevated cardiac output owing to maldistribution of blood flow. In this case where inadequate pressure is the dominant problem, an assessment of organ system perfusion is made (urine output, mentation, lactic acid concentration), and then noradrenaline is initiated to raise mean arterial pressure. The increased afterload will decrease cardiac output so that this intervention is only appropriate when cardiac output is high. For example, an increase in mean arterial pressure from 45 to 60 mm Hg may improve urine output and mentation, whereas the associated decrease in cardiac output from 14 L/min to 9 L/min will still result in adequate oxygen delivery. However, if cardiac output started at 6 L/min, a decrease to 4 or 3 L/min may be detrimental and lead to inadequate oxygen delivery and adverse outcome.

Assessment of organ system perfusion is the most important component of vasopressor therapy—the increase in blood pressure is, by itself, irrelevant and often distracts from careful reassessment of adequacy of oxygen delivery. If urine output increases, mentation improves, and lactate levels decrease, then vasopressor therapy has achieved its goals, and there is no need to increase mean arterial pressure further even if the mean arterial pressure that reverses these signs of hypoperfusion is 55 mm Hg. If the measures of organ system perfusion are not improved by vasopressor therapy, then arbitrarily driving mean arterial pressure much above 70 mm Hg is rarely useful in septic shock and usually detrimental because cardiac output will decrease further and excessive vasoconstrictor tone will impair blood flow distribution. If evidence of hypoperfusion persists, then inadequate volume resuscitation, cardiac output, hemoglobin, and oxygen saturation are more likely the problem. Failure of vasopressor therapy to improve measures of organ perfusion should lead to early discontinuation of this therapy.

IS THERE A ROLE FOR DELAYED RESUSCITATION OF HYPOVOLEMIA?

During brisk ongoing hemorrhage, massive crystalloid or colloid resuscitation increases blood pressure and the rate of hemorrhage so that patient outcome may be worse. This does not mean that resuscitation is detrimental—this simply means that control of active bleeding is more important than volume replacement. Preventing blood loss conserves pre-warmed, oxygen-carrying, protein-containing, biocompatible intravascular volume and is therefore far superior to replacing ongoing losses with fluids deficient in one or more of these areas. We believe that delayed or inadequate volume resuscitation, after blood loss is controlled, is a significant error which will have a detrimental impact on patient outcome.

IS THERE A ROLE FOR SUPRANORMAL RESUSCITATION?

A number of investigators propose that resuscitation of shock to supranormal values of cardiac output and whole body oxygen delivery may be beneficial. Other studies demon-
FIGURE 20-1 An approach to inotropic drug and vasoactive use in septic shock is illustrated. Initial volume resuscitation is rapidly taken to the end point of the heart "too full" to ensure that intravascular hypovolemia does not contribute further to the shock state. The patient is then reevaluated. If evidence of multiple organ hypoperfusion persists, then inotropic/vasoactive drugs should be used. If cardiac output and oxygen delivery are low or normal and blood pressure is adequate, then dopamine (up to 5 μg/kg per minute) is started. Further increases in cardiac output can be accomplished using dobutamine (up to 20 μg/kg per minute). Be aware that if dobutamine is started before adequate volume resuscitation has corrected hypovolemia, significant further hypotension will occur. In contrast, if cardiac output is excessively high yet blood pressure is very low, then noradrenaline can be started. Vasoconstrictor therapy with noradrenaline must be assessed by measuring the physiologic response (increased urine output, improved mentation, decreased lactate concentration), since the increase in blood pressure alone does not indicate therapeutic success. In fact, the increase in blood pressure will decrease cardiac output so that increasing blood pressure beyond what is necessary to effect a salutary physiologic response is detrimental. If vasoconstriction does not improve the physiologic end points, then it should be discontinued. A range of presentations combining various degrees of low cardiac output and excessively low blood pressure is typical of septic shock. Therefore, in severe septic shock it is reasonable to combine dobutamine (for cardiac output) with noradrenaline (to maintain the minimum pressure required for physiologic flow distribution) or, in occasional instances combined agents such as dopamine (up to 20 μg/kg per minute) or adrenaline. In every case the infusion rate is titrated down to the lowest rate that maintains the physiologic goal.

These apparently discrepant studies highlight important issues. Physicians aiming at supranormal goals for resuscitation tend to increase the speed of resuscitation so that organ system hypoperfusion is reversed more rapidly. However, once organ system hypoperfusion is reversed, careful comparison confirms that there is no benefit in driving the cardiovascular system further, and excessive volume infusion will worsen pulmonary and tissue edema, and excessive use of inotropic and vasoactive drugs will increase tissue oxygen demand and impair distribution of blood flow and oxygen delivery. Taken together, we interpret these studies as further support for the notion that aggressive initial resuscitation with rapid reversal of organ system hypoperfusion is beneficial, but subsequently driving the cardiovascular system to supranormal values is detrimental.
CATHETERS AND FREQUENT MEASUREMENTS DURING INITIAL RESUSCITATION

After an airway is established and breathing ensured, correction of the circulatory abnormality always requires good intravenous access. For large-volume administration, two peripheral intravenous catheters of gauge 16 or larger are required. Alternatively or additionally, a large-bore central venous catheter may be used to infuse volume or vasoactive drugs and to facilitate early insertion of a right heart catheter if it is required (see below); this central catheter should be connected to a pressure transducer for early recording of the central venous pressure (CVP) to evaluate its response to volume challenges. ECG monitoring is easily accomplished and usefully measures heart rate and rhythm to detect early, and so facilitate rational treatment of, tachy- or bradyarrhythmias aggravating the low-flow state.

The urinary bladder should be catheterized to measure urine output and to facilitate urine sampling. A nasogastric or orogastric tube to decompress the stomach and later to deliver medication and nutrition is useful in the intubated patient. Measuring arterial pressure using a peripheral arterial or femoral arterial catheter is useful because in the patient in shock with low cardiac output or low blood pressure, cuff pressures may be inaccurate. Arterial blood-gas and other blood samples are then readily obtained. Using the ventilator and other devices, extensive measurements of pulmonary mechanics and function can occur in intubated patients including respiratory rate, tidal volume, Fio₂, peak, mean, and end-expiratory airway pressures, static end-inspiratory and end-expiratory airway pressures, end-tidal CO₂ concentration, and O₂ consumption and CO₂ production.

Placement of a pulmonary artery catheter allows detailed repeated cardiovascular measurements. CVP, right ventricular pressures, pulmonary artery pressures, pulmonary artery occlusion pressure, and thermodilution cardiac output can be measured as frequently as necessary to identify hemodynamic abnormalities and to measure the effect of therapeutic interventions as tests of clinical hypotheses. For example, using a pulmonary artery catheter, following a rapid crystalloid fluid infusion, a small rise in CVP or pulmonary artery occlusion pressure suggests that the ventricle is operating on the compliant-partially full portion of the diastolic pressure-volume relationship. However, a sharp rise in CVP or Ppw suggests that the intravascular space and ventricle are quite full so that further volume infusion will likely result in marked increases in filling pressures and increase the risk of pulmonary edema. One recent study conducted with a case-control approach suggested that right heart catheterization may actually be associated with increased mortality in critically ill patients.

Many have questioned the interpretation of the data reported in this single study, and shock was not the only indication for catheterization (for further discussion see Chap. 14). We believe that right heart catheterization should not delay appropriate resuscitation in shock, as described above, but that when properly interpreted, data from this procedure can guide final titration of therapies. Early 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 can replace the more invasive right heart catheterization.
If a question that a vascular pressure, flow, or image can answer is not asked or if the answer to that question will not alter therapy, then the catheter or other transducer should be discontinued, since it will most likely only contribute to confusion and complications. Indeed, we encourage the same urgency in discontinuing invasive hemodynamic measurements when answers to diagnostic and therapeutic questions are already evident as we encourage the early implementation of these measures. One helpful test of the continued need for right heart catheter measurements is to ask whether a new catheterization is warranted to obtain the information revealed by the current catheter; if not, remove it! Repeated physical examination is often the most effective monitoring that can be done.

**EARLY DEFINITIVE THERAPY**

The initial hour of urgent resuscitation must implement and evaluate therapy directed at the working diagnosis. Detection and treatment of other factors aggravating the hypoperfusion state are aided by a systematic review to ensure that "secondary" conditions are not overlooked during volume and vasoactive drug resuscitation (see Table 20-4).

**CORRECTING CONTRIBUTING CAUSES OF SHOCK** During the rapid initial assessment of the patient in shock, and initial therapy aimed at supporting respiration and circulation, it is important to consider early institution of other definitive therapy and the potential benefit of early input from consultant experts. For example, in suspected septic shock, institution of antibiotic therapy for infection should not be overlooked in the first hour (Table 20-4). Early surgical consultation for potential surgical problems (abdominal sepsis or other abscesses, gastrointestinal hemorrhage, tho-racostomy for pneumothorax) should be obtained. Bradycardia requires atropine, isoproterenol, and/or a paced rhythm; tachyarrhythmias merit lidocaine (ventricular), digoxin (supraventricular), or defibrillation (Table 20-4 and Chap. 23). Expert cardiology consultation is helpful early, especially where invasive reperfusion of the coronary circulation, transvenous pacemakers, or pericardiocentesis needs consideration.

Continuous and early application of techniques to anticipate, prevent, or correct hypothermia prevents secondary coagulopathy, coma, and nonresponsiveness to volume and pharmacologic resuscitation (see Table 20-4). The diagnosis and correction of acidemia rely on ventilator therapy to keep $P_{aco}$; (hence tissue $P_{aco}$) low while confirming the presence and magnitude of anion gap acidosis without the osmolar gap of exogenous poisons (methanol, ethylene glycol). Concurrent exclusion of ketoacidosis (alcoholic or diabetic) suggests the commonest cause in shock—lactic acidosis. Beyond reestablishing perfusion and oxygen delivery, describing intercurrent liver dysfunction or ischemic organs as sources of reduced clearance or increased production are important adjuncts to early assessment of the severity and prognosis of lactic acidosis. Legitimate uncertainty exists concerning the treatment of lactic acidosis with intravenous NaHCO₃, in part because intracellular acidosis may be made worse, lactic acid production may increase, and treatment-associated ionized hypocalcemia may depress cardiovascular function. Our approach is to hyperventilate the patient to $P_{aco}$ equalling 25 mm Hg and to measure ionized calcium; if it is reduced, we administer calcium. When pH remains
TABLE 20-4 Urgent Resuscitation of the Patient with Shock—Managing Factors Aggravating the Hypoperfusion State

Respiratory therapy
Protect the airway—consider early elective intubation. Prevent excess respiratory work—ventilate with small volumes Avoid respiratory acidosis—keep Paco, low Maintain oxygen delivery—Flo, PEEP, hemoglobin

Infection in presumed septic shock—(see Chaps. 41 and 42) Empirical rational antibiosis for all probable etiologies Exclude allergies to antibiotics Search, incise, and drain abscesses (consider laparotomy)

Arrhythmias aggravating shock (see Chap. 23) Bradycardia (rate < 80 min in shock)
Correct hypoxemia—Flo, of 1.0
Atropine 0.6 rng, repeat x 2 for effect
Increase dopamine to 10 /g/kg per min
Add isoproterenol (1-10 /g/min)
Consider transvenous pacer Ventricular ectopy, tachycardia
Udocaine
Detect and correct K+, Ca++, Mg
Detect and treat myocardial ischemia Supraventricular tachycardia
Consider defibrillation early
Digoxin for rate control of atrial fibrillation Sinus tachycardia > 140/min
Detect and treat pain and anxiety Midazolam fentanyl drip Morphine
Detect and treat hypovolemia

Metabolic (Lactic) Acidosis
Characterize to confirm anion gap without osmolar gap Rule out or treat ketoaddosis, aspirin intoxication Hyperventilate to keep Pacoa of 25 mm Hg Calculate bicarbonate deficit and replace half if pH < 7.0 Correct ionized hypocalcemia Consider early dialysis

Hypothermia
Maintain skin dry and covered with warmed blankets Warm vascular volume expanders Aggressive rewarming if temperature < 35°C (95°F)

< 7.0, we calculate the HC03 deficit and administer half the correcting dose of NaHCO3 and more calcium. If the correction is much less than expected, we institute a further search for the source of excess lactate production and consider early hemodialysis against a bicarbonate bath with high ionized calcium. The evidence for these preferences is not conclusive, and some would argue against any treatment of lactic acidosis in the setting of shock other than treating the shock itself (see Chap. 74).

Goals of Therapy of Shock

The goal of therapy is to reverse the pathophysiologic abnormalities of shock with adequate therapeutic intervention but to avoid adverse consequences of excessive therapy. This involves continuously testing the clinical hypothesis of "too little versus too much." There are no specific "numbers" to
aim for, although evaluation of the type of shock and clinical assessment of the pathophysiologic abnormalities aids the physician in choosing the best therapeutic intervention that, when administered, will act as a test of the clinical assessment. Accordingly, we encourage the urgent restoration of an adequate circulating volume to restore cardiac output and \( C_{\geq 2} \) delivery, aided if necessary by vasoactive drugs and complemented by respiratory therapy to rest respiratory muscles and effect saturation of an adequate circulatory hemoglobin; then, we encourage an equally urgent reduction of each of these many interventions to the least level effecting the same goals of respiratory and cardiovascular management aided by diminishing ancillary measurements as uncertainty decreases concerning etiology and management of shock.

GOALS OF RESPIRATORY MANAGEMENT

The initial goal of airway intubation and mechanical ventilation is to correct inadequate oxygenation and ventilation, to rest the respiratory muscles so to limit their need for the limited blood flow, and to protect the airway. Initially a high \( F_{\text{io}} \) is chosen, and mechanical ventilation attempts to do all the work of breathing so that respiratory muscle oxygen consumption is minimized. Often this is best accomplished by using a controlled mechanical ventilation mode with a low trigger threshold to allow patient-initiated assisted breaths; by delivering an adequate minute ventilation to reduce ventilator drive; by using a high enough inspiratory flow rate to rapidly unload and relax any contracting inspiratory muscles; and by administering adequate doses of sedatives and analgesics. During this initial period of hemodynamic instability, assist control ventilation may be more beneficial than pressure support or intermittent mandatory ventilation modes to reduce patient work of breathing.\(^{23}\) If the patient continues to work hard on the mechanical ventilator, then muscle paralysis may improve the efficiency of mechanical ventilation and speed resolution of the acute shock state. If sedation can rest the patient, then paralytics should be avoided because of their potential for long-term effects on neuromuscular function.\(^{24-25}\)

Immediately after initiating mechanical ventilatory support the goal of minimizing therapeutic intervention (reducing toxic \( F_{\text{io}} \), lowering PEEP, liberating the patient from mechanical ventilation), while ensuring that the pathophysiologic abnormalities are reversed, starts in earnest.\(^9\) When blood-gas data are available, the least-toxic \( F_{\text{io}} \) consistent with adequate arterial oxygenation is sought. The least PEEP consistent with adequate arterial saturation of sufficient circulatory hemoglobin on a nontoxic \( F_{\text{io}} \), is used. Although PEEP can reduce venous return in the patient in shock, note that PEEP often increases output in patients with cardio-genic shock and pulmonary edema,\(^ {9,40}\) so the physician should not delay trying PEEP to fix the hypoxemia. Similarly, when septic or hypovolemic shock is complicated by pulmonary vascular leak, these patients often tolerate PEEP to correct hypoxemia without reducing their cardiac output or blood pressure provided their vascular volume is adequate.

Reversing the reasons for airway intubation and mechanical ventilation is the most important aspect of the process of liberating the patient from mechanical ventilation. For example if a patient has been paralyzed and sedated to de-
crease the oxygen demand of the respiratory muscles and the reason for increased demand (e.g., shock and acidosis) has been reversed, then paralysis should quickly be discontinued and the patient allowed to trigger the ventilator. Indeed, if the indication for assisted ventilation is gone, and frequently this happens quickly, then the patient should be allowed to do as much of the work of breathing as is consistent with useful exercise of the respiratory muscles without fatigue. Specific ventilator modes which facilitate this are considered in detail in Chap. 32. Intubation and mechanical ventilation should be discontinued as rapidly as is safely possible because intubation and mechanical ventilation are associated with significant ongoing risk.

**GOALS OF CARDIOVASCULAR MANAGEMENT**

Cardiovascular management aims to maintain a cardiac output and oxygen delivery adequate to reverse tissue hypoperfusion but avoid adverse effects of excessive therapy by seeking the lowest ventricular filling pressures and lowest vasoactive drug infusions required to achieve this goal.  

Tables of normal hemodynamic values are frequently misleading, because an appropriate value for one patient in shock or recovering from shock is often inappropriate for another patient in shock—and usually well outside the normal range. For example, a normal cardiac output in a septic patient may be inappropriately low so that there is continued evidence of tissue hypoperfusion. However, vigorous resuscitation with fluid and vasoactive drugs to achieve a normal blood pressure may be excessive. At a lower blood pressure, a patient with sepsis may have no evidence of ongoing tissue hypoperfusion, and fluid administration to increase the blood pressure to a numerical goal may result in tissue and pulmonary edema that may be disadvantageous. Vasoconstrictors to maintain a normal blood pressure at a numerical goal may result in worsened distribution of cardiac output and increase oxygen demand of tissues so that some vital tissue beds may become even more hypoxic.

Clinical assessment of the mechanism of shock is important in choosing specific "inotropic" or "vasoactive" agents. For example, dopamine beneficially increases contractility in some shock states, but it also increases venous return by constricting the capacitance veins even in hypovolemic shock and may acutely appear beneficial. The continued use of these agents in hypovolemic shock, masking inadequate fluid resuscitation, is dangerous. Dobutamine increases ventricular contractility and reduces afterload, which may result in increased cardiac output and oxygen delivery in cardiogenic shock. However, if contractility is already good, then dobutamine may only serve to decrease afterload and preload, which, in the hypovolemic patient, may cause dangerous hypotension and hypoperfusion. Dopamine in the range of 0.5 to 5 \mu g/kg per minute may selectively improve renal and mesenteric blood flow in cardiogenic shock but probably is not beneficial in sepsis (see above). In high cardiac output hypotensive septic shock, norepinephrine may improve renal blood flow by increasing arterial pressure above a critical threshold required to perfuse the kidneys. However, at higher doses, dopamine and noradrenaline redistribute blood flow away from the kidney, gut, and vital organs. Thus, depending on the mechanism of shock, spe
cific vasoactive agents may be beneficial or detrimental. Use of any of these agents should not be for theoretical benefit but for readily observable improvement in indicators of organ perfusion.

**TEMO**

One of the most important contributions the intensivist can make to the care of a shock patient is to establish an appropriately rapid management tempo. For example, careful evaluation of the need for radiographic examination weighed against the time spent doing these tests away from other care or determining when the best time is to place a pulmonary artery catheter weighed against the time that it will divert the physician’s attention from other matters depend very much on the intensivist’s judgment and familiarity with the clinical setting. Frequently, appropriate decision-making regarding sequence and tempo of care can markedly decrease the duration of initial assessment and resuscitation.

The mirror image of urgent implementation is rapid liberation of the resuscitated patient from excessive therapy. It is not uncommon for the patient with hypovolemic or septic shock to stabilize hemodynamically on positive-pressure ventilation with high circulating volume and several vasoactive drugs infusing at a high rate (e.g., dopamine 20 μg/kg per minute). Too often, hours or days of “weaning” pass, when a trial of spontaneous breathing, diuresis, and sequential reduction of the drug dose by half each 10 minutes can return the patient to a much less treated stable state within the hour. Of course, this rapid discontinuation may be limited by intercurrent hemodynamic or other instability, but defining each limit and Justifying ongoing or new therapy is the essence of titrated care in this postresuscitation period. Utilizing the sophisticated critical care nursing and monitoring of the critical care unit to maintain the tempo of recovery to the preshock state should reduce the duration and complications of critical care.

**WHAT JUST HAPPENED?**

Our approach to the shock patient includes formulating an early working diagnoses, or clinical hypothesis, and using the appropriate therapy to test this hypothesis. The outcome dictates the next therapeutic intervention or invites a refined or alternative explanation for the hypoperfused state. Accurate formulation of clinical hypotheses leads to more rapid and efficient patient care. Accurate hypothesis formulation depends on understanding the pathophysiology of the different types of shock, especially when the outcome of the initial therapy did not fit with the working diagnosis. Then, overlapping etiologies of shock or special types of pathophysiology must be considered during this pause at the end of the urgent resuscitation (see Table 20-I). The move to a search for new etiologies is aided when the interventions were adequate to test the initial hypothesis. During the same period of reconsideration, therapies initiated in haste can be reduced to the minimum required to maintain their end point, while the physician reconsiders the ongoing diagnosis and treatment in the light of the broader differential of the types of shock. These numerous possibilities are best approached in categories of presentation (Table 20-5).
TABLE 20-5 Causes of and Contributors to Shock

<table>
<thead>
<tr>
<th>Decreased Pump Function of the Heart—Cardiogenic Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular failure</td>
</tr>
<tr>
<td>Systolic dysfunction—decreased contractility</td>
</tr>
<tr>
<td>Myocardial infarction Ischemia and global hypoxemia</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
</tr>
</tbody>
</table>
| Depressant drugs: 
  - β blockers, calcium channel blockers, 
  - antiarrhythmics                                    |
| Myocardial contusion                                    |
| Respiratory acidosis                                    |
| Metabolic derangements: acidosis, hypophosphatemia, hypocalcemia |
| Diastolic dysfunction—increased myocardial diastolic stiffness |
| Ischemia Ventricular hypertrophy                         |
| Restrictive cardiomyopathy                              |
| Consequence of prolonged hypovolemic or septic shock    |
| Ventricular interdependence                              |
| External compression (see cardiac tamponade below)      |
| Greatly increased afterload Aortic stenosis             |
| Hypertrophic cardiomyopathy                             |
| Dynamic outflow tract obstruction Courseduction of the aorta |
| Malignant hypertension Valve and structural abnormality |
| Mitral stenosis, endocarditis, mitral aortic regurgitation |
| Obstruction owing to atrial myxoma or thrombus Papillary |
| muscle dysfunction or rupture Ruptured septum or free wall |
| Arrhythmias Right ventricular failure Decreased contractility |
| Right ventricular infarction, hypoxia, acidosis          |
| Greatly increased afterload Pulmonary embolism Pulmonary |
| vascular disease Hypoxic pulmonary vasoconstriction, PEEP, high alveolar pressure |
| Addoxis ARDS, pulmonary fibrosis, sleep disordered breathing, |
| chronic obstructive pulmonary disease Valve and structural abnormality |
| Obstruction due to atrial myxoma, thrombus, endocarditis |
| Arrhythmias                                              |
| High Cardiac Output Hypotension                         |
| Septic shock                                            |
| Sterile endotoxemia with hepatic failure                |
| Arteriovenous shunts                                    |
| Dialysis                                                |
| Paget’s disease                                         |

<table>
<thead>
<tr>
<th>Decreased Venous Return with Normal Pumping Function—Hypovolemic Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac tamponade (increased right atrial pressure—central</td>
</tr>
<tr>
<td>hypovolemia) Pericardial fluid collection</td>
</tr>
<tr>
<td>Blood</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Pericarditis with effusion Constrictive pericarditis High</td>
</tr>
<tr>
<td>intrathoracic pressure</td>
</tr>
<tr>
<td>Tension pneumothorax</td>
</tr>
<tr>
<td>Massive pleural effusion</td>
</tr>
<tr>
<td>Positive-pressure ventilation High intraabdominal pressure</td>
</tr>
<tr>
<td>Acites</td>
</tr>
<tr>
<td>Massive obesity</td>
</tr>
<tr>
<td>After extensive intraabdominal surgery Intravascular</td>
</tr>
<tr>
<td>hypovolemia (reduced mean systemic pressure)</td>
</tr>
<tr>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Aortic dissection and other internal sources Renal losses</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Osmotic diuresis</td>
</tr>
<tr>
<td>Diabetes (insipidus, mellitus) Gastrointestinal losses</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Gastric suctioning</td>
</tr>
<tr>
<td>Loss via surgical stomas Redistribution to extravascular space</td>
</tr>
<tr>
<td>Bums</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Postsurgical</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Decreased venous tone (reduced mean systemic pressure)</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Sedatives</td>
</tr>
<tr>
<td>Narcotics</td>
</tr>
<tr>
<td>Diuretics Anaphylactic shock Neurogenic shock</td>
</tr>
<tr>
<td>Increased resistance to venous return</td>
</tr>
<tr>
<td>Tumor compression or invasion</td>
</tr>
<tr>
<td>Venous thrombosis with obstruction</td>
</tr>
<tr>
<td>PEEP Pregnancy</td>
</tr>
<tr>
<td>Other Causes of Shock with Unique Etiologies</td>
</tr>
<tr>
<td>Thyroid storm</td>
</tr>
<tr>
<td>Myxedema coma</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>Hemoglobin and mitochondrial poisons</td>
</tr>
<tr>
<td>Cyanide</td>
</tr>
<tr>
<td>Carbon monoxide</td>
</tr>
<tr>
<td>Iron intoxication</td>
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</tbody>
</table>

Types of Shock

A number of classifications of shock are possible, in part dependent on the exact definition of shock; here we initially emphasize inadequate organ system perfusion and hypotension. Inadequate perfusion can result primarily from
decreased pump function of the heart, decreased venous return despite normal pump function, or high cardiac output hypotension caused by reduced arterial tone, associated with abnormal blood flow distribution so that some capillary beds are not adequately perfused (see Table 20-5). Shock caused by decreased pump function of the heart is com-
monly cardiogenic shock resulting from left ventricular ischemia. For high right atrial pressure-hypotension not obviously caused by left ventricular ischemia, greatly elevated pulmonary arterial pressure (most commonly pulmonary embolism), right ventricular ischemia, and dysfunction of heart valves must be excluded. Of course, right atrial pressure may be increased by abnormal pressures surrounding the heart in the absence of ventricular dysfunction. Because of this clinical presentation we have included cardiac tamponade in the high right atrial pressure hypotension category. Note that tamponade might have been classified with hypovolemic shock as decreased venous return (Table 20-1). Decreased venous return despite normal pump function is most commonly owing to hemorrhagic or dehydration hypovolemia, but we emphasize other mechanisms including decreased venous tone caused by drugs, neurologic injury, and adrenal insufficiency, particularly for nonresponsive hypovolemia. Septic shock is the most common cause of high cardiac output hypotension resulting from abnormal arterial tone and blood flow distribution, although other causes such as severe liver failure, severe pancreatitis, trauma with tissue damage eliciting a significant inflammatory response, anaphylactic shock, thyroid storm, Paget’s disease and other peripheral shunts share this mechanism. Defining shock as anaerobic metabolism of multiple organ systems, often signaled by lactic acidosis, allows classification of the shock state as anaerobic metabolism of multiple organ systems, often signaled by lactic acidosis, allows classification of the shock state associated with metabolic poisons, such as carbon monoxide, which results in histotoxic hypoxia caused by an inadequate uptake of oxygen by the mitochondria (see Table 20-5).

Other shock states, particularly septic shock, may also involve an inability of tissues to extract delivered oxygen, but we note that the lactic acidosis of sepsis is not necessarily caused by anaerobic metabolism (see below).

In describing and distinguishing between the types of shock, it is helpful to call to mind the Starling relationships between left ventricular stroke volume and left atrial pressure. When cardiac output and stroke volume are reduced, a low pulmonary wedge pressure (Ppw approximately equal to left atrial pressure) signals hypovolemic shock, but a high Ppw signals cardiogenic shock. In all hypotensive states, baroreceptor reflexes are stimulated to raise cardiac output via venoconstriction, to raise blood pressure via arterial constriction, and to increase heart rate and contractility. Distinguishing types of shock is further aided by understanding venous return curves, especially as they are coupled with cardiac function curves (right atrial pressure versus cardiac output, see below).

Accordingly, we use these relationships in the following discussion to compare and contrast cardiovascular mechanisms responsible for cardiogenic shock (Fig. 20-2), hypovolemic shock (see Fig. 20-3), and septic shock (see Fig. 20-4). Our goal is to link patho-physiology of the circulation to the broader differential diagnosis of the types of shock in Table 20-5 to facilitate the accurate etiologic diagnosis and management based on additional hemodynamic measures as required by the response to urgent resuscitation.

FIGURE 20-2 Cardiovascular mechanics in cardiogenic shock. The upper panel compares the abnormalities of systolic and diastolic left ventricular pressure-volume (ordinate-abscissa) relationships during cardiogenic shock (continuous) with normal pressure-volume relationships (dashed lines). The primary abnormality is that the end-systolic pressure-volume relationship (sloped straight lines) is shifted to the right mainly by a marked reduction in slope (decreased contractility). As a result, at similar or even lower systolic pressures the ventricle is not able to eject as far so that end-systolic volume is greatly increased and stroke volume is therefore decreased. To compensate for the decrease in stroke volume, the curvilinear diastolic pressure-volume relationship shifts to the right, which indicates decreased diastolic stiffness (increased compliance). To maximize stroke volume, diastolic filling increases even further, associated with an increase in end-diastolic pressure.

Why end-diastolic pressure increases is determined from the pump function and venous return curves illustrated in the bottom panel as a plot of cardiac output (ordinate) versus right atrial end-diastolic pressure (abscissa). The decrease in contractility from the top panel results in a shift of the curvilinear cardiac function curve from its normal position (dashed curve, bottom panel) down to the right (continuous curve, bottom panel). Since end-diastolic pressure and cardiac output are determined by the intersection of the cardiac function curve (curvilinear relationships, bottom panel) with the venous return curve (straight lines, bottom panel), the shift of the cardiac function curve immediately results in a decrease in cardiac output and an increase in end-diastolic pressure.

Compensatory mechanisms (fluid retention by the kidneys, increased sympathetic tone) act to maintain venous return by increasing mean systemic pressure (Pms, the venous pressure when cardiac output 0) from 16 to 25 mm Hg as indicated by the rightward shift from the dashed straight line to the continuous straight line in the bottom panel. The effect is that end-diastolic pressure increases so that stroke volume (upper panel) and cardiac output (bottom panel) are increased toward normal.
FIGURE 20-3 Cardiovascular mechanics in hypovolemic shock (axes labeled as in Fig. 20-2). During hypovolemic shock the primary abnormality is a decrease in the intravascular volume so that mean systemic pressure decreases as illustrated by a shift of the venous return curves from the normal relationship (straight dashed line, lower panel) leftward (straight continuous line, lower panel). This hypovolemic venous return curve now intersects the normal cardiac function curve (dashed curvilinear relationship, lower panel) at a much lower end-diastolic pressure so that cardiac output is greatly reduced.

In the upper panel, the increased sympathetic tone accompanying shock results in a slight increase in contractility, as illustrated by the slight left shift of the left ventricular end-systolic pressure-volume relationship (from the dashed straight line to the solid straight line in the upper panel). However, since the slope of the end-systolic pressure-volume relationship is normally quite steep, the increase in contractility cannot increase stroke volume or cardiac output much and is therefore an ineffective compensatory mechanism in patients with normal hearts.

If volume resuscitation to correct the primary abnormality is delayed for several hours, the diastolic pressure-volume relationship shifts from its normal position (dashed curve, upper panel) resulting in increased diastolic stiffness (continuous curve, upper panel). Increased diastolic stiffness results in a decreased stroke volume and therefore a depressed cardiac function curve (continuous curve, lower panel) compared to normal (dashed curve, lower panel). This decrease in cardiac function due to increased diastolic stiffness probably accounts for irreversibility of severe prolonged hypovolemic shock.
DECREASED PUMP FUNCTION—CARDIOGENIC SHOCK

Pump function is measured as the output of a pump for a given input. The diagnosis of decreased pump function as the cause of shock is made by finding evidence of inappropriately low output (cardiac output) despite normal or high input (right atrial pressure). Cardiac output is the most important "output" of the heart and is clinically assessed in the same way that perfusion was assessed during the urgent initial examination. Better estimates are later obtained by thermodilution measurement using a pulmonary artery catheter, nuclear medicine scans, and Doppler echocardiographic techniques. Right atrial pressure is the most easily measured "input" of the whole heart and is initially assessed by examination of jugular veins. Following catheter insertion, CVP can be measured accurately. Other outputs, such as stroke work or left ventricular ejection fraction, and other inputs, such as left ventricular end-diastolic pressure (LVEDP) or volume (LVEDV), are useful to determine the specific cause of decreased pump function. Left and right ventricular dysfunction can each be caused by decreased systolic contractility, increased diastolic stiffness, greatly increased afterload (including obstruction), valvular dysfunction, or abnormal heart rate and rhythm.

CAUSES OF LEFT VENTRICULAR FAILURE

Acute or acute on chronic left ventricular failure resulting in shock is the classic example of cardiogenic shock and is identified as a subset of decreased pump function by evidence of a low cardiac output in relation to high left ventricular filling pressures. Clinical findings of low cardiac output and increased left ventricular filling pressures include, in addition to assessment of perfusion, pulmonary crackles in dependent lung regions, presence of a third heart sound, absence of crisp heart sounds, and clinical evidence of ventricular dilation. These findings are not always present or unambiguous. Therefore, pulmonary artery catheterization is helpful and often essential in establishing the diagnosis and titrating therapy. Cardiogenic shock then is usually associated with a cardiac index < 2.2 L/m² per minute when the pulmonary artery occlusion pressure has been raised to more than 18 mm Hg.

Systolic Dysfunction

Figure 20-2 illustrates the pathophysiologic abnormalities of cardiogenic shock resulting from decreased left ventricular contractility. The primary abnormality is that the end-systolic pressure-volume relationship is shifted down and to the right (see Fig. 20-2, upper panel) so that, at the same afterload, the ventricle cannot eject as far (decreased contractility). The result of this is that left ventricular pump function is reduced. That is, the pump function curve is also shifted down and to the right (see Fig. 20-2, lower panel) so that at similar preloads cardiac output is reduced. Three mechanisms which counter the fall in cardiac output are illustrated. The diastolic ventricle becomes more compliant, possibly from stress relaxation of the pericardium and myocardium, so that stroke volume increases at the same end-diastolic pressure (rightward shift of the diastolic pressure-volume relationship in upper panel). Afterload decreases resulting in increased stroke volume (see Fig. 20-2, upper panel). Finally,
FIGURE 20-4 Cardiovascular mechanics in septic shock (axes labeled as in Fig. 20-2). Septic shock has important independent effects on left ventricular pressure-volume relationships, on the venous return curve, and on the arterial vascular resistance. Depressed systolic contractility indicated by a decreased slope of the left ventricular end-systolic pressure-volume relationship from normal (dashed sloped line, upper panel) to sepsis (continuous sloped line, upper panel) is caused in part by a circulating myocardial depressant factor; yet the end-systolic volume remains about normal owing to the reduced afterload. Survivors of septic shock have a large end-diastolic volume even at reduced diastolic pressure associated with dilation of their diastolic ventricles indicated by a shift of the normal diastolic pressure-volume relationship (dashed curve, upper panel) to the right (right hand continuous, upper panel). As a result, stroke volume is increased. However, in nonsurvivors stroke volume falls because of a leftward shift of the diastolic pressure-volume relationship (left hand continuous curve, upper panel), indicating increased diastolic stiffness and impaired diastolic filling.

The cardiac function curve illustrated in the bottom panel for survivors is normal (dashed curvilinear relation) or slightly increased (continuous curvilinear relation owing to reduced afterload). The peripheral circulation during septic shock is often characterized by high flows and low vascular pressures. It follows that the resistance to venous return is decreased as indicated by a steeper venous return curve (continuous straight line, lower panel) compared to normal (straight dashed lines, lower panel). This accounts for the high venous return and large end-diastolic volumes and stroke volumes. As with other interventions, resistance to venous return may be decreased in part by redistribution of blood flow to vascular beds with short time constants. However, the nonsurvivors may have significantly depressed cardiac function (downward shifted continuous curve, lower panel) because of the additive effects of decreased systolic contractility and unpaired diastolic filling. Depending on the relative contribution of the abnormalities of ventricular mechanics and peripheral vascular changes, cardiac output is usually normal or high even at relatively normal end-diastolic pressures until diastolic dysfunction limits cardiac output by reducing diastolic volume even at high diastolic pressures.

mean systemic pressure ($P_{ms}$) rises (see Fig. 20-2, lower panel) aided by avid fluid retention by the kidneys and by increased venous tone mediated by the sympathetic nervous system. Thus, the Frank-Starling mechanism of increasing cardiac output by increasing diastolic filling is used.

As a result of a decrease in contractility the patient presents with elevated left and right ventricular filling pressures and a low cardiac output. Mixed venous oxygen saturation may be well below 50% because cardiac output is low. In the presence of physiologic pulmonary shunt that accompanies pulmonary edema, the low saturation of mixed venous blood shunting by the lung contributes to substantial arterial desaturation. Accordingly, arterial desaturation aggravates the low oxygen delivery due to reduced cardiac output, as does intercurrent anemia.

Acute myocardial infarction or ischemia is the most common cause of left ventricular failure leading to shock. The principle effect of myocardial infarction is to depress systolic contractility, which in completely infarcted areas becomes zero or even negative (paradoxical regional wall motion). Earlier series described shock occurring in 10% to 20% of patients with transmural myocardial infarction. How
ever, the recent use of fibrinolytic therapy and the possible beneficial effects of early surgical revascularization have reduced the incidence of cardiogenic shock to approximately 5%.\textsuperscript{28,29} Infarction of > 40% of the myocardium is often associated with cardiogenic shock.\textsuperscript{30} Anterior infarction is more likely to lead to shock than inferior or posterior infarction. Details of the diagnosis and management of ischemic heart disease are discussed in Chap. 24; other causes of decreased left ventricular contractility in critical illness are discussed in more detail in Chap. 21, as each may contribute to shock.

**Diastolic Dysfunction**

Increased left ventricular diastolic chamber stiffness contributing to cardiogenic shock occurs during myocardial ischemia, and in a range of less common disorders including late stages of hypovolemic shock and septic shock (see Table 20-4); note that all causes of tamponade listed in Table 20-4 need to be considered in a systematic review of causes of diastolic dysfunction.\textsuperscript{31} Cardiac function is depressed since stroke volume is decreased by decreased end-diastolic volume caused by increased diastolic chamber stiffness.
Diastolic dysfunction in a hypertensive patient with low cardiac output and high filling pressures is often identified by a small (rather than large) LVEDV by bedside echocardiography. Conditions resulting in increased diastolic stiffness are particularly detrimental when systolic contractility is decreased because decreased diastolic stiffness (increased compliance) is a normal compensatory mechanism. Establishing the diagnosis of increased diastolic chamber stiffness is often difficult, and increased diastolic chamber stiffness is best identified by echocardiography as contributing to hypotension in patients with low cardiac output and high ventricular diastolic pressures by a small diastolic volume and a good ejection fraction with very small end-systolic volume.

Increased diastolic stiffness is difficult to treat except when it is caused by an acute reversible cause such as ischemia (or the causes of tamponade listed in Table 20-5). Fluid infusion results in large increases in diastolic pressure without much increase in diastolic volume. Positive inotropic agents are associated with the development of histologic contraction band changes which may worsen diastolic compliance. Afterload reduction when systolic function is normal decreases blood pressure without increasing cardiac output, except when nitroprusside corrects the diastolic stiffness. Indeed, if conventional therapy of cardiogenic shock aimed at improving systolic function is ineffective, then increased diastolic stiffness should be strongly considered as the cause of decreased pump function. Heart-rate-responsive cardiac output is another subtle clue suggesting impaired diastolic filling. Heart rate does not normally alter cardiac output except at very low heart rates when further diastolic filling does not occur during the long diastole because the steep portion of the diastolic pressure-volume relationship is reached, or at very high heart rates when diastole is too short to allow complete ventricular relaxation and filling. However, if diastolic filling is limited by tamponade or a stiff ventricle then very little further filling occurs late in diastole even though mean systemic pressure driving venous return may be high. In this case, increasing heart rate from 80 to 100 or 100 beats per minute may result in a significant increase in cardiac output, which may be therapeutically beneficial and also a diagnostic clue.

Valvular Dysfunction

Acute mitral regurgitation, owing to cordal or papillary muscle rupture or papillary muscle dysfunction, most commonly is caused by ischemic injury. The characteristic murmur and the presence of large v waves on the pulmonary artery occlusion pressure trace suggest significant mitral regurgitation, which may be quantified using Doppler echocardiographic examination. Rupture of the ventricular septum with left-to-right shunt is detected using Doppler echocardiographic examination or by observing a step-up in oxygen saturation of blood from the right atrium to the pulmonary artery. Rarely, acute obstruction of the mitral valve by left atrial thrombus or myxoma may also result in cardiogenic shock. These conditions are generally surgical emergencies. More common, valve dysfunction aggravates other primary etiologies of shock. Aortic and mitral regurgitation reduces forward flow and raises LVEDP whatever the state of contractility, and this regurgitation is ameliorated by effective arteriolar dilation, as by nitroprusside infusion.
that vasodilator therapy can effect large increases in card output without much change in mean blood pressure, pu pressure, or diastolic pressure, so right heart catheterization and repeat echocardiography, to confirm increased card output and reduced valvular regurgitation, are essential titrating effective vasodilator doses. By contrast, occasion patients are noted to decrease their blood pressure and ca diac output on inotropic drugs like dobutamine; then e eluding dynamic ventricular outflow tract obstruction I echocardiography or treating it by increasing preload, after load, and end-systolic volume are essential.

**Cardiac Arrhythmias**

Not infrequently, arrhythmias aggravate hypoperfusion i: other shock states. Ventricular tachyarrhythmias are ofte) associated with cardiogenic shock; sinus tachycardia am atrial tachyarrhythmias are often observed with hypova lemie and septic shock (see Table 20-4). Specific therapy o tachyarrhythmias depends on the specific diagnosis as discussed in Chap. 23. Inadequately treated pain and unsuspected drug withdrawal should be included in the ICU differential diagnosis of tachyarrhythmias; whatever their etiology, the reduced ventricular filling time can reduce cardiac output and so aggravate shock. Bradyarrhythmias contributing to shock may respond acutely to atropine or iso-proterenol infusion and then pacing; hypoxia or myocardial infarction as the cause should be sought and treated. Symptomatic hypoperfusion resulting from bradyarrhythmias, even in the absence of myocardial infarction or high-degree atrioventricular (AV) block, is an important indication for temporary pacemaker placement that is sometimes overlooked.

**Treatment of Left Ventricular Failure**

Management of patients with cardiogenic shock requires repeatedly testing the hypothesis of "too little versus too much." Clinical examination is not accurate enough so that a pulmonary artery catheter is almost always required. Initial therapy for cardiogenic shock follows from consideration of the pathophysiology illustrated in Fig. 20-2 and includes optimizing filling pressures, increasing contractility by improving the ratio of myocardial oxygen supply to demand or by using inotropic drugs, and optimizing afterload. Temporary mechanical support with an intraaortic balloon pump (IABP) is often extremely useful in cardiogenic shock and should be considered early on as a support device in patients who may benefit from later surgical therapy. Important additional therapy includes early institution of thrombolytic therapy in acute coronary thrombosis and revascularization or surgical correction of other anatomic abnormalities where appropriate. Cardiac transplantation and mechanical heart implantation are considered when other therapy fails.

Filling pressures are optimized to improve cardiac output but avoid pulmonary edema. Depending on the initial presentation, cardiogenic shock frequently spans the spectrum of hypovolemia (so that fluid infusion helps) to hyper-vo lemia with pulmonary edema (where reduction in in-tractascular volume results in substantial improvement). If gross fluid overload is not present, then a rapid fluid bolus should be given. In contrast to patients with hypovolemie or septic shock, a smaller bolus (250 mL) of crystalloid solution
**CHAPTER 20 SHOCK**

Should be infused as fast as possible. Immediately after infusion the patient’s circulatory status should be reassessed. If there is improvement but hypoperfusion persists, then further infusion with repeat examination is indicated to attain an adequate cardiac output and oxygen delivery while seeking the lowest filling pressure needed to accomplish this goal. If there is no improvement in oxygen delivery and evidence of worsened pulmonary edema or gas exchange, then the limit of initial fluid resuscitation has been defined. Crystalloid solutions are used particularly if the initial evaluation is uncertain because crystalloid solutions rapidly distribute to the entire extracellular fluid compartment. Therefore, after a brief period only one-quarter to one-third remains in the intravascular compartment, and evidence of intravascular fluid overload rapidly subsides.

Contractility increases if ischemia can be relieved by decreasing myocardial oxygen demand or by improving myocardial oxygen supply by increasing coronary blood flow (coronary vasodilators, thrombolytic therapy, surgical revascularization, IABP counterpulsation) or by increasing the oxygen content of arterial blood. Inotropic drug infusion attempts to correct the physiologic abnormality by increasing contractility (see Fig. 20-2). However, this occurs at the expense of increased myocardial oxygen demand. Afterload is optimized to maintain arterial pressures high enough to perfuse vital organs (including the heart) but low enough to maximize systolic ejection. When systolic function is normal, afterload reduction often reduces blood pressure with little increase in cardiac output; when systolic function is much reduced, vasodilator therapy may improve systolic ejection and increase perfusion, even to the extent that blood pressure rises. In patients with very high blood pressure, the end-systolic volume increases considerably such that stroke volume and cardiac output fall unless LVEDV and LVEDP are greatly increased; this sequence is reversed by judicious afterload reduction.

**Diagnosis and Management of Right Ventricular Failure**

Right ventricular failure as a cause of cardiogenic shock is often identified by elevated right atrial pressure and low cardiac output not explained by left ventricular failure or cardiac tamponade. The most common causes of shock owing to right ventricular failure are right ventricular infarction and pulmonary embolism resulting in greatly increased right ventricular afterload. Right ventricular infarction is found in approximately half of inferior myocardial infarctions and is complicated by shock only 10% to 20% of the time. Isolated right ventricular infarction with shock is uncommon. The hemodynamic findings of right ventricular infarction must be distinguished from cardiac tamponade and constrictive pericarditis and include Kussmaul's sign, low cardiac output, high filling pressures, and often equalization of right atrial, right ventricular diastolic, pulmonary artery diastolic, and pulmonary artery occlusion pressures. Pulmonary crackles are classically absent. Therapy includes fluid infusion and dobutamine. Because bradyarrhythmias are common and AV conduction is frequently abnormal, AV sequential pacing often dramatically improves cardiac output and blood pressure in shock caused by right ventricular infarction. IABP counterpulsation may also be useful as are early fibrinolytic therapy and angioplasty when indicated (see Chap. 24).
Right ventricular ischemia, with or without coronary artery disease, probably is a more important cause of right ventricular dysfunction than generally recognized. In shock states systemic arterial pressure is often low, and right ventricular afterload (pulmonary artery pressure) may be high owing to emboli, hypoxemic pulmonary vasoconstriction, addemetic pulmonary vasoconstriction, sepsis, or adult respiratory distress syndrome (ARDS). Therefore, right ventricular perfusion pressure is low leading to right ventricular ischemia and decreased contractility, which, in the face of normal or high right ventricular afterload, results in right ventricular dilation. Subsequent right-to-left shift of the interventricular septum limits left ventricular filling. Cardiac output is then limited by right ventricular systolic ejection and left ventricular diastolic filling.

Therapy of right ventricular failure caused by decreased right ventricular perfusion and increased afterload is evolving. Animal studies suggest that, acutely in right ventricular shock caused by pulmonary embolism, interventions such as norepinephrine infusion may increase systemic arterial pressure more than pulmonary arterial pressure, resulting in improved right ventricular perfusion. Improved right ventricular function and total cardiac function may result. This approach has not been carefully tested in patients in shock owing to right ventricular failure. Established approaches include verifying that pulmonary emboli are present and initiating therapy with anticoagulation, fibrinolytic agents, or surgical embolectomy, as necessary. Hypoxic pulmonary vasoconstriction may be reduced by improving alveolar and mixed venous oxygenation by increasing Flo2 or increasing oxygen delivery by other means such as blood transfusion. More aggressive correction of acidemia should be considered in this setting. Pulmonary vasodilator therapy may be useful in some patients if pulmonary artery pressures can be lowered without significantly lowering systemic arterial pressures. Inhaled nitric oxide, prostaglandin E1, and many other agents have been variably successful. Measurements of pulmonary artery pressure, systemic pressure, cardiac output, and oxygen delivery before and after a trial of a specific potential pulmonary vasodilator are essential (see Chap. 25).

Compression of the Heart by Surrounding Structures

Compression of the heart (cardiac tamponade) limits diastolic filling and can result in shock with inadequate cardiac output despite very high right atrial pressures. Diagnosis of cardiac tamponade is made physiologically using right heart and pulmonary artery catheterization to demonstrate a low cardiac output together with elevated and approximately equal right atrial, right ventricular diastolic, pulmonary artery diastolic, and pulmonary artery occlusion pressures (particularly their waveforms). The diagnosis is often best confirmed anatomically using echocardiographic examination demonstrating pericardial fluid, diastolic collapse of the atria and right ventricle, and right-to-left septal shift during inspiration. Septal shift during inspiration and increased afterload that accompany decreased intrathoracic pressure during inspiration account for the clinically observed pulsus paradoxus. Although pericardial tamponade by accumulation of pericardial fluid is the most common cause of cardiac tamponade, other structures surrounding the heart may also produce tamponade. Tension pneumothorax tamponades the heart so that the patient is hypotensive and in shock de-
spite distended jugular veins. Massive accumulations of pleural fluid may also occasionally tamponade the heart. Pneumopericardium may occasionally result in cardiac tamponade and shock in adults, but this complication is more common in infants. Greatly elevated abdominal pressures may elevate the diaphragm and raise intrathoracic pressure enough to impair diastolic filling.

Decreasing the pressure of the tamponading chamber by needle drainage of the pericardium, pleural space, and peritoneum can rapidly and dramatically improve venous return, blood pressure, and organ system perfusion. Therefore the goal of therapy is to accomplish this decompression as rapidly and safely as possible. In patients who are hemodynamically stable, fluid infusion is a temporizing therapy which increases mean systemic pressure so that venous return increases even though right atrial pressure is high. In hemodynamically stable patients, if it is safe to take the time needed to get ultrasonic guidance for needle aspiration or surgical drainage, then this should be done. Otherwise, in an emergency, blind needle drainage is necessary.

DECREASED VENOUS RETURN—HYPOVOLEMIC SHOCK

The pressure driving venous return back to the right atrium is described as mean systemic pressure minus right atrial pressure, where the mean systemic pressure is determined by the vascular volume and by the unstressed volume and capacitance of the systemic vessels. Venous return to the heart when right atrial pressure is not elevated may be inadequate owing to decreased intravascular volume (hypo-volemic shock), to decreased tone of the venous capacitance bed so that mean systemic pressure is low (e.g., drugs, neurogenic shock), and occasionally to increased resistance to venous return (e.g., obstruction of the inferior vena cava). In the presence of shock, decreased venous return is determined to be a contributor to shock by finding low left and right ventricular diastolic pressures, often in an appropriate clinical setting such as trauma or massive gastrointestinal hemorrhage.

HYPOVOLEMIC SHOCK

Hypovolemia is the most common cause of shock caused by decreased venous return and is illustrated in Fig. 20-3. Intravascular volume is decreased so that the venous capacitance bed is not filled, leading to a decreased pressure driving venous return back to the heart. This is seen as a left shift of the venous return curve in Fig. 20-3, lower panel, so that cardiac output decreases at a low end-diastolic pressure (intersection of the venous return curve and cardiac function curve). Endogenous catecholamines attempt to compensate by constricting the venous capacitance bed and thereby raising the pressure driving venous return back to the heart so that 25% reductions in intravascular volume are nearly completely compensated for. Orthostatic decrease in blood pressure by 10 mm Hg or increase in heart rate of more than 30 beats per minute may detect this level of intravascular volume reduction. When approximately 40% of the intravascular volume is lost, sympathetic stimulation can no longer maintain mean systemic pressure resulting in decreased venous return and clinical shock.

After sufficient time (more than 2 hours) and severity (> 40% loss of intravascular volume), patients often cannot be
This observation highlights the urgency with which patients should be resuscitated. Clearly, the pathophysiology of hypovolemic shock is more extensive than just the volume deficit. A "no reflow" phenomenon is described so that after stagnation, neutrophils become adherent to endothelial surfaces and, even after adequate fluid resuscitation, may block capillary beds so that tissue hypoxia is not alleviated. Gut ischemia and systemic release of inflammatory mediators contribute to the pathophysiology. In addition, reduction in cardiac function (the rightward shift of the cardiac function curve in Fig. 20-3, lower panel) is observed so that even after restoration of left and right atrial pressures, cardiac output remains low. This reduced cardiac function is caused by increased diastolic stiffness developing during hypovolemic shock, which impairs ventricular filling as illustrated by the left shift of the diastolic pressure-volume relationship in Fig. 20-3, upper panel. Shock following trauma is a form of hypovolemic shock where a significant systemic inflammatory response, in addition to intravascular volume depletion, is present (see Chap. 88). Intravascular volume may be decreased because of loss of blood and significant redistribution of intravascular volume to other compartments, i.e., "third spacing." Release of inflammatory mediators may result in pathophysiologic abnormalities resembling septic shock. Cardiac dysfunction may be depressed from direct damage from myocardial contusion, from increased diastolic stiffness, from right heart failure, or even circulating myocardial depressant substances. Shock related to burns similarly is multifactorial with a significant component of intravascular hypovolemia and a systemic inflammatory response (see Chaps. 94 to 96). Other causes of shock caused by decreased venous return include severe neurologic damage or drug ingestion resulting in hypotension caused by loss of venous tone. As a result of decreased venous tone, the mean systemic pressure falls, thereby reducing the pressure gradient driving blood flow back to the heart so that cardiac output and blood pressure fall. Obstruction of veins owing to compression, 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 caused by decreased venous return is rapid initial fluid resuscitation. Warmed crystalloid solutions are readily available. Colloid-containing solutions result in a more sustained increase in intravascular volume. However, in the setting of demonstrated or potential leaking endothelial surfaces (e.g., ARDS), the colloid rapidly redistributes into the entire extravascular water compartment. Pulmonary edema and tissue edema may be aggravated. The role of hypertonic saline and other resuscitation solutions is currently uncertain. Alternatively, transfusion of packed red blood cells increases oxygen-carrying capacity and expands the intravascular volume and is therefore a doubly useful therapy. In an emergency, initial transfusion often begins with type-specific blood before a complete crossmatch is available. An optimum hematocrit has not yet been defined and certainly varies for varying clinical problems. Blood viscosity starts to rise rapidly as hematocrit rises above 45%. Therefore, in patients who may have an inadequate oxygen delivery, it is reasonable to transfuse blood to raise the hematocrit toward
this level. After a large stored red blood cell transfusion, clotting factors, platelets, and serum ionized calcium decrease and therefore should be measured and replaced if necessary (see Chap. 62).

As additional support to fluid resuscitation, catecholamines such as dopamine and epinephrine increase venous tone, mean systemic pressure, and venous return at doses < 10 \( \mu \text{g/kg per minute} \) for dopamine and < 10 \( \mu \text{g per minute} \) for epinephrine (see Table 20-3); at higher doses, these agents increase arterial resistance. Infusion of these agents may aid in quickly restoring blood pressure. However, this apparently salutary effect of catecholamines is not a result of increased cardiac contractility during hypovolemic shock in an otherwise healthy person. Continued administration of these agents is inappropriate and dangerous because the problem is inadequate fluid administration, not decreased ventricular contractility.

Recognizing inadequate venous return as the primary abnormality of hypovolemic shock alerts the physician to several commonly encountered and potentially lethal complications of therapy. Airway intubation and mechanical ventilation increase negative intrathoracic pressures to positive values and thus raise right atrial pressure. The already low pressure gradient driving venous return to the heart worsens, resulting in marked reduction in cardiac output and blood pressure. Yet ventilation treats shock by reducing the work of respiratory muscle, so ventilation should be implemented early with adequate volume expansion. Sedatives and analgesics are often administered at the time of airway intubation, resulting in reduced venous tone because of direct relaxing effect on the venous capacitance bed or because of a decrease in circulating catecholamines. Thus, the pressure gradient driving venous return falls. Therefore, in the hypovolemic patient these medications may markedly reduce cardiac output and blood pressure and should be used with caution and with ongoing volume expansion.

**HIGH CARDIAC OUTPUT HYPOTENSION—SEPTIC SHOCK**

Septic shock is the most common example of shock that may be caused primarily by reduced arterial vascular tone and reactivity, often associated with abnormal distribution of blood flow. Gram-negative bacilli are the cause in approximately two-thirds of the cases, and approximately one-third of patients with gram-negative bacteremia develop septic shock. Evidence of end-organ hypoperfusion and dysfunction may be present at low, normal, or high cardiac outputs and oxygen deliveries. During evaluation and resuscitation, normal or increased cardiac output with low SVR hypotension is manifested by a large pulse pressure, warm extremities, good nailbed capillary filling, and a low diastolic and mean blood pressure. This high cardiac output hypotension is often accompanied by an abnormal temperature and white blood cell count and differential and an evident site of sepsis. However, the diagnosis is sometimes initially unclear when septic shock is combined with cardiogenic or hypovolemic shock, which limit the usual increase in cardiac output, oxygen delivery, and mixed-venous oxygen saturation.

A number of pathophysiologic mechanisms contribute to inadequate organ system perfusion in septic shock. There
may be abnormal distribution of blood flow at the organ system level, within individual organs, and even at the capillary bed level. The result is a mismatch between oxygen supply and demand. Some organs, tissues, or capillary beds receive more flow and oxygen delivery than required so that oxygenated blood is functionally shunted by them while other organs, tissues, or capillary beds have an inadequate oxygen delivery and therefore are unable to maintain aerobic metabolism and normal function. In addition, there may be a cellular defect in metabolism so that even cells exposed to adequate oxygen delivery may not maintain normal aerobic metabolism. It should be noted that the evidence for tissue hypoxia in septic shock is not conclusive. So many other abnormalities of oxygen and substrate metabolism may exist and contribute to the abnormality of septic shock that it is a naive assumption that increasing cardiac output and oxygen delivery further will have a beneficial effect.

The cardiovascular abnormalities of septic shock, as illustrated in Fig. 20-4, are extensive and include systolic and diastolic abnormalities of the heart, abnormal arterial tone, abnormalities of capillary flow, and altered tone of the venous bed. Depressed systolic contractility illustrated as a right-ward shift of the end-systolic pressure-volume relationship in Fig. 20-4, upper panel, has been shown to occur in septic shock, leading to a renewed focus on therapy for associated heart failure. At least part of the depression in systolic contractility is caused by a circulating myocardial depressant factor of sepsis that may be dialyzable. Leukocytes that are slowed and retained in the coronary microcirculation also contribute to decreased ventricular contractility. Part of the depression of contractility may relate to a change in oxygen and substrate metabolism. The myocardial oxygen extraction ratio is decreased during sepsis, which could indicate a defect in its ability to extract oxygen; if so, that decreased oxygen consumption in the face of continued oxygen demand may result in decreased systolic contractility. In addition, the metabolic substrate for myocardial metabolism changes so that free fatty acids are no longer the prime substrate and more lactic acid is metabolized. Decreased systolic contractility associated with septic shock is reversible over 5 to 10 days as the patient recovers.

Despite this clear evidence of decreased contractility in sepsis, its contribution to the pathophysiology and treatment of septic shock is not so clear. Note that these "depressed" ventricles often pump cardiac outputs > 10 L/min with normal values of preload, so this amount of systolic dysfunction is probably a minor contributor to the hypoperfusion state of sepsis. Further, inotropic therapy may be responsible for subsequent diastolic dysfunction observed in hypovolemic shock. Ventricles of survivors of septic shock dilate during diastole as is the normal response to decreased ventricular contractility. However, ventricles of non-survivors do not dilate, suggesting that they are stiffer than ventricles of the survivors. Decreased arterial resistance is almost always observed in septic shock. Early in septic shock a high cardiac output...
state exists with normal or low blood pressure. The low arterial resistance is associated with impaired arterial autoregulation. Redistribution of blood flow to low-resistance, short-time-constant vascular beds (such as skeletal muscle) results in decreased resistance to venous return as illustrated in Fig. 20-4 (lower panel) by a steeper venous return curve. As a result, cardiac output may be increased even when cardiac function is decreased (see Fig. 20-4, lower panel) because of decreased contractility (see Fig. 20-4, upper panel). Hypovolemia, caused by redistribution of fluid out of the intravascular compartment and to decreased venous tone, impedes venous return during septic shock. The microcirculation is also affected so that capillary blood flow is abnormal with increased numbers of leukocytes adhering to endothelial surfaces and altering red blood cell distribution.

Initial therapy of septic shock is fluid administration to correct any intercurrent component of hypovolemia. While fluid resuscitation is ongoing, the lowest filling pressures compatible with an adequate cardiac output and oxygen delivery are sought, yet it is hard to know what is adequate. ARDS or increased pulmonary capillary permeability edema may be associated with sepsis so that pulmonary edema may occur at much lower pulmonary artery occlusion pressures. In this setting colloid infusion should be avoided, since it will likely worsen the pulmonary edema. Blood transfusion is a useful therapy as it will expand the intravascular space and increase the oxygen-carrying capacity of the blood and therefore increase oxygen delivery via two mechanisms. Early institution of antibiotic therapy is central to successful therapy (see Table 20-4). Initially the antibiotic choice is not specific and is based in part on the potential pathogens (see Chap. 41). As microbiology data become available, the antibiotic regimen should be made more specific; not infrequently, sterile endotoxemia or gut-derived transient bacteremia mimics the hemodynamics of septic shock, especially in patients with hepatic failure or multisystem organ failure (MSOF) (see Chap. 17).

Other therapeutic interventions are of less certain value. Steroid therapy had previously been proposed as therapy of septic shock; however, several studies have convincingly demonstrated no benefit. Treatment with endorphin antagonists, usually naloxone, may be of benefit in some patients, although this benefit may not become evident for many hours. Therapy using antibodies to inflammatory mediators (antibodies to endotoxin or tumor necrosis factor-α) or using antagonists of inflammatory mediators (IL-1ra) are promising in some animal models but have not yet been successful in clinical trials. Because some of the mediators of septic shock may be dialyzable, dialysis or a variant of hemofiltration may prove useful. Therapy aimed at preventing tissue damage caused by mediators of inflammation (using ibuprofen), by oxygen radicals (using N-acetyl cysteine and analogous compounds), and by intracellular calcium overload (using verapamil) has been proposed. One recent multicenter trial of ibuprofen treatment for sepsis syndrome and septic shock failed to demonstrate a beneficial effect on progression of organ failures, duration of ICU care, or mortality. Since the many pathways activated by the sepsis cascade feature prominent involvement of the vascular endothelium, and nitric oxide synthesis appears upregulated, nitric oxide has been questioned as a potential mediator of the hyperdynamic circulation and low periph
eral vascular resistance. When indiscriminant blockade of nitric oxide synthase is performed, peripheral vascular resistance is seen to rise in patients with sepsis but at the cost of a reduction of cardiac output, a phenomenon similar to the injudicious use of vasoconstrictor agents. Whether more selective approaches to blockade of nitric oxide synthesis or action will prove beneficial awaits further basic and clinical investigation. Accordingly, current effective therapy for septic shock includes rational early antibiosis and adequate expansion of the circulating volume.

OTHER TYPES OF SHOCK
As detailed in Table 20-5, there are many less common etiologies of shock, and the diagnosis and management of several causes of high right atrial pressure hypotension are discussed elsewhere in this book (see Chaps. 21, 25, and 27). A few other types of hypovolemic shock merit early identification by their characteristic features and lack of response to volume resuscitation including neurogenic shock and adrenal insufficiency. Anaphylactic shock results from the effects of histamine and other mediators of anaphylaxis on the heart, circulation, and the peripheral tissues (see Chap. 103). Despite increased circulating catecholamines and the positive inotropic effect of cardiac H₂ receptors, histamine may depress systolic contractility via H₁ stimulation and other mediators of anaphylaxis. Marked arterial vasodilation results in hypotension even at normal or increased cardiac output. Like septic shock, blood flow is redistributed to short-time-constant vascular beds. The endothelium becomes more permeable so that fluid may shift out of the vascular compartment into the extravascular and intracellular compartments, resulting in intravascular hypovolemia. Venous tone and therefore venous return are reduced, so the mainstay of therapy of anaphylactic shock is fluid resuscitation of the intravascular compartment and includes epinephrine and antihistamines as adjunctive therapy.

Neurogenic shock is uncommon. In general, in a patient with neurologic damage that may be extensive, the cause of shock is usually associated with blood loss. Patients with neurogenic shock develop decreased vascular tone, particularly of the venous capacitance bed, which results in pooling of blood in the periphery. Therapy with fluid will increase mean systemic pressure. Catecholamine infusion will also increase mean systemic pressure, and stimulation of alpha receptors will increase arterial resistance, but these are rarely needed once circulation volume is repleted.

A number of endocrinologic conditions may result in shock. Adrenal insufficiency (Addison disease, adrenal hemorrhage and infarction, Waterhouse-Friderichsen syndrome, adrenal insufficiency of sepsis and systemic inflammation) or other disorders with inadequate catecholamine response may result in shock or may be important contributors to other forms of shock. Whenever inadequate catecholamine response is suspected, diagnosis should be established by measuring serum cortisol and conducting a corticotropin stimulation test, whereas presumptive therapy proceeds using dexamethasone (see Chap. 76). Hypothyroidism and hyperthyroidism may in extreme cases result in shock; thyroid storm is an emergency requiring urgent therapy with Lugol’s solution, propylthiouracil, steroids, propranolol, fluid resuscitation, and identification.
of the precipitating cause (see Chap. 77). Pheochromocytoma may lead to shock by markedly increasing afterload and by redistributing intravascular volume into extravascular compartments. In general, the therapeutic approach involves treating the underlying metabolic abnormality, resuscitating with fluid to produce an adequate cardiac output at the lowest adequate filling pressure and infusing inotropic drugs, if necessary, to improve ventricular contractility if it is decreased. Details of diagnosis and therapy of shock associated with poisons (carbon monoxide, cyanide) are discussed in Chap. 99.

Organ System Pathophysiology of Shock

Shock has a hemodynamic component which has been the focus of much of the preceding discussion. In addition, shock has a systemic inflammatory component that is important to recognize, and characterize clinically, because this component is often much more important to clinical outcome. The hemodynamic alterations of shock result in hypoperfusion and inadequate oxygen and substrate delivery to tissues. This leads to impaired organ function owing to inadequate ATP generation and inadequate clearance of toxic metabolic products including lactate and CO₂. Inadequate energy supply results in decreased function of organs which do a great deal of high-energy work, including the heart (decreased pump function), the kidneys (decreased solute reuptake and creatinine clearance), the gut (decreased absorptive capacity), and others. Later, energy supplies are inadequate to maintain membrane potentials and accomplish basic cellular work. Reversing the hypoperfusion state should correct all the abnormalities quickly—as long as the inflammatory component of shock is not triggered.

INFLAMMATORY COMPONENT OF SHOCK

Shock is invariably associated with some degree of inflammatory response, although this component of shock varies greatly. A severe systemic inflammatory response (e.g., sepsis) can result primarily in shock. Conversely, shock results in an inflammatory response because ischemia-reperfusion injury will be triggered to some extent following successful hemodynamic resuscitation of shock of any kind. Ischemia-reperfusion causes release of pro-inflammatory mediators, chemotactic cytokines, and activation of leukocytes. Because of the multiorgan system involvement of shock, the inflammatory response of ischemia-reperfusion involves many organ systems. Rapid hemodynamic correction of hypovolemic or cardiogenic shock may result in a minimal systemic inflammatory response. However, trauma with significant tissue injury or prolonged hypoperfusion states usually elicits profound systemic inflammatory responses. Because the resolution and repair phases of the inflammatory response are complex and take time, this component of shock is important to recognize and characterize clinically because it has prognostic value with profound effects on the subsequent clinical course.

A systemic inflammatory response results in elevated levels of circulating pro-inflammatory mediators (TNF-a, interleukins, prostaglandins, etc.) which activate endothelial cells and leukocytes. Subsequent production of nitric oxide by activated vascular endothelial cells via inducible nitric oxide
Synthase results in substantial vasodilation. Products of the arachidonic acid pathway generated during the systemic inflammatory response contribute to systemic vasodilation (prostaglandin I₂) and pulmonary hypertension (thromboxane A₂). Activated endothelial cells and leukocytes upregulate expression of cellular adhesion molecules and their corresponding ligands, resulting in accumulation of activated leukocytes in pulmonary and systemic, capillaries and post-capillary venules. Expression of chemotactic cytokines by endothelial and parenchymal cells contributes to flow of activated leukocytes into the lungs and systemic tissues. Activated leukocytes release destructive oxygen free radicals, resulting in further microvascular and tissue damage. Damaged and edematous endothelial cells, retained leukocytes, and fibrin and platelet plugs associated with activation of the complement and coagulation cascades, block capillary beds in a patchy manner leading to increased heterogeneity of microvascular blood flow. As a result of the significant damage to the microvasculature, oxygen uptake by metabolizing tissues is further impaired. A severe systemic inflammatory response leads to very high levels of circulating pro-inflammatory mediators, leukopenia and thrombocytopenia owing to uptake in excess of production, disseminated intravascular coagulation owing to excessive activation of the coagulation cascades, diffuse capillary leak, marked vasodilation that may be quite unresponsive to high doses of vaso-pressors, and generalized organ system dysfunction.

Whereas the hemodynamic component of shock is often rapidly reversible, the systemic inflammatory component is not and, as a result, often is the most important component of shock leading to adverse sequelae including multiple organ dysfunction. As suggested above by the abbreviated description of the systemic inflammatory response, this response involves multiple interconnected systems. A number of points in this complex web have been targeted by therapeutic interventions including steroids, antibodies to TNF, and IL-1 receptor antagonist. These approaches have not yet been successful, in part because of the limited nature of these interventions when considered against the background complexity of the systemic inflammatory response. The resolution and repair phases of an inflammatory response follow a frustratingly slow time course:

- Recruitment of adequate and appropriate leukocyte populations, walling off or control of the initial inciting stimuli, modulation of the subsequent inflammatory response toward clearance with apoptosis of inflammatory and damaged cells (Th-1 type of response) or, when the inflammatory stimulus is not as easily cleared, toward a more chronic response with recruitment of new populations of mononuclear leukocytes and fibrin and collagen deposition (Th-2 type of response).

During this repair and resolution phase, current therapy involves vigilant supportive care of the patient to prevent and avoid the multiple common complications associated with multiple organ system dysfunction and mechanical ventilation.

**INDIVIDUAL ORGAN SYSTEMS**

The central nervous system is vulnerable to hypoperfusion because of the hemodynamic component of shock, but the inflammatory component of shock may also contribute to ongoing central nervous system dysfunction. Altered men-
tal status ranging from mild confusion to coma is a frequently observed effect of shock on neurologic function, when brain blood flow falls by approximately 50%. However, patients recovering from shock infrequently suffer a neurologic deficit unless they have concomitant cerebrovascular disease. One exception is that encephalopathy may follow hypovolemic shock in pediatric patients. Thus, in general, the brain is selectively protected against hypo-perfusion compared to other organ systems. The brain, like the heart, maintains a fairly constant oxygen extraction ratio; to meet its metabolic needs under a wide variety of circumstances, it autoregulates cerebral blood flow. Maximal cerebral vasodilation is reached, and decreased neurologic function is observed, when mean arterial pressure falls below 50 to 60 mm Hg in normal individuals.

However, cerebral blood flow may be adequate at even lower pressures in septic shock and other shock states. In addition, elevated PCO₂ dilates and decreased PCO₂ constrains cerebral vessels, after a step change in Pco₂. This effect lasts for less than a day, when equilibration restores cerebral vascular resistance at the new Pco₂. Finally, profound hypoxia results in markedly decreased cerebral vascular resistance. Altered neurologic function may contribute in simple ways, such as impaired ability to protect the airway, to more complex ways, such as decreased release of corticotropin-releasing factor leading to decreased corticotropin release and relative adrenal insufficiency.

Cardiac hypoperfusion owing to shock leads to decreased cardiac function and further hypoperfusion implying a positive feedback loop leading to cardiovascular collapse. Up to the point of cardiovascular collapse, the heart is preferentially protected from the adverse effects of shock, particularly by excellent coronary autoregulation. Normally coronary autoregulation results in a constant and high (70%) myocardial oxygen extraction ratio and is sufficient to maintain adequate coronary blood flow down to very low mean arterial pressures. Whereas myocardial oxygen demand during shock may be elevated because of increased heart rate and increased levels of circulating catecholamines, low afterload and low preloads reduce myocardial oxygen demand. Despite these compensatory mechanisms, myocardial oxygen demand eventually exceeds oxygen supply leading to segmental and global myocardial dysfunction with ST and T wave changes apparent on the ECG. Myocardial perfusion is redistributed away from the endocardium, and this maldistribution is further aggravated by circulating catecholamines. If severe hypoxemia or anemia contribute to limited myocardial oxygen delivery, then the heart may shift to anaerobic metabolism with a concomitant decrease in systolic contractility and output. Unless quickly reversed, this downward spiral rapidly leads to death. Metabolic acidosis and respiratory acidosis result in intracellular myocardial acidosis and decreased contractility. As lactic acid levels rise, ionized calcium levels fall and contribute to decreased contractility. Severe systemic inflammatory responses accompanying shock (septic shock, severe pancreatitis, complicated trauma) have additional effects on the heart. Circulating myocardial depressant factors including TNF-α, interleukins, platelet activating factor, and others contribute to decreased systolic contractility in septic shock in part by increased myocardial nitric oxide production via inducible nitric oxide synthase. Leukocytes are retained in
the myocardium, and release of oxygen free radicals appears to contribute to decreased contractility. The ability of the myocardium to extract oxygen is decreased, and the normal metabolic substrate of myocardial metabolism shifts from predominantly free fatty acids to lactate. During hypovolemic shock and in nonsurvivors of septic shock, increased diastolic stiffness develops, resulting in decreased cardiac pump function. Arrhythmias frequently occur and lead to further reduction in cardiac pump function.

More than any other organ system, the lungs are involved in the inflammatory component of shock. ARDS is the name given to lung injury caused by the impact of the systemic inflammatory response on the lung and has aptly been called “shock lung.” Inflammatory mediators and activated leukocytes in the venous effluent of any organ promptly impact on the pulmonary capillary bed leading to activation of pulmonary vascular endothelium and plugging of pulmonary capillaries with leukocytes. Ventilation perfusion matching is impaired and shunt increases. Increased ventilation associated with shock results in increased work of breathing to the extent that a disproportionate amount of blood flow is diverted to fatiguing ventilatory muscles. Therapy with vasoactive agents may further worsen the shunt. The problem of maintaining oxygen delivery, balanced against the need for low pulmonary venous pressures to avoid worsened pulmonary edema, is aggravated. Decreased pulmonary gas exchange leads to hypoxemia, respiratory acidosis, and worsened metabolic acidosis, all of which may depress cardiac function or contribute to decreased delivery of oxygen to other vital organ systems. Stiff lungs or increased pressures in structures surrounding the heart may impair diastolic filling of the ventricle and thereby worsen the shock state; pulmonary hypertension associated with shock, ARDS, and PEEP further impairs cardiac function by increasing right ventricular afterload with concomitant right-to-left septal shift. There is little evidence that acute lung injury per se causes ventricular dysfunction.

Autoregulation by the brain and heart may divert blood flow from splanchnic organs resulting in ischemic injury of the liver, pancreas, and gut. Early in shock increased catecholamines, glucagon, and glucocorticoids increase hepatic gluconeogenesis leading to hyperglycemia. Later when synthetic function fails, hypoglycemia occurs. Clearance of metabolites and immunologic function of the liver are also impaired during hypoperfusion. Typically, centrilobular hepatic necrosis leads to release of transaminases as the predominant biochemical evidence of hepatic damage, and bilirubin levels may be high. Shock may lead to gut ischemia before other organ systems become ischemic even in the absence of mesenteric vascular disease. Mucosal edema, submucosal hemorrhage, and hemorrhagic necrosis of the gut may occur. Hypoperfusion of the gut has been proposed as a key link in the development of MSOF following shock, particularly when ARDS precedes sepsis (see Chap. 17), i.e., loss of gut barrier function results in entrance of enteric organisms and toxins into lymphatics and the portal circulation. Since the immunologic function of the liver is impaired, bacteria and their toxic products, particularly from portal venous blood, are not adequately cleared. These substances as well as inflammatory mediators produced by hepatic reticuloendothelial cells are released into the systemic circulation and may be an important initiating event of a dif-
fuse systemic inflammatory process that leads to 
MSOF or to the high cardiac output hypotension of endotoxemia.
Increased hepatic function during shock impairs normal clearance of drugs such as narcotics and benzodiazepines, lactic acid, and other metabolites that may adversely affect the cardiovascular. In addition, pancreatic ischemic damage may result in the systemic release of a number of toxic substances including a myocardial depressant factor.

The glomerular filtration rate falls as renal cortical blood flow is reduced by decreased arterial perfusion pressures and by afferent arteriolar vasoconstriction owing to increased sympathetic tone, catecholamines, and angiotensin. The ratio of renal cortical to medullary blood flow decreases. Renal hypoperfusion may lead to ischemic damage with acute tubular necrosis while debris and surrounding tissue edema obstruct tubules. Loss of tubular function is compounded by loss of concentrating ability because medullary hypertonicity decreases. Impaired renal function or renal failure leads to worsened metabolic acidosis, hyperkalemia, impaired clearance of drugs and other substances; all contribute to the poor outcome of patients in shock with renal failure. Decreased renal perfusion pressure results in increased renin, angiotensin, and aldosterone levels with resultant redistribution of blood flow.

Shock impairs reticuloendothelial system function leading to impaired immunologic function.

Coagulation abnormalities and thrombocytopenia are common hematologic effects of shock. Disseminated intravascular coagulation occurs in approximately 10% of patients with hypovolemic and septic shock. Shock combined with impaired hematopoietic and immunologic function seen with hematologic malignancies or following chemotherapy is nearly uniformly lethal.

Endocrine disorders, from insufficient or ineffective insulin secretion to adrenal insufficiency, adversely affect cardiac and other organ system function. Conceivably, impaired parathyroid function is unable to maintain calcium homeostasis. As a result ionized hypocalcemia is observed during lactic acidosis or its treatment with sodium bicarbonate infusion.

SHOCK AND THERAPEUTIC INTERVENTIONS

Hypoperfusion alters the efficacy of drug therapy by slowing delivery of drugs, altering pharmacokinetics once delivered, and decreasing the clearance of drugs. For example, subcutaneous injection of medications may fail to deliver useful quantities of a drug in the setting of decreased perfusion. When adequate perfusion is reestablished, the drug may be delivered in an unpredictable way at an inappropriate time. Thus, parenteral medications should be given intravenously to patients with evidence of hypoperfusion. In marked hypoperfusion states, peripheral intravenous infusion may also be ineffective, and central venous administration may be necessary to effectively deliver medications. Once the drug is delivered to its site of action it may not have the same effect in the setting of shock. For example, catecholamines may be less effective in an acidotic or septic state. Since there may be significant renal and hepatic hypoperfusion, drug clearance is frequently greatly impaired. With these observations in mind, it is appropriate to consider for each drug, necessary changes in route, dose, and interval of administration in shock patients.
Many therapeutic interventions commonly used in the ICU may worsen the shock state. For example, airway intubation and mechanical ventilation using positive airway pressures increase pleural pressure from normal negative values to positive values. Right atrial pressure, therefore, increases to reduce the pressure gradient driving venous return back to the heart. The necessary use of analgesics and sedatives in critically ill patients may have important additional detrimental effects. Analgesics and sedatives may reduce venous tone either directly or by decreasing sympathetic stimulation. As a result cardiac output and oxygen delivery may fall. In a patient with already decreased intravascular volume or an impaired ability to mount a further sympathetic response, the impediment to venous return resulting from positive-pressure ventilation may result in marked reduction in cardiac output and blood pressure.

The increase in intrapulmonary pressures following intubation and mechanical ventilation are frequently amplified by addition of PEEP, by development of intrinsic PEEP, and by inverse ratio and other modes of ventilation. Increased intrapulmonary pressures expand and recruit alveoli and redistribute alveolar edema to the interstitial space, improving arterial oxygenation. However, since the lung is more distended, it may become less compliant owing to its curvilinear volume-pressure relationship so that, despite no change in tidal volume, mean and peak airway pressures rise leading to barotrauma. In addition, lung previously in West's zone 2 or 3 may now be in West's zone 1 conditions, which means physiologic dead space increases. As a result Pco; detrimentally rise at the same minute ventilation.

Volume resuscitation with electrolyte solutions may worsen tissue edema. If endothelial membranes are leaky, then colloid administration may even be worse. Inotropic and vasoactive drugs may improve blood pressure or cardiac output but may worsen the distribution of blood flow so that perfusion of some vital organs may be decreased. For arrhythmias that impair cardiac function, antiarrhythmic agents may be necessary but calcium channel blockers, lidocaine, disopyramide, and others may reduce myocardial contractility and worsen the shock state. In summary, during shock many common therapeutic interventions may have important adverse consequences. This is further reason to regard therapeutic interventions as tests, with clear recognition that if they are not beneficial they will be stopped.

Bicarbonate therapy of metabolic acidosis associated with shock may have adverse consequences. Bicarbonate reduces ionized calcium levels further with potentially detrimental effect on myocardial contractility. Because bicarbonate and acid reversibly form carbon dioxide and water, a high Pco; is observed. Particularly during bolus infusion, acidic blood containing bicarbonate may have a very high Pco; which readily diffuses into cells resulting in marked intra-cellular acidosis; recall that hypoperfusion already increases tissue PCO, by carrying off the tissue CO; production at a higher mixed venous PCO, owing to reduced blood flow. Intracellular acidosis results in decreased myocardial contractility. These adverse consequences of bicarbonate therapy may account partly for the lack of benefit observed with bicarbonate therapy of metabolic acidosis.
PART III CARDIOVASCULAR DISORDERS

Outcome

Untreated, shock leads to death. Even with rapid, appropriate resuscitation, shock is associated with a high initial mortality rate, and tissue damage sustained during shock may lead to delayed sequelae. A number of studies have identified several important predictors. Cardiogenic shock is associated with approximately a 90% mortality with medical management alone, and blood lactate, cardiac output or stroke work, and arterial pressure predict outcome. A blood lactic acid level in excess of 5 mmol/L is associated with 90% mortality in cardiogenic shock and high mortality in other shock states. These mortality rates have fallen during the last decade of interventional cardiology and aggressive antibiosis (see Chaps. 40, 43). In septic shock a falling cardiac output predicts death, and high concentrations of bacteria in blood and a failure to mount a febrile response predict a poor outcome. Age and preexisting illness are important determinants of outcome. MSOF is an important adverse outcome, leading to a mortality rate in excess of 60%, as discussed extensively in Chap. 17.

CASE PRESENTATION

A 61-year-old man collapsed at home and was brought to the hospital. He had been generally unwell and had lost 20 lb over several months. He had a past history of an adenocarcinoma of the lung resected 5 years previously and had an intermittent history of peptic ulcer disease. He was a smoker and had a history of alcohol abuse.

Initial examination showed him to be diaphoretic with cool ashen gray skin and central cyanosis. He was obtunded with a Glasgow coma score of 9. His heart rate was 120, blood pressure was 180/105, temperature was 34.5°C (94.7°F), and respiratory rate was 28 with a Kussmaul's pattern. His pupils were 2 mm and reactive; his neck was supple. His trachea was midline, and the left lung base was dull to percussion with increased transmission of breath sounds and coarse crackles. Cardiovascular examination revealed thready peripheral pulses despite the measured blood pressure with cold, cyanotic extremities with markedly slowed nail bed capillary refill. His jugular veins were easily seen and flat while he was supine. His heart sounds were normal. Bowel sounds were absent, and rectal examination disclosed dark blood in his rectum. Urine output over the first 30 minutes was 4 mL.

Shortly after clinical examination and after initiating volume resuscitation, his hemoglobin was found to be 164 g/L, white blood cell count was 19.8, anion gap was 30, creatinine was 584 mM/L, and BUN was 48.4 mM/L. Arterial blood gases—pH, 7.30; Pco2, 28; and Po2, 54—showed metabolic acidosis with incomplete respiratory compensation and hypoxemia. Chest x-ray demonstrated increased opacification of his left lower lobe. ECG was unchanged from 1 year previously and suggested an old anteroseptal infarction.

Despite his high blood pressure, he was clearly in shock because he had evidence of multisystem organ hypoperfusion based on cardiovascular and neurologic examinations, skin and extremities, and urine output. Although several types of shock may have been contributing, he was clearly hypovolemic. He was also working hard to breathe, probably because he was acidotic, hypoxic, and
possibly septic. This evaluation constitutes the clinical hypothesis. Based on this, two large-bore peripheral intravenous catheters were inserted, ECG monitoring initiated, the patient was intubated, and mechanical ventilation using 100% oxygen and the assist-control mode was begun. Simultaneously, he was given 4 L of warmed normal saline over 30 minutes with repeat physical examination after each liter, which tested and confirmed the primary clinical hypothesis of hypovolemia. His urinary bladder was catheterized, and a nasogastric tube was placed. Physical examination was completed. As fluid resuscitation continued, his blood pressure fell to 120/70, and heart rate decreased to 110. Perfusion of his extremities improved, and his urine output in the second half hour increased to 55 mL. Laboratory tests and chest x-ray results became available and suggested the possibility of sepsis. Accordingly, early therapy also included broad-spectrum antibiotics including ampicillin and an aminoglycoside for gut organisms, and other interventions included naloxone, thiamine, and urgent surgical consultation regarding possible bowel ischemia.

Following initial resuscitation, his acidosis improved but did not resolve, and an arterial lactate level was found to be 10 mM/L. To test the clinical hypothesis that he continued to have inadequate organ system perfusion despite a normal blood pressure and evidence of improved peripheral perfusion, a pulmonary artery catheter was inserted. His right atrial pressure was 5, pulmonary artery pressure was 35/15, a pulmonary artery occlusion pressure was 8, cardiac output was 7.5 L/min, and cardiac index was 4.2 L/m² per minute; the mixed venous saturation was 78%. Laparotomy disclosed infarcted bowel in the region of the watershed between the superior mesenteric and inferior mesenteric arteries. Blood cultures grew pneumococcal.

CASE DISCUSSION

Our synthesis after the first day of therapy was that the patient had developed pneumococcal pneumonia and sepsis. While obtunded at home for some period of time, he became hypovolemic so that he presented with mixed septic and hypovolemic shock. His preexisting vascular disease plus markedly increased sympathetic tone allowed him to maintain a high blood pressure even though his cardiac output was low. Bowel ischemia developed as a result of shock and vascular disease, contributing to septic hemodynamics and lactic acidosis. This case illustrates the common finding that initially shock may result from several causes; therapy is also a test of the clinical hypothesis and points out the important interaction between shock, organ systems, and therapy.

References


76. Hogg JC: The interaction between polymorphonuclear cells and pulmonary endothelium, in Weir EK, Reeves JT (eds):


