It is been estimated that severe sepsis occurs at an incidence of 3.0 cases per 1000 persons per year, resulting in approximately 750,000 affected persons annually in the United States. Of those affected, 500,000 (67%) require intensive or intermediate care unit (ICU) services. Recent estimates indicate that the rate of severe sepsis hospitalizations doubled during the last decade and that age-adjusted population-based mortality is increasing. Sepsis affects the cardiovascular system through multiple mechanisms, and often these derangements result in tissue hypoperfusion. Tissue hypoperfusion is often present in the setting of overt shock, but it can also be present in patients without obvious shock physiology. If left untreated, tissue hypoperfusion contributes to the development of multiple organ dysfunction and ultimately, death. This article provides an overview of the pathophysiology, recognition, and treatment of sepsis-induced hypoperfusion.

PATHOPHYSIOLOGY

The clinician identifies tissue hypoperfusion by synthesizing the clinical impression with quantitative data, such as vital signs, urine output, and direct measurements of oxygenation. When the clinical impression and quantitative data suggest widespread organ hypoperfusion, emergent resuscitation must restore normal tissue oxygenation, and substrate delivery must occur to prevent further deterioration. At the cellular level, hypoperfusion first affects the mitochondria. The vast majority of aerobic chemical energy comes from mitochondrial combustion of fuel substrates (fats, carbohydrates, ketones) plus oxygen into carbon dioxide, and water. Mitochondria are affected first in conditions of inadequate tissue perfusion, and when they are provided inadequate oxygen, the cell catabolizes fuels to lactate, which accumulates and diffuses into the blood.

One of the key components in identifying and treating tissue hypoperfusion in sepsis is understanding the cardiovascular derangements encountered during sepsis.
Although the understanding of sepsis pathophysiology has evolved dramatically over the past several decades, the understanding of sepsis-induced cardiovascular derangements and how they develop continues to be incomplete. Understanding these cardiovascular manifestations is important in as much as they are the targets of therapeutic intervention in patients with tissue hypoperfusion.

Sepsis causes 2 major hemodynamic effects that must be considered: relative hypovolemia and cardiovascular depression. Sepsis produces relative hypovolemia from venous and arterial dilatation, which reduces right ventricular filling. Additionally, there is often absolute hypovolemia from insensible losses and sepsis-induced capillary leak, which leads to relative loss of intravascular volume into third spaces. If volume resuscitation is initiated, it will lead to low systemic vascular resistance, normal or increased cardiac output, and elevated mixed venous oxygenation—a constellation known as hyperdynamic shock syndrome—in most patients. These hemodynamic abnormalities are collectively referred to as distributive shock because of the presumed hypoperfusion to various tissues due to maldistribution of flow.

Evidence has shown that septic shock causes myocardial dysfunction simultaneously with vasodepression and capillary leak. Through direct measurements of cardiac contractility, investigators have shown reduced left ventricular ejection fraction, increased end-diastolic and end-systolic volumes (increased compliance) and normal or decreased stroke volume, reduced systemic vascular resistance, and compensatory tachycardia as the characteristic pattern of sepsis-induced heart dysfunction. Fluid therapy will usually modify this pattern by increasing stroke volume; however, in normotensive and hypotensive subjects, impaired ejection fraction and ventricular dilation remain present, and their presence peaks in the first few days and reverses within the first week of sepsis onset in survivors.

Tissue hypoperfusion can be present even in the presence of normal blood pressure and adequate cardiac output, a state sometimes referred to as cryptic shock. This hypoperfusion may be related to preferential maldistribution of blood flow at the regional or microvascular level. It also may be related to mitochondrial dysfunction in the presence of adequate substrate delivery. Derangements of small vessel perfusion are largely a function of intrinsic events in the microcirculation. The causes of microcirculatory flow alterations in sepsis are multifactorial and include endothelial cell dysfunction, increased leukocyte and platelet adhesion, fibrin deposition, erythrocyte stiffness, altered local perfusion pressures due to regional redistribution of blood flow, and functional shunting. Although research on septic shock is classically focused on macrocirculatory hemodynamics that reflect the distribution of blood flow globally throughout the body, a functioning microcirculation is another critical component of the cardiovascular system that is necessary for effective oxygen delivery to tissues. Regardless of the cause, it seems as if early and aggressive hemodynamic intervention can impart the best opportunity to limit the damage caused by tissue hypoperfusion, including attenuating the inflammatory response and endothelial injury.

CLINICAL FEATURES
If effective tissue perfusion is not restored in a timely manner, the incipient cellular dysfunction and organ failure may become irreversible. Therefore, rapid recognition of tissue hypoperfusion requires the integration of information from bedside assessment synthesized with quantitative data. Heart rate can be normal or low in states of hypoperfusion, especially in cases complicated by prescribed drugs that depress heart rate. Arterial blood pressure can be normal or even high when significant tissue
hypoperfusion is present, probably due to adrenergic reflexes. Although arterial blood pressure as a sole indicator of hypoperfusion is an unreliable marker, its presence can be an important indicator of tissue hypoperfusion. A recent study found that nonsustained hypotension in the emergency department confers a significantly increased risk of death during hospitalization in patients admitted with sepsis. This should impart reluctance to dismiss nonsustained hypotension, including a single measurement, as not clinically significant or meaningful.\(^2\)\(^3\) The heart rate to systolic blood pressure ratio (shock index) may provide greater evidence of hypoperfusion, especially in the setting of normotension, than either measurement alone; a normal ratio is less than 0.8. Urine output provides an excellent indicator of regional (organ) tissue perfusion and is readily available in most patients.\(^3\) A scoring system for the detection of tissue hypoperfusion in sepsis was proposed by Spronk and colleagues,\(^1\)\(^7\) and it includes hemodynamic variables, peripheral circulation, microcirculatory variables, systemic markers of tissue oxygenation, and organ dysfunction. Although the bedside calculation of a score for tissue hypoperfusion is not likely to be necessary, the incorporation of an indicator of tissue hypoperfusion into the clinical assessment may improve identification of hypoperfusion, particularly in subtle cases. Table 1 provides a list of variables that can assist with detecting tissue hypoperfusion. Regional tissue hypoperfusion can be, and often is, present in the absence of evidence of global hypoperfusion. Several of these common variables will be covered with more depth.

### Lactate

Lactate is a commonly used indicator of tissue hypoperfusion, particularly in sepsis. Lack of oxygen delivery to the cell prompts a stall in transfer of electrons to the mitochondrial electron transport chain, subsequently decreasing acetyl coenzyme A entry into the tricarboxylic acid cycle.\(^4\) As mitochondrial oxidative phosphorylation fails and energy metabolism becomes dependent on anaerobic glycolysis, the production of cellular lactate increases sharply, resulting in eventual diffusion into the blood during prolonged cell ischemia. Elevated circulating lactate concentration thus indicates

<table>
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<td><strong>Global</strong></td>
<td><strong>Organ or Regional</strong></td>
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<td>Hypotension</td>
<td>Low urine output</td>
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<tr>
<td>Tachycardia</td>
<td>Elevated levels of bilirubin or liver transaminases</td>
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<td>Low cardiac output</td>
<td>Elevated levels of cardiac enzymes</td>
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<td>Mottled skin</td>
<td>Impaired microcirculatory flow (sidestream dark-field video microscopy)</td>
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<tr>
<td>Delayed capillary refill</td>
<td>Increased tonometric CO(_2) gap (gastric tonometry)</td>
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<td>Altered mental state</td>
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<tr>
<td>Hyperlactemia</td>
<td>Decreased tissue oxygenation or delayed occlusion test slope (near infrared spectroscopy)</td>
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<tr>
<td>Low mixed venous oxygen saturation</td>
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<td>Low central venous oxygen saturation</td>
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widespread inadequate tissue oxygenation. Arterial samples have traditionally been used to measure lactate concentrations in the blood; however, venous lactate values closely approximate arterial values. If lactate is measured via a peripheral venous sample, the values are accurate even if a tourniquet is used and the sample is not immediately placed on ice (provided the sample is processed within 15 minutes).

Measurement of serum lactate levels provides a marker of global tissue hypoxia in the host, and its prognostic value for predicting survival in shock from various causes in animal models and humans has been well established. The finding of an elevated serum lactate level (>4 mmol/L), even in the context of normal macrocirculatory markers of perfusion (ie, cryptic shock), carries a worse prognosis and higher mortality than does a normal (<2 mmol/L) serum lactate level. In these situations, hyperlactemia indicates ongoing tissue hypoperfusion due to misdistribution of flow in the microcirculation even after resuscitation and normalization of the macrocirculation. One study has shown an additional important reason to measure lactate levels in septic patients; it reports an association between lactate elevations and outcome even in the absence of obvious clinical markers of illness severity (organ dysfunction and/or shock). This report also found that the prognostic value of lactate levels reached a plateau of around 8 mmol/L in patients with normotension; however, that same plateau was not reached in patients with obvious shock until lactate levels reached 18 mmol/L. This suggests that high lactate levels need to be interpreted in the context of the clinical scenario and that simply thinking of lactate levels in compartments or groups (low, intermediate, and high) may marginalize the value of this test.

Lactate clearance is defined by the equation $\left(\frac{\text{lactate}_{\text{initial}} - \text{lactate}_{\text{delayed}}}{\text{lactate}_{\text{initial}}} \times 100\right)$, where lactate$_{\text{initial}}$ is the measurement on presentation and lactate$_{\text{delayed}}$ is another measurement after a prespecified time period, usually 2 to 6 hours. Two studies have suggested the value of monitoring for a lactate clearance of 10% or more during the early resuscitation of subjects with severe sepsis showing evidence of hypoperfusion. One of these studies found a 41% higher mortality rate among those subjects who failed to reach a lactate clearance of 10% or more compared with those that effectively cleared lactate (60% vs 19% mortality, respectively) during the early resuscitative period. In a multivariate logistic regression analysis, lactate nonclearance was the strongest independent predictor of in-hospital mortality (odds ratio [OR], 4.9; 95% confidence interval [CI], 1.5–15.9) when compared against other variables, including low central venous oxygen saturation (ScvO$_2$) values and persistent hypotension after volume resuscitation. A recently completed multicenter randomized controlled trial demonstrated that lactate clearance of 10% or more is non-inferior to the use of continuous ScvO$_2$ monitoring in determining adequacy of resuscitation and oxygen supply/demand relationship during the early resuscitation of severe sepsis and septic shock. Taken together, these data demonstrate the utility of lactate not only as a prognostic marker in sepsis but also as a valuable endpoint of early resuscitation.

**Venous Oxygen Saturation**

The balance between oxygen delivery (DO$_2$) and oxygen demand is often ascertained clinically by the measurement of mixed venous oxygen saturation (SvO$_2$), which normally ranges from 65% to 75%. Any decrease in supply, or increase in demand, or both, can cause SvO$_2$ to drop and thus can provide evidence of global tissue hypoxia. Measurements of SvO$_2$ have traditionally been made using blood from the pulmonary artery (PA). The PA is often used because it represents the location of maximum venous mixing, theoretically providing the best true estimate of SvO$_2$. Previous studies have targeted SvO$_2$ as a therapeutic endpoint of resuscitation in critically ill subjects, largely with disappointing results.
To obtain an $\text{SvO}_2$, one must place a PA catheter. Many studies have questioned the value of PA catheters, and in the last decade, 5 randomized controlled trials investigating the management of critically ill patients with PA catheters have been published.\textsuperscript{46-50} None have found survival or length-of-stay benefit in patients managed with PA catheters. Thus investigators have sought surrogate physiologic measurements that can accurately estimate $\text{SvO}_2$. Numerous studies have compared values of $\text{SvO}_2$ with measurements via a chest central venous catheter placed at the junction of the superior vena cava and right atrium ScvO\textsubscript{2}. In general, these studies have demonstrated higher ScvO\textsubscript{2} measurements compared with $\text{SvO}_2$ in shock states, which can be attributed to coronary sinus mixing and a redistribution of blood away from splanchnic, renal, and mesenteric beds.\textsuperscript{51,52} Most correlation studies have reported absolute ScvO\textsubscript{2} values 5% to 18% higher than the $\text{SvO}_2$. However, $\text{SvO}_2$ and ScvO\textsubscript{2} values almost invariably track in the same direction over time, suggesting that following trends of ScvO\textsubscript{2} allows for reasonable assumptions about similar trends in $\text{SvO}_2$.\textsuperscript{51,53}

The only randomized controlled trial to use ScvO\textsubscript{2} as a therapeutic endpoint of resuscitation in severe sepsis and septic shock was conducted by Rivers and colleagues.\textsuperscript{21} This study reported a 16% absolute reduction in mortality when ScvO\textsubscript{2} was targeted for normalization ($\geq$70%) using blood transfusion and inotropic medications. Subsequent observational trials have noted a lower percentage of patients with a low ScvO\textsubscript{2} after adequate resuscitation, causing some to question its utility.\textsuperscript{54} As a result, the relative importance of ScvO\textsubscript{2} as a resuscitation endpoint probably deserves more investigation.

**Other Techniques**

Near infrared spectroscopy is a noninvasive method of assessing tissue perfusion. Through the use of varying wavelengths of light, oxygenation of hemoglobin in the microvasculature of tissue ($\text{StO}_2$) can be measured. Although the absolute value of $\text{StO}_2$ in patients with shock can overlap significantly with that of healthy controls, the rate of recovery to a baseline value following an ischemic challenge by pneumatic cuff (occlusion testing) is slower in patients with septic shock than in healthy controls.\textsuperscript{55-57} This phenomenon is assumed to be due to impaired mitochondrial function in patients with sepsis. One prospective trial demonstrated this slow recovery to baseline after occlusion testing to be independently predictive of survival in a small group of sepsis patients.\textsuperscript{55} No trials to date have evaluated the use of $\text{StO}_2$, either absolute values or occlusion testing, as a resuscitation endpoint.

Sublingual capnometry measures carbon dioxide levels in the sublingual space in an attempt to measure splanchnic perfusion indirectly.\textsuperscript{58} Initial studies of this technique suggest that there is good correlation with microcirculatory flow changes\textsuperscript{59} and that it possibly has better ability to predict outcome than does measurement of $\text{SvO}_2$ and lactate levels.\textsuperscript{60}

Sidestream dark-field video microscopy is another noninvasive method of assessing the microcirculation; however, it is presently only used as a research technique and has not found a widespread application in clinical medicine. The technique uses optical filtration of polarized light that is absorbed by hemoglobin so that red blood cells appear dark. This permits noninvasive direct visualization of blood flow in the sublingual microcirculatory network in human subjects using a hand-held video microscope. The technique has been validated in experimental and human studies.\textsuperscript{61-63} One of the major limitations of this technique is the variability of image acquisition and interpretation. Although this technique and other devices require
further study, the emerging theme is the need to evaluate the microcirculation in patients with sepsis to identify occult tissue hypoperfusion.

RESUSCITATION

Once sepsis-induced tissue hypoperfusion is identified, prompt and aggressive resuscitation should be initiated with the goal of restoring normal perfusion to target tissues. Patients in whom tissue hypoperfusion is suspected or confirmed should be monitored in a resource-rich area, such as the emergency department or intensive care unit. Continuous cardiac, pulse oximetry, and blood pressure monitoring should be routine. Noninvasive blood pressure monitoring measurements made by the oscillometric method with stepped cuff deflation has been compared with direct catheter-measured arterial pressure; the method has been shown to fairly accurately represent true blood pressure among automated methods when directly compared with aortic catheter-measured pressure. The oscillometric method with stepped cuff deflation has a standard error of the mean arterial blood pressure measurement of 4 mm Hg across a wide range of mean arterial pressure measurements and has a low occurrence of clinically significant (± 10 mm Hg) or serious (± 20 mm Hg) measurement errors. However, continuous arterial pressure monitoring with an indwelling catheter is more accurate and provides continuous pressure reading. It should be strongly considered in patients with extremely low blood pressures or those on continuous infusions of vasoactive medications.

Quantitative resuscitation refers to the concept of using a protocol that targets predefined physiologic or laboratory endpoints, such as central venous pressure and mean arterial pressure, during resuscitation of critically ill patients. The aim of such a protocol is to achieve the predefined goals by using various therapeutic interventions in a stepwise manner with the ultimate purpose of decreasing morbidity and mortality. To date, many large studies have investigated the quantitative approach to resuscitation with mixed results, leading to uncertainty. However, a meta-analysis of the treatment effect of such a resuscitation strategy on hospital mortality in patients with sepsis reported conclusive results. Data from 9 randomized controlled trials conducted over the last 2 decades found that subjects resuscitated with an early quantitative strategy had a 50% mortality reduction (OR, 0.50; 95% CI, 0.37–0.69) compared with those resuscitated later in the clinical course. The investigators thus demonstrated a clear survival benefit afforded by quantitative resuscitation in the treatment of sepsis, when initiated early in the disease process, that is, at or near the time of recognition. The benefit of quantitative resuscitation was completely lost if the interventions were initiated late.

The question of the optimal endpoints of resuscitation to target in early sepsis resuscitation remains a topic of debate. Many previous studies have targeted measurements that require PA catheterization (cardiac output, cardiac index, DO₂, SvO₂), a procedure that is not practical in many settings (eg, emergency department). Thus, clinicians should consider the use of more generalizable methods to assess for adequacy of hypoperfusion reversal. The recently published Surviving Sepsis Campaign (SSC) international consensus guidelines advocate use of central venous pressure of 8 to 12 mm Hg, mean arterial pressure greater than or equal to 65 mm Hg, urine output greater than or equal to 0.5 mL/kg/h, and ScvO₂ greater than or equal to 70% (continuous or intermittent). An example of an early sepsis resuscitation protocol is provided in Fig. 1. Regardless of the
SUMMARY

The understanding of sepsis is continuously evolving. An overview of sepsis-induced tissue hypoperfusion has been provided herein. It is of critical importance that the clinician understands the pathophysiology of this emergent condition and is able to synthesize the available data in a rapid fashion so that tissue hypoperfusion is readily detected. Once detected, aggressive and endpoint-directed resuscitation should be implemented to reverse the hypoperfusion and to prevent further deterioration, organ dysfunction, and death.

endpoints, the clear themes in present day sepsis resuscitation are early, aggressive, and endpoint driven.
REFERENCES


