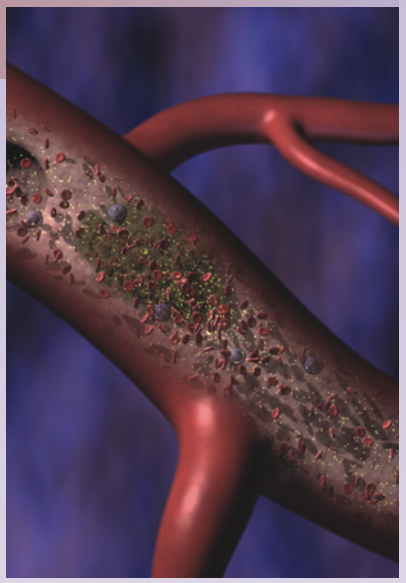
Cardiovascular Aspects of Septic Shock

Pathophysiology, Monitoring, and Treatment



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Septic shock is one of the most feared medical conditions. Mortality due to severe sepsis is approximately 29%, with 215 000 deaths each year (comparable to the number of deaths due to acute myocardial infarction).[1,2] The keys to decreasing the mortality include early recognition of septic shock, resolution of the inflammatory response, elimination of the causative organism, and provision of supportive care.[3-7] In this article, we focus on the cardiovascular aspects of septic shock, including a review of cardiovascular pathophysiology and recommendations for state-of-the-art cardiovascular monitoring and treatment options.

Pathophysiology

Shock is an imbalance between oxygen supply and demand, which results in a systemic clinical syndrome characterized by hypotension and hypoperfusion leading to cellular dysfunction. Sepsis is a systemic response to infection, and septic shock is sepsis with hypotension and abnormalities in perfusion.[8] There are 4 general types of shock: hypovolemic, cardiogenic, obstructive, and distributive.

* This article has been designated for CE credit. A closed-book, multiple-choice examination follows this article, which tests your knowledge of the following objectives:

1. Describe the primary effects of septic shock on the cardiovascular system
2. Recognize the role of various monitoring modalities in the patient with septic shock
3. Identify current recommendations for treatment of septic shock

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Septic shock, which is primarily distributive or vasodilatory shock (ie, abnormal distribution of blood volume due to vasodilatation), reflects the end of a continuum of progressive pathophysiological deterioration that culminates in hypotension that is poorly responsive to adequate fluid resuscitation. This hypotension is accompanied by hypoperfusion and organ dysfunction.[8,9]

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In general, septic shock is associated with 3 major pathophysiological effects within the cardiovascular system: vasodilatation, maldistribution of blood flow, and myocardial depression. In septic shock, the absolute intravascular volume may be normal; however, because of acute vasodilatation, relative hypovolemia occurs. In contrast to other types of shock that are primarily due to decreased intravascular volume (hypovolemic) or decreased cardiac output (cardiogenic or obstructive), a defining characteristic of septic shock is the maldistribution of blood flow in the microcirculation.[10,11] Additionally, myocardial depression may occur. The relative hypovolemia, myocardial depression, and maldistribution result in decreased oxygen delivery (Do_2) and subsequent tissue hypoxia. Current research suggests that an impaired cellular ability to extract and use oxygen (cytopathic hypoxia) may also be a factor contributing to cellular dysfunction and organ failure in septic shock.[12]

Vasodilatation

In septic shock, proinflammatory cytokines and other metabolites (prostaglandins) cause an increase in endothelial-derived nitric oxide (a major mediator in vasodilatation and hypotension). Nitric oxide causes changes in cell wall transport mechanisms and in intracellular factors, which lead to a decrease in intracellular calcium and subsequently vasodilatation as well as resistance to vasopressor agents.[5,13] Three mechanisms are thought to cause the resistance to vasopressor agents[13]: activation of the adenosine triphosphate–sensitive potassium (K_{ATP}) channel by decreased intracellular levels of ATP (hypoxia) and increased intracellular concentrations of hydrogen ions and lactate; activation of the inducible form of nitric oxide synthase, which causes increased levels of nitric oxide; and a decrease in the levels of circulating vasopressin (a vasoconstrictor).

Activation of the K_{ATP} channel causes hyperpolarization of the plasma membrane, which inhibits depolarization and the influx of calcium into the cell, thus inhibiting vasoconstriction. The mechanism by which nitric oxide causes resistance to vasopressor agents most likely is activation of potassium channels with resultant hyperpolarization. With the progression of septic shock, levels of circulating vasopressin decrease because of a yet-to-be-described mechanism.[13,14] The decreased levels contribute to the failure of a reflex vasoconstrictor mechanism.

Maldistribution of Blood Flow

Although septic shock is usually associated with vasodilatation (as manifested by a decrease in systemic vascular resistance), not all vessels are dilated. Some vessels (arterioles) remain vasoconstricted, a situation that leads to maldistribution of blood flow.[10] The vasoconstriction, and subsequent maldistribution, is thought to be caused by various inflammatory mediators (eg, tumor necrosis factor) and endothelin (a factor released from the endothelium that causes vasoconstriction).[15]

Inadequate tissue perfusion also occurs because of vascular occlusion. Polymorphonuclear leukocytes may bind abnormally to the endothelium because of endotoxin and inflammatory mediators. These leukocytes and erythrocytes also plug the microvasculature because of the decreased deformability of the cells.[11] In septic shock, endothelial cells are stimulated by proinflammatory mediators (tumor necrosis factor and interleukin-1 [IL-1]) and endotoxin, causing activation of the coagulation cascade, creation of microvascular plugs, and, subsequently, maldistribution of blood flow.[16,17] The maldistribution contributes to tissue hypoxia.

Downregulation of factors that affect coagulation also occurs, with a resultant procoagulant state. One

factor in the coagulation cascade that has received increased attention is activated protein C. In approximately 85% of patients with septic shock, protein C levels are decreased,[18] and the presence and severity of the deficiency of activated protein C are associated with poor clinical outcomes.[19] Endogenous activated protein C has anti-inflammatory, antithrombotic, and profibrinolytic effects[20] (Figure 1). The anti-inflammatory effects of activated protein C involve inhibition of the release of inflammatory mediators (IL-1, IL-6, and tumor necrosis factor-α) by monocytes, inhibition of the rolling of monocytes and neutrophils on the injured endothelium, and limitation of neutrophil adhesion to the endothelium.[22] Additionally, through its inhibitory effects on thrombin formation (described later), activated protein C limits the initiation of the inflammatory response. Thrombin stimulates the release of IL-8 and the synthesis of platelet-activating factor. IL-8 and platelet-activating factor cause the activation, recruitment, and binding of neutrophils and monocytes, which lead to a proinflammatory response in patients with sepsis.[23]

The coagulation system primarily affected by sepsis is the tissue factor pathway (extrinsic pathway). Under normal conditions, tissue factor is expressed when the endothelium is injured. In sepsis, thrombin and IL-6 stimulate endothelial cells and macrophages to upregulate the expression of tissue factor. Regardless of the mechanism that initiates the coagulation cascade, tissue factor activates factor VII. This step is controlled by the enzyme tissue factor pathway inhibitor (TFPI). Factor VIIa in conjunction with factor VIIIa (from the intrinsic coagulation cascade) cause activation of factor X. Factor Xa in combination with factor Va, phospholipids, and calcium creates a complex that converts prothrombin to thrombin. Thrombin then cleaves the fibrinogen molecule to create fibrin, which subsequently develops a fibrin clot.

Protein C is activated when thrombin interacts with endothelial cells, which have protein-bound thrombomodulin (a clotting enzyme that activates thrombin). Activated protein C acts in a feedback loop to limit thrombin formation by inactivation of factors Va and VIIIa. In sepsis, thrombomodulin is cleaved from the endothelium; thus, protein C activation is decreased. Additionally, TFPI activity is decreased because of proteases released by neutrophils, decreasing the feedback inhibition of the activation of factor VII. The combination of the increased activation of the tissue factor pathway and the decreased effects of TFPI and activated protein C leads to a procoagulant state.[24]

The profibrinolytic effects of activated protein C are mediated through tissue plasminogen activator, an enzyme that converts plasminogen to plasmin. Plasmin dissolves clots

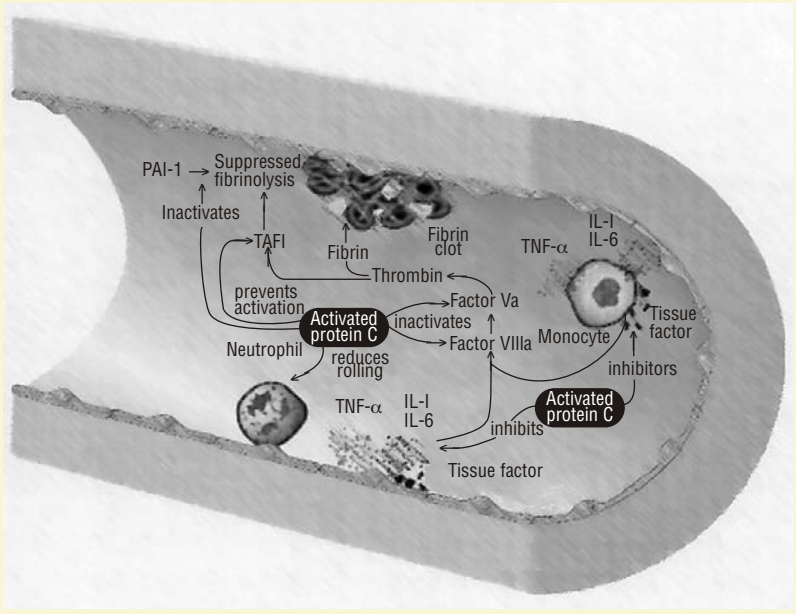

Figure 1 Proposed mechanism of action of activated protein C. The cascade of events that lead to the prothrombotic, proinflammatory, and antifibrinolytic state in sepsis has multiple routes. Activated protein C has desirable effects at various points in this cascade. The anti-inflammatory effect is exerted through the ability of activated protein C to inhibit the production of inflammatory cytokines by monocytes and limit the adhesion and rolling of neutrophils and monocytes. The protein also inactivates various components of the coagulation cascade, namely factors Va and VIIIa, that normally lead to the formation of thrombin and eventual development of a fibrin clot. Additionally, by reducing the production of thrombin and the actions of plasminogen activator inhibitor (PAI-1), activated protein C enhances the fibrinolytic system, allowing more rapid dissolution of fibrin clots.

Abbreviations: IL, interleukin; TAFI, thrombin-activatable fibrinolysis inhibitor; TNF-α, tumor necrosis factor-α.

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by degrading fibrin and fibrinogen. Tissue plasminogen activator is inhibited by the enzyme plasminogen activator inhibitor-1. Activated protein C limits the activity of plasminogen activator inhibitor-1, thus increasing fibrinolysis and promoting the degradation of microthrombi. Activated protein C also exerts an indirect profibrinolytic effect by inhibiting the release of thrombin-activatable fibrinolysis inhibitor. Under normal circumstances, thrombin-activatable fibrinolysis inhibitor protects the clot by restricting the binding of tissue plasminogen activator and further activation of plasminogen. Again, in sepsis, decreased levels of activated protein C reduce this fibrinolytic activity.

The importance of altered coagulation in increasing morbidity and mortality in severe sepsis was indicated in the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, which involved the administration of recombinant activated protein C, drotrecogin alfa (activated), to patients with severe sepsis.[22,25] Compared with administration of a placebo, treatment with drotrecogin alfa (activated) at a dose of 24 μg/kg per hour for 96 hours, which mimics the effects of endogenous activated protein C (anti-inflammatory, antithrombotic, and profibrinolytic effects),[26] resulted in a 16% decrease in the relative risk of death, despite a 1.5% increase in risk for serious bleeding.[18,27-30] Additionally, compared with patients who received the placebo, patients who received drotrecogin alfa (activated) had less cardiovascular dysfunction, a faster resolution of cardiovascular or pulmonary dysfunction, and a slower onset of hematologic dysfunction.[25] This reduction in organ dysfunction may contribute to the overall reduction in mortality associated with this medication. For further information on this topic, several excellent articles[21,22,31,32] on sepsis and, more specifically, activated protein C and drotrecogin alfa (activated) are available.

The humoral response to sepsis leads to altered vascular permeability. Proinflammatory mediators (eg, bradykinin) and cytokines (eg, tumor necrosis factor) along with activated leukocytes increase vascular permeability, allowing fluid and protein to leak out of the intravascular space into the interstitial space. This leakage further decreases the circulating blood volume and interferes with the diffusion of oxygen to the tissues.[33]

Compared with similarly resuscitated trauma patients, patients with septic shock, despite the hyperdynamic state, have myocardial depression, which is often manifested as decreased ejection fraction, ventricular dilatation, and a flattening of the Frank–Starling curve after fluid resuscitation.

Myocardial Depression

With adequate fluid resuscitation, patients with septic shock typically have a hyperdynamic state characterized by increased cardiac output and decreased systemic vascular resistance (with or without a decrease in mean arterial pressure [MAP]).[34] Compared with similarly resuscitated trauma patients, patients with septic shock, despite the hyperdynamic state, have myocardial depression, which is often manifested as decreased ejection fraction, ventricular dilatation, and a flattening of the Frank-Starling curve after fluid resuscitation.[35,36]

Overt myocardial depression in septic shock occurs in a few patients and is characterized by reversible biventricular dilatation, decreased ejection fraction, altered myocardial compliance, and decreased contractile response to fluid resuscitation and catecholamines.[34,37,38] Although damage to myocardial cells (as indicated by increased troponin levels) may occur, myocardial depression is not primarily caused by altered coronary perfusion or global ischemia, but rather by myocardial depressant factors.[39,40] These substances, most likely tumor necrosis factor-α and IL-1β, are released as a part of the inflammatory cascade and appear to cause myocardial depression through pathological generation of nitric oxide and cyclic guanosine monophosphate along with altered signal transduction by β-adrenergic receptors.[3,34,36,41] The altered β-adrenergic signal transduction may be due to decreased levels of a cell membrane protein

necessary for β-adrenergic binding and signal transduction and subsequently impaired activation of cyclic adenosine monophosphate.[42,43]

The acute cardiovascular changes (dilatation, decreased ejection fraction, and so on) persist for up to 4 days and then, in survivors, return to normal during a period of 7 to 10 days. Paradoxically, survivors are more likely than nonsurvivors to initially have greater myocardial depression.[34] However, compared with nonsurvivors, survivors have an early improvement in ventricular function.[44,45]

Monitoring Outcomes of Therapy

Recognition of the early signs and symptoms of septic shock is pivotal in improving patients' outcomes. The diagnostic characteristics of septic shock[46,47] are summarized in Table 1. Appropriate monitoring of patients with septic shock is imperative, with specific consideration given to detecting changes in perfusion and tissue oxygenation. Basic monitoring should include pulse oximetry, electrocardiography, and invasive blood pressure monitoring. Central venous pressure monitoring or pulmonary artery catheterization, along with measurements of venous oxygen saturation (mixed [$S\bar{v}O_2$] or central venous [$ScvO_2$]), may be useful in evaluating cardiovascular status if a patient is refractory to initial volume resuscitation or if oxygenation indices will be used as the end point of resuscitation.[6,48]

Table 1 Diagnostic criteria for sepsis

Infection, documented or suspected, and some of the following:

General variables
- Fever (core temperature >38°C)
- Hypothermia (core temperature <36°C)
- Heart rate >90/min
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (>20 mL/kg over 24 hours)
- Hyperglycemia (plasma glucose >120 g/dL) in patients without diabetes

Inflammatory variables
- Leukocytosis (WBC count >12 000/μL)
- Leukopenia (WBC count <4000/μL)
- Normal WBC count with >10% immature forms

Hemodynamic variables
- Arterial hypotension (SBP <90 mm Hg, MAP <70 mm Hg or an SBP decrease >40 mm Hg in adults)
- SvO_2 >70%
- Cardiac index >3.5 L/min/m^2

Organ dysfunction variables
- Arterial hypoxemia (PaO_2/FIO_2 <300)
- Acute oliguria (UOP <0.5 mL/kg/hr)
- Creatinine increase >0.5 mg/dL
- Coagulation abnormalities (INR >1.5 or aPTT >60 seconds)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count <100 000/μL)
- Hyperbilirubinemia (plasma total bilirubin >4 g/dL)

Tissue perfusion variables
- Hyperlactatemia (>1 mmol/L)
- Decreased capillary refill or mottling

Abbreviations: aPTT, activated thromboplastin time; FIO_2, fraction of inspired oxygen; INR, international normalized ratio; SBP, systolic blood pressure; SvO_2, venous oxygen saturation; UOP, urine output; WBC, white blood cell count.

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Monitoring Tissue Oxygenation

As noted earlier, septic shock is the result of hypotension, hypoperfusion, maldistribution of blood, and the inability of cells to use oxygen. Therefore, monitoring and evaluating specific indicators of tissue hypoxia (eg, serum levels of lactate, $S\bar{v}O_2$ or $ScvO_2$, gastric intramucosal PCO_2 [$PiCO_2$]) is warranted in critically ill patients because the standard indices of hemodynamic stability (ie, blood pressure, heart rate, and urine output) may be normal despite continued tissue hypoxia. In one study,[49] 36 critically ill patients who were resuscitated to a heart rate of 50/min to 120/min and a MAP of 70 to 110 mm Hg continued to have signs of tissue hypoxia: lactate level greater than 2 mmol/L and $ScvO_2$ less than 65%. Additionally, although interventions were undertaken to improve tissue oxygenation for these patients (as indicated by achieving a goal of a lactate level <2 mmol/L and an increase in $ScvO_2$ to >65%), no changes in the blood pressure or heart rate occurred. Similar results have been observed in patients with cardiogenic shock[50] and in trauma victims.[51]

Use of standard end points (eg, MAP >60 mm Hg) may be insufficient to ensure adequate tissue perfusion. LeDoux et al[52] did a study of patients with septic shock who required vasopressor therapy to maintain MAP at 60 mm Hg or greater despite fluid resuscitation to a pulmonary artery occlusion pressure (PAOP) of 12 mm Hg or greater. These patients subsequently had their MAP increased from 65 mm Hg to 85 mm Hg with norepinephrine. Although the norepinephrine caused the cardiac index to increase, no improvement occurred in indicators of tissue perfusion (lactate level, $PiCO_2$). For example, the patients' mean (SD) lactate level was 3.1 (0.9) mmol/L at a MAP of 65 mm Hg and 3.0 (0.9) mmol/L at

a MAP of 85 mm Hg. Therefore, standard hemodynamic indices may not be sensitive indicators of changes in tissue oxygenation, and the use of global (Do_2 and oxygen consumption [$\dot{V}o_2$], serum lactate levels, and $S\bar{v}o_2$ or $Scvo_2$) and regional indices (gastric tonometry or sublingual capnometry) may be necessary (Table 2). A discussion of the basic principles underlying the monitoring of each of these indices and evidence-based examples of the usefulness of the measurements are presented in the following sections.

Global Oxygenation

Several global indicators of tissue oxygenation are used in critical care. The calculation and/or direct measurement of Do_2 and $\dot{V}o_2$, $S\bar{v}o_2$, and serum levels of lactate may provide insight into overall oxygenation status.

Oxygen Delivery and Consumption

Do_2 is the amount of oxygen delivered to the tissues each minute and is described by the following equation:

$$Do_2 = Cao_2 \times CO \times 10,$$

where Cao_2 is arterial oxygen content (the amount of oxygen carried in 100 mL of arterial blood) and CO is cardiac output. Cao_2 is calculated by multiplying the oxygen saturation of arterial blood (Sao_2) by the hemoglobin (Hgb) concentration and a constant (1.36) that describes the amount of oxygen that 1 g of hemoglobin is capable of transporting.

$$Cao_2 = Sao_2 \times Hgb \times 1.36$$

For example, $Cao_2 = (0.99 \times 15\ g/dL \times 1.36)$ = approximately 20 g/dL.

In order to calculate Do_2, the Cao_2 is multiplied by the cardiac output by 10. A normal Do_2 is approximately 1000 mL/min. If the cardiac index (calculated as cardiac output in liters per minute divided by body surface area in meters squared) is used rather than the cardiac output, a normal indexed Do_2 (Do_2I) is approximately 500 mL/ (min · m^2).

Evaluation of the factors that affect Do_2 provides important infor-

Table 2 Tissue oxygenation indices

Index/Parameter	Value
Oxygen delivery (Do_2)	Normal ~1000 mL/min Indexed to cardiac index (Do_2I) ~500 mL/(min · m^2)
Oxygen consumption ($\dot{V}o_2$)	Normal ~250 mL/min Indexed to cardiac index ($\dot{V}o_2I$) ~125 mL/(min · m^2)
Oxygen extraction ratio (OER)	Normal 0.25 Comment: If Do_2 is decreased, $\dot{V}o_2$ is maintained by increased oxygen extraction
Cardiac index–OER ratio	Normal 12 (cardiac index of 3 and an OER of 0.25) Plot on graph to evaluate patients' cardiovascular function A ratio <10 indicates inadequate cardiovascular response necessitating increased oxygen extraction Comment: In septic shock, a ratio <10 may indicate myocardial depression or inadequate fluid resuscitation
Mixed venous oxygen saturation ($S\bar{v}o_2$)	Normal ~65%-75% A value <50% indicates severe oxygen deficit
Central venous oxygen saturation ($Scvo_2$)	Normal ~70% Comment: $Scvo_2$ > right atrial oxygen saturation > $S\bar{v}o_2$
Lactate concentration	Normal <2 mmol/L Monitor trends; failure of lactate levels to decrease with treatment has poor prognostic implications Rule out other causes of increased lactate levels (epinephrine, washout effect)
Gastric mucosal Pco_2 ($Pico_2$)	Normal $Pico_2$-$Paco_2$ gap 2-10 mm Hg A gap >20 mm Hg is associated with increased complications and mortality Goal: Maintain $Pico_2$-$Paco_2$ gap <25 mm Hg to avoid anaerobic metabolism Comment: Further research into the end points of resuscitation for septic shock is needed
Partial pressure of sublingual carbon dioxide ($Pslco_2$)	Normal $Pslco_2$-$Paco_2$ gap <10 mm Hg Gradient >25 mm Hg indicates onset of anaerobic metabolism Comment: Further research into the end points of resuscitation for septic shock is needed

mation for guiding therapy to optimize tissue oxygenation. For example, if Do_2 is decreased, the initial assessment should include an evaluation of the 3 primary factors that affect it: cardiac output, Sao_2, and hemoglobin concentration. However, a normal Do_2 cannot be taken as an indicator of normal values for these 3 factors. For example, if the hemoglobin concentration or Sao_2 decreases, the Do_2 will remain the same if the cardiac output can increase. In a patient with cardiac disease, an increase in cardiac output may not be possible, and decreased Do_2 will occur unless interventions are implemented to improve the Sao_2 or hemoglobin concentration. Thus, the isolated assessment of any single factor that affects Do_2 may lead to an erroneous evaluation of a patient's Do_2 status.

$\dot{V}o_2$, which represents all oxidative reactions in the body, can be estimated by using the Fick equation, which is the product of cardiac output and the arteriovenous oxygen content difference (arterial oxygen saturation-venous oxygen saturation):

$$\dot{V}o_2 = [CO \times 1.36 \times Hgb \times (Sao_2 - Svo_2)] \times 10$$

Direct measurement of $\dot{V}o_2$ at the bedside can also be accomplished by using indirect calorimetry with a metabolic cart. However, this measurement is cumbersome and requires that the patient's condition be relatively stable.

Despite these limitations, Do_2 and $\dot{V}o_2$ measurements have been used to guide therapy aimed at optimizing patients' hemodynamic status and creating normal or supranormal Do_2. The rationale for supranormal Do_2 was based on the fact that a theoretical oxygen debt develops when an imbalance exists between oxygen supply and consumption. The goal of normal or supranormal Do_2 (cardiac index $> 4.5\ L \cdot min^{-1} \cdot m^{-2}$, $Do_2I > 600\ mL/(min \cdot m^2)$, $\dot{V}o_2 > 170\ mL/(min \cdot m^2)$) was to reverse the oxygen debt.[53,54] Initial studies suggested that "supranormalization" of Do_2 improved survival in high-risk surgical patients.[55,56] However, controlled clinical trials did not reveal any benefit, and attempts to achieve a supranormal state may cause adverse outcomes in some patients.[54,57-59] The current interpretation of these earlier results is that the relationship between the achievement of supranormal Do_2 and survival may simply reflect a patient's physiological reserve rather than be a direct beneficial effect of the increased Do_2.

Recent evidence[6,60] suggests that although achieving normal Do_2 is important, the timing of the initiation of goal-directed therapy may be the critical factor. In a study[6] of 263 patients who had severe sepsis or septic shock when they arrived at the emergency department, a random sample of 133 received standard care (volume resuscitation, blood transfusion, and vasoactive medications adjusted to achieve a central venous pressure of 8-12 mm Hg, MAP ≥ 65 mm Hg, and urine output ≥ 0.5 mL/kg per hour). The other 130 patients received 6 hours of early goal-directed therapy, that is, a combination of standard care and additional resuscitation to achieve an $Scvo_2$ greater than 70% as an indicator of adequate tissue oxygenation. In-hospital mortality was 30.5% for the group given early goal-directed therapy and 46.5% for the group given standard therapy, an absolute reduction in in-hospital mortality of 16% for the patients given goal-directed therapy. These results are in contrast to the lack of changes in outcomes or the increases in morbidity and mortality that occurred in other studies[54,57] when optimization strategies were used in patients who already had organ dysfunction.

Oxygen Extraction Ratio Rather than a simple evaluation of Do_2 and $\dot{V}o_2$, a more sensitive indicator of the adequacy of the balance between Do_2 and oxygen demand, the oxygen extraction ratio (OER), can be used. The OER is described by the following equation, in which $C\bar{v}o_2$ indicates mixed venous oxygen content:

$$OER = (Cao_2 - C\bar{v}o_2)/Cao_2 = [(Hgb \times 1.36 \times Sao_2) - (Hgb \times 1.36 \times S\bar{v}o_2)]/(Hgb \times 1.36 \times Sao_2) = (Sao_2 - S\bar{v}o_2)/Sao_2$$

The last equation is particularly useful because the Sao_2 and $S\bar{v}o_2$ values can be readily measured at the bedside. A normal OER is approximately 0.25 (ie, 25% of the oxygen delivered is consumed). Under normal conditions, as the Do_2 varies, the $\dot{V}o_2$ remains stable because of variations in oxygen extraction, that is, the $\dot{V}o_2$ is independent of the Do_2. However, if the Do_2 decreases below a critical level, the $\dot{V}o_2$ becomes dependent on the amount of oxygen delivered.[61] Although oxygen extraction increases in an attempt to maintain adequate tissue oxygenation, a point is reached at which no further oxygen can be extracted and anaerobic metabolism ensues. No absolute value exists at which this critical level is reached, but in anesthetized patients, the critical point can occur at a Do_2I of $330\ mL/(min \cdot m^2)$ (8 mL/min per kilogram).[62,63] Conversely, in 9 patients with septic shock and 8

patients without septic shock, differences in the critical level for Do_2I (3.8 vs 4.5 mL/min per kilogram) were not significant,[59] although the absolute value is considerably lower than that observed in the anesthetized patients. Additionally, an overall whole-body OER of 0.60 to 0.75 is generally considered the critical point for the onset of anaerobic metabolism.[59,64]

The OER may be prognostic. In a study[65] of critically ill surgical patients, the OER was increased in patients who had an increased length of stay in the intensive care unit. OERs were 0.36 for patients whose stay was greater than 5 days and 0.31 for those whose stay was fewer than 5 days. Similar results occurred in patients with severe sepsis or septic shock.[66] The increased OER reflects compensation for decreased Do_2.

Ratio of Cardiac Index to OER Evaluation of the OER relative to the cardiac index may provide additional information in determining whether a patient's cardiac index is sufficient to meet the oxygen demands of the body.[67,68] If the cardiac response to increased oxygen demands is insufficient, the body will respond by extracting more oxygen (ie, an increased OER with a subsequent decrease in the Svo_2). The relationship between the cardiac index and the OER can be assessed to provide insight into the patient's cardiac function, particularly if the patient is anemic. The normal cardiac index–OER ratio is 12 (for a cardiac index of 3.0 and an OER of 0.25); a value of 10 reflects the lower limits of normal (eg, a cardiac index of 2.5 and a normal OER of 0.25). Normally an increase in $\dot{V}o_2$ is responded to by an increase in cardiac output, OER, or both. However, if cardiac function is impaired such that the cardiac output does not increase, the only response to the increased oxygen requirements is an increase in oxygen extraction. This altered response will lead to a decrease in the cardiac index–OER ratio. For example, if the cardiac index is 2.0 and the OER is 0.30, the cardiac index–OER ratio is 6.7.[67] Conversely, in patients with sepsis with an increased cardiac index and a normal or low OER, the ratio will be increased.[68] For example, if the cardiac index is 4.5 and the OER is 0.22, the ratio is 20.

Yalavatti et al[69] studied 60 patients with septic shock who did or did not have cardiac disease who were also anemic (hemoglobin ≤ 10 g/dL). In the patients with septic shock and underlying heart failure, the cardiac index–OER ratio was less than 10 in a majority of patients, indicating a greater increase in OER (mean 0.35, SD 0.09) than in cardiac index (mean 3.0, SD 1.0) to meet the oxygen demands. In contrast, in patients without cardiac disease the cardiac index–OER was greater than 10 in 16 of 20 patients (cardiac index: mean 3.9, SD 0.9; OER: mean 0.29, SD 0.08). In the remaining 4 patients in this latter group, 3 were hypovolemic and 1 had sepsis-induced myocardial depression. Of note, the PAOP did not differ significantly between patients with and without hypovolemia in the group without cardiac disease. Thus, the cardiac index–OER ratio was useful in identifying a relative intolerance to anemia and in unmasking myocardial depression or hypovolemia.[69]

In patients with a cardiac index–OER ratio less than 10 and normal cardiac function, further evaluation of volume status is warranted. An algorithm for interpretation of the cardiac index–OER ratio is provided in Figure 2.

Lactate Levels Under aerobic conditions, the complete oxidation of 1 molecule of glucose via the tricarboxylic acid cycle produces 38 molecules of ATP (Figure 3). An intermediary mole-

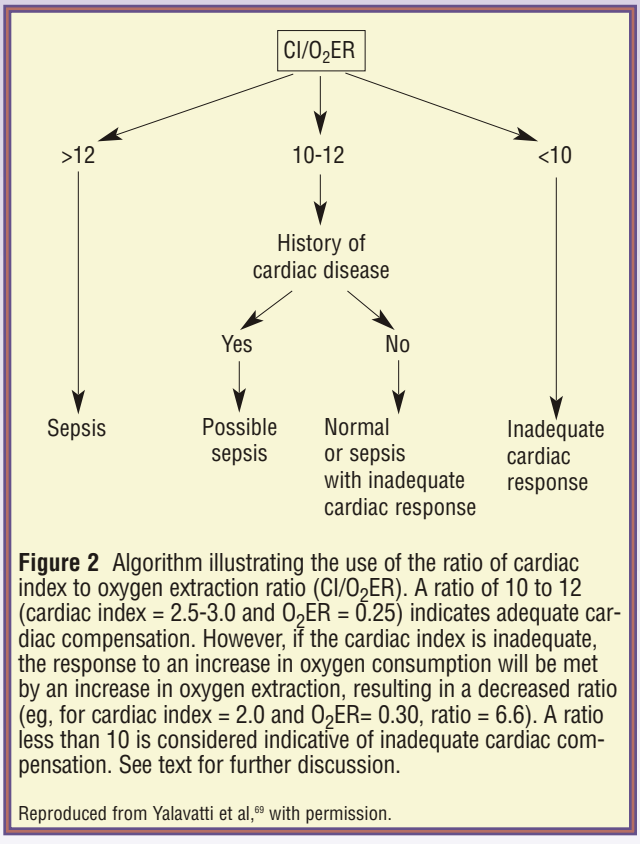

Figure 2 Algorithm illustrating the use of the ratio of cardiac index to oxygen extraction ratio (CI/O_2ER). A ratio of 10 to 12 (cardiac index = 2.5-3.0 and O_2ER = 0.25) indicates adequate cardiac compensation. However, if the cardiac index is inadequate, the response to an increase in oxygen consumption will be met by an increase in oxygen extraction, resulting in a decreased ratio (eg, for cardiac index = 2.0 and O_2ER= 0.30, ratio = 6.6). A ratio less than 10 is considered indicative of inadequate cardiac compensation. See text for further discussion.

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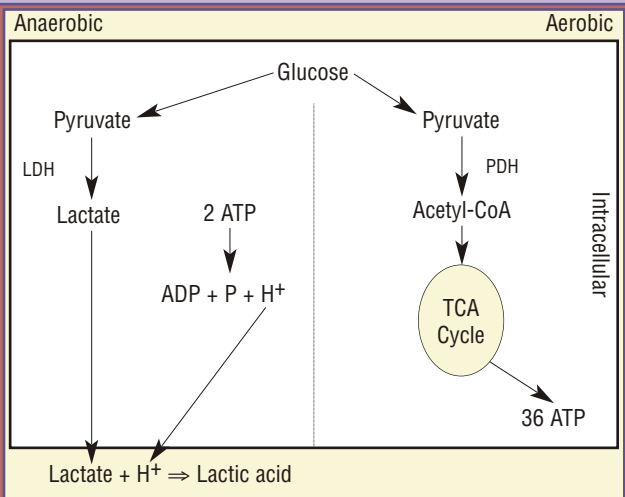

Figure 3 Lactate production. Under aerobic conditions, glucose is metabolized to pyruvate. The pyruvate is converted to acetyl coenzyme A (Acetyl-CoA) by pyruvate dehydrogenase (PDH). The acetyl-CoA enters the tricarboxylic acid (TCA) cycle and undergoes oxidative phosphorylation. Oxygen is key to the final steps in this process. Under anaerobic conditions, pyruvate cannot enter the TCA cycle and is converted to lactate by lactic dehydrogenase (LDH). The breakdown of pyruvate leads to the formation of 2 molecules of adenosine triphosphate (ATP). The ATP molecules are subsequently broken down to adenosine diphosphate (ADP) and phosphorus (P), resulting in the release of hydrogen ions (H^+). The hydrogen ions bind with the lactate to form lactic acid.

cule in this process is pyruvate, which is transported into the mitochondria and subsequently converted to acetyl coenzyme A (the substance that enters the tricarboxylic acid cycle). Oxygen plays a key role in the final step of this process. Under anaerobic conditions, the absence of oxygen inhibits the oxidative process and the tricarboxylic acid cycle stops. As a result, pyruvate, which can no longer enter the mitochondria, is instead converted to lactate. Thus, lactate is an end product of anaerobic metabolism, and an increased level (>2 mmol/L) is considered a surrogate indicator of tissue hypoxia.

Increased levels of lactate (>4 mmol/L), particularly levels that do not decrease with treatment, are prognostic of organ failure and poor outcomes in patients with septic shock.[70-72] However, the use of lactate levels as a bedside indicator of tissue hypoxia is complicated in patients with septic shock.[73] First, a vascular bed (eg, the gut) may be hypoxic without an increase in the serum concentration of lactate; thus, a normal serum lactate level does not necessarily indicate that a patient does not have regional tissue hypoxia.[74] Additionally, in patients with septic shock, increased lactate levels have been observed under conditions in which oxygen delivery was adequate, or, conversely, when the oxygen delivery was increased, the lactate levels did not decrease.[75] One factor that may contribute to this effect is increased levels of endogenous epinephrine or the administration of exogenous epinephrine, which increases lactate production in well-oxygenated tissues.[76,77]

General recommendations for the use of lactate are to follow trends rather than a single measurement and to first rule out causes of tissue hypoxia before assuming that other factors are contributing to the increased lactate levels. Gastric tonometry and, more recently, sublingual capnography (see following) also show the delay between the onset of tissue hypoxia and increased levels of serum lactate and conversely the delay between the resolution of hypoxia and a decrease in lactate. Therefore, hypoxia may still occur when patients with septic shock have a normal lactate level.

Mixed Venous Oxygen Saturation

$S\bar{v}O_2$ reflects the venous effluent from all vascular beds. The $S\bar{v}O_2$, which is obtained from blood aspirated from the pulmonary artery, and can be directly measured by using CO-oximetry, is described by the following equation:

$$S\bar{v}O_2 = SaO_2 - [(\dot{V}O_2/CO) \times 1.36 \times Hgb] \times 10$$

Under conditions of normal oxygenation, stable $\dot{V}O_2$, and normal hemoglobin levels, $S\bar{v}O_2$ has been used as a surrogate indicator of cardiac output. However, $S\bar{v}O_2$ is affected by factors that increase or decrease $\dot{V}O_2$ and DO_2. Thus, its interpretation must be viewed in light of other factors that can affect $\dot{V}O_2$ (Table 3) and cause an imbalance between oxygen supply and demand.

A low $S\bar{v}O_2$ reflects decreased DO_2 and/or increased $\dot{V}O_2$ at the tissue level. The 3 primary factors that affect DO_2 (cardiac output, hemoglobin

Table 3 Factors that affect oxygen consumption

Factors that cause increases	Factors that cause decreases
Fever	Decreased body temperature
Pain	Analgesia
Anxiety/agitation	Sedation
Shivering	Anesthesia
Nursing care (bathing, turning)	
Sepsis/septic shock	

level, and Sa_{O_2}) should be assessed. Additionally, clinical factors that increase the $\dot{V}o_2$ should be considered.

In septic shock the challenge is to interpret a high $S\bar{v}_{O_2}$ (>70%), which may indicate increased D_{O_2} in a hyperdynamic system or conversely the inability of the tissues to extract oxygen (cytopathic hypoxia). Additionally, a normal $S\bar{v}_{O_2}$ does not rule out regional tissue hypoxia, particularly in vascular beds that have a limited contribution to the total $S\bar{v}_{O_2}$ (eg, gastrointestinal tract and brain).[78] In these instances, the use of more sensitive indicators of tissue oxygenation (ie, lactate levels, Pi_{CO_2}, or sublingual capnography) may be necessary.

Central Venous Oxygen Saturation

An alternative to $S\bar{v}_{O_2}$ is Scv_{O_2}, which is measured by using an oximetric catheter located in the superior vena cava. Depending on the clinical condition, the Scv_{O_2} generally matches the $S\bar{v}_{O_2}$. Generally, the Scv_{O_2} is an overestimation of the $S\bar{v}_{O_2}$ by approximately 1% to 3%, but wide individual variability with differences as high as 23% can occur; thus, the values are not interchangeable.[79,80]

Clinically, the Scv_{O_2} can be used to track changes, and a low Scv_{O_2} (< 60%), which indicates an even lower $S\bar{v}_{O_2}$, can be used as an indicator of impaired D_{O_2}. The Scv_{O_2} may also be a marker of tissue hypoxia that remains unresolved despite normalization of vital signs. In a study by Rady et al,[49] 50% of critically ill patients without sepsis who were resuscitated to normal vital signs (MAP 70-110 mm Hg) continued to have increased lactate levels (> 2 mmol/L) and decreased Scv_{O_2} levels (< 65%). More recently, Scv_{O_2} greater than 70% rather than routine measurements (heart rate, MAP, urine output) was used as a goal for resuscitation for patients with severe sepsis and septic shock.[6,80] As previously discussed, patients who received early goal-directed therapy had a significant reduction in mortality compared with those who received standard care. The investigators[6,80] in this study advocate use of Scv_{O_2} because placement of a central venous catheter (standard or oximetric) can be accomplished early in therapy, whereas placement of a pulmonary artery catheter for $S\bar{v}_{O_2}$ monitoring may be delayed.

Regional Oxygenation

Although global oxygenation indices provide useful information about the overall status of the body, these indices may be normal in patients who have hypoperfusion and hypoxia of an isolated vascular bed. The gastrointestinal tract is one of the most sensitive vascular beds to hypoperfusion.[81,82] Because decreased splanchnic perfusion precedes the overt signs and symptoms of shock, such as hypotension and increased lactate levels, the gut has been referred to as the "canary of the body."[83]

Gastric Tonometry Gastric tonometry was originally designed to measure the intramucosal pH (pHi).[84] The pHi was shown to be a better predictor of organ dysfunction and mortality than oxygen-derived variables (D_{O_2} and $\dot{V}o_2$).[85] Additionally, a pHi greater than 7.35 (normal range 7.35-7.45) is predictive of survival, particularly when used in conjunction with serum lactate levels.[71,86] Use of pHi as a goal for therapy improved outcomes in patients who had severe sepsis without end-organ damage.[87] However, in a more recent study,[88] in which pHi was also used as an end point of resuscitation, no improvement in outcomes was detected for any group of patients. In this study,[88] ICU patients received standard resuscitation (crystalloids/colloids to increase the PAOP to 15 mm Hg and then were given vasoactive medications in addition to insulin therapy, blood transfusions, and mechanical ventilation) to achieve the following targets: MAP greater than 70 mm Hg, systolic blood pressure greater than 90 mm Hg, urine output greater than 0.5 mL/kg per minute, hemoglobin concentration more than 8 g/dL, Sa_{O_2} more than 94%, and correction of uncompensated respiratory acidosis. If the pHi remained less than 7.35 one hour after these targets were achieved, or after maximal therapy to achieve the targets, patients in the intervention group were given additional colloid solution and then a dobutamine infusion (5-10 µg/kg per minute) adjusted to achieve a pHi greater than 7.35. Patients in the control group were managed according to the specified targets without additional interventions to achieve the target pHi. The results indicated that the 2 groups had no significant differences in ICU length of stay; organ dysfunction; or ICU, hospital, or 30-day mortality.

A limitation of gastric tonometry is that the pHi is calculated, a step that requires an assumption that the levels of bicarbonate in the gastric mucosa are equivalent to the levels in arterial blood. This assumption is not always correct. This limitation and the difficult process required to obtain a gastric pH measurement have restricted the widespread use of this technique.[84]

Use of the difference between the $Pico_2$ and the $Paco_2$, known as the $Pico_2$-$Paco_2$ gap, is now recommended.[89] The $Pico_2$ is obtained by aspirating gas samples from an air-filled balloon on the end of a gastric tube. Currently, no standardized normal value exists for the $Pico_2$-$Paco_2$ gap; recommended values range from 2 to 10 mm Hg (ie, $Pico_2$ = 50 mm Hg and $Paco_2$ = 40 mm Hg).[90] Although a $Pico_2$-$Paco_2$ gap greater than 25 to 35 mm Hg indicates the onset of anaerobic metabolism, a gap of 40 mm Hg is neither a sensitive nor a specific indicator of severe splanchnic hypoperfusion.[91] Of clinical usefulness, an increase in the gap greater than 20 mm Hg was associated with increased complications and mortality,[90,92] and in trauma patients, a value greater than 18 mm Hg was predictive of multiorgan dysfunction syndrome and death.[93] The current recommendation is to maintain a gap less than 25 mm Hg in order to avoid anaerobic metabolism,[90,94] although no clinical trials have indicated the usefulness of the measurement as an end point of resuscitation.

Although gastric tonometry provides potentially useful clinical information, its use at the bedside is limited. This semi-invasive system requires up to 90 minutes for equilibration, and for accurate measurements, the patient must have feedings withheld for a minimum of 1 hour before measurements are obtained or have the gastric contents removed by aspiration immediately before the measurement.[95,96] Recent research[97] suggests that the $Pico_2$ stabilizes after 24 to 48 hours of enteral nutrition, and stopping the nutrition may not be necessary after this point. Because of these limitations, other areas along the gastrointestinal tract (esophagus and sublingual mucosa) have been considered for monitoring.

Sublingual Capnometry New technology is now available for the intermittent measurement of the partial pressure of sublingual carbon dioxide ($Pslco_2$), which is used as a surrogate marker of gastrointestinal perfusion. $Pslco_2$ is measured by using a sublingual device (Figure 4) that consists of a disposable sensor covered with a membrane permeable to carbon dioxide. The sensor contains a fluorescent dye that emits a light in direct proportion to the amount of carbon dioxide present. Fiberoptic technology is used to detect the changes in the fluorescence, and these light signals are converted into numeric values. The probe is placed under the tongue in contact with the sublingual mucosa, and a measurement is available in approximately 2 to 4 minutes.

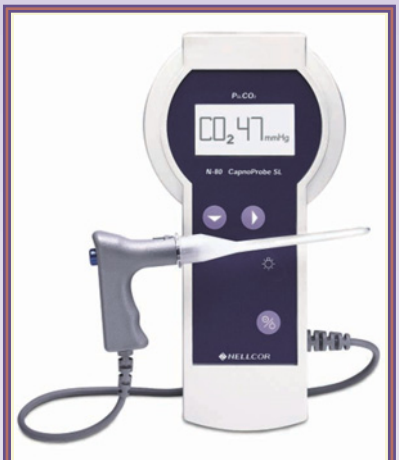

Figure 4 Sublingual capnography probe. The CapnoProbe system (Nellcor, Pleasanton, Calif) uses fiber-optic technology to measure the partial pressure of carbon dioxide in the sublingual tissue ($Pslco_2$). The carbon dioxide diffuses across the sensor's semipermeable membrane into a fluorescent dye solution. The dye emits light in proportion to the amount of carbon dioxide present. The amount of light emitted is converted into a numerical value.

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In animal models of both hemorrhagic shock and septic shock, the $Pslco_2$ was comparable to measurements obtained with gastric tonometry.[98,99] Additionally changes in $Pslco_2$ closely follow changes in blood flow to the gastrointestinal tract.[99,100] In models of hemorrhagic shock and septic shock, $Pslco_2$ increased more rapidly than did lactate levels, which remained unchanged for 1 to 6 hours.[98,101] After replacement of blood in an animal model of hemorrhage, the $Pslco_2$ value rapidly returned to baseline in contrast to the lactate level, which did not begin to decrease for 1 hour.[98]

In the original study[78,102] introducing this technology, a $Pslco_2$ greater than 70 mm Hg was 100% predictive of circulatory shock, whereas a $Pslco_2$ less than 70 mm Hg was predictive of survival. Although the absolute $Pslco_2$ value may have prognostic implications, interpretation of $Pslco_2$ is difficult because of the direct relationship between $Paco_2$ and $Pslco_2$.[103] For example, if a patient is hyperventilating (ie, decreased $Paco_2$) the $Pslco_2$ will also decrease. Conversely, if the $Paco_2$ is increased, the $Pslco_2$ will also increase, in a parallel fashion; thus, the gap between $Pslco_2$ and $Paco_2$ will remain unchanged (Figure 5).

The $Pslco_2$-$Paco_2$ gradient may be a useful indicator of hypoperfusion. When the oxygen supply to the tissues begins to decrease, the tissue Pco_2 increases slightly relative to the $Paco_2$. However, when perfusion decreases below a critical level, a marked increase in tissue Pco_2 occurs,

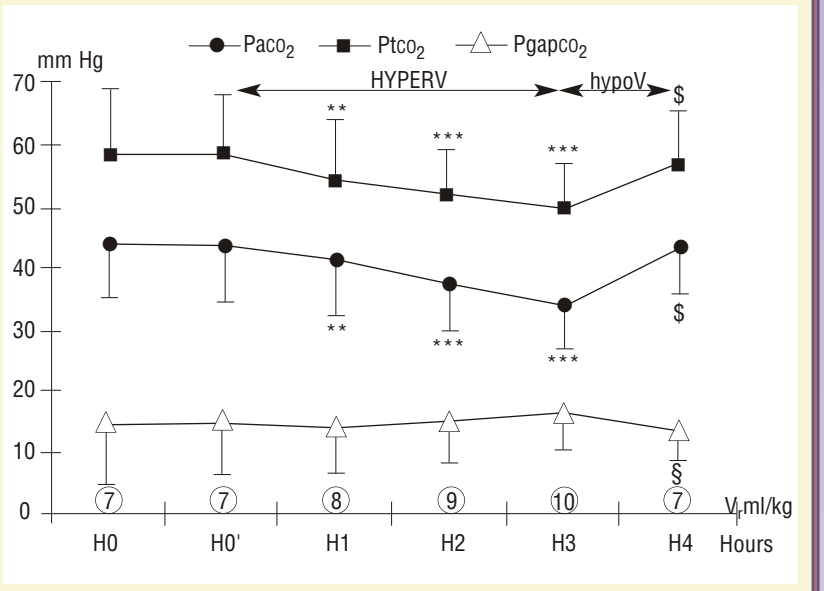

Figure 5 Changes in $Paco_2$, gastric intramucosal carbon dioxide tension ($Ptco_2$), and gastric-arterial carbon dioxide tension difference ($P_{gap}co_2$) induced by hourly modifications of alveolar ventilation level. Progressive increase in tidal volume (HYPER = hyperventilation). Note the significant decrease in $Paco_2$ and the concurrent decrease in $Ptco_2$, such that the gap ($P_{gap}co_2$) remains essentially unchanged. During a decrease in tidal volume (hypoV = hypoventilation) both the $Paco_2$ and the $Ptco_2$ increase in a parallel fashion.

Reprinted from Bernardin et al,[104] with permission.

which reflects the generation of carbon dioxide from bicarbonate as the bicarbonate buffers hydrogen ions produced by anaerobic metabolism.[104-107] The increased tissue Pco_2 relative to the $Paco_2$ can be detected as an increase in the $Pslco_2$-$Paco_2$ gradient (Figure 6).

A normal $Pslco_2$-$Paco_2$ gradient is less than 10 mm Hg (eg, $Pslco_2$ = 50 mm Hg and $Paco_2$ = 40 mm Hg). In a study[78] of critically ill patients (a majority with severe sepsis), the $Pslco_2$-$Paco_2$ gradient was significantly different between survivors (mean 9.2 mm Hg, SD 5.0 mm Hg) and nonsurvivors (mean 17.8 mm Hg, SD 11.5 mm Hg). Similar results occurred in patients with circulatory shock (defined as the need for vasopressor agents to maintain the MAP >60 mm Hg, urine output < 0.5 mL/kg per hour, and an increased lactate level).[101] Although the $Pslco_2$-$Paco_2$ gradient did not differ between survivors and nonsurvivors at the time of admission, at 24 hours after admission the survivors had a significantly lower gradient (mean 14 mm Hg, SD 3 mm Hg) than the nonsurvivors did (mean 29 mm Hg, SD 4 mm Hg).[101]

In patients with septic shock, the results regarding the relationship between the sublingual indices and other indicators of tissue hypoxia (eg, lactate levels) have been mixed, with changes in $Pslco_2$ occurring much earlier than changes in lactate concentrations.[102,108] Current evidence suggests that the clinical usefulness of $Pslco_2$ monitoring is the rapid detection of changes in gastric perfusion as an indicator of circulatory shock. The prognostic value of $Pslco_2$ and its use as an end point of resuscitation remain to be shown, particularly in patients with septic shock.

In summary, the use of standard hemodynamic indices (heart rate, blood pressure, MAP) may be insufficient in identifying patients with continued tissue hypoxia, and monitoring of global or regional oxygena-

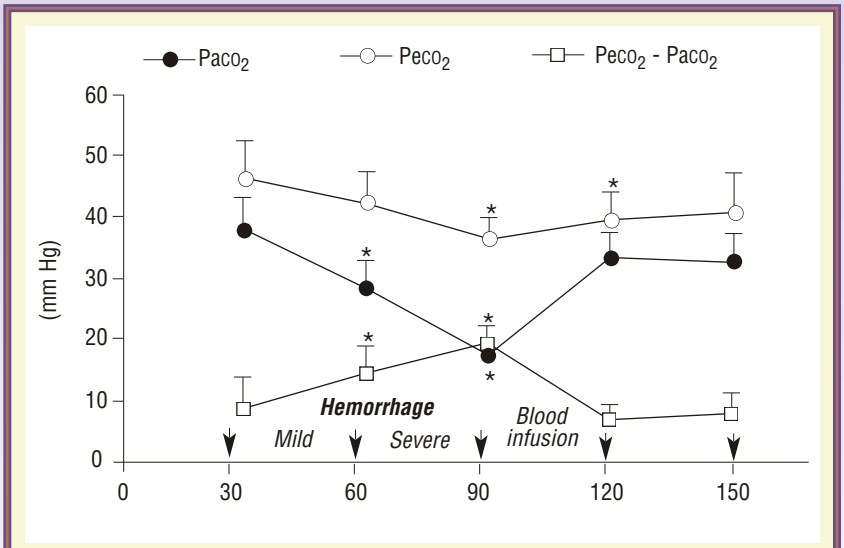

Figure 6 Changes in $Paco_2$, partial esophageal carbon dioxide tension ($Peco_2$), and esophageal-arterial gap in 7 anesthetized, spontaneously breathing rats subjected to mild and severe hemorrhagic hypotension followed by blood reinfusion ($P < .05$ with the baseline as control).

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tion indices may be needed. Furthermore, the use of indices reflective of the balance between oxygen supply and demand (OER, cardiac index–OER ratio, $S\bar{v}O_2$, $ScvO_2$) may be more beneficial than simply optimizing DO_2. The use of regional indices (sublingual capnography) may provide an earlier warning of inadequate perfusion than use of more global measures (eg, lactate levels) does, although the beneficial effects of the use of regional indices as end points of resuscitation remain to be shown. Interventions to attain supranormal oxygenation levels are no longer recommended. However, early goal-directed therapy initiated before the onset of organ dysfunction may decrease morbidity and mortality in patients with sepsis and septic shock.

Hemodynamic support for patients with septic shock can be classified into 3 main categories: fluid resuscitation, vasopressor therapy, and inotropic therapy.

Treatment

Guidelines from 3 major consensus panels are used to direct the hemodynamic support of adult patients with septic shock.[3,4,7,109] On the basis of these guidelines, the treatment of septic shock can be viewed as having 3 main goals: maintain an adequate MAP, identify and eliminate the cause of infection, and interrupt the pathogenic process leading to septic shock. While these goals are being addressed, adequate organ system perfusion and function must be maintained, on the basis of cardiovascular monitoring.

In this article, we focus on the first priority: maintenance of an adequate MAP. Hemodynamic support for patients with septic shock can be classified into 3 main categories: fluid resuscitation, vasopressor therapy, and inotropic therapy.

Fluid Resuscitation

Fluid resuscitation is the initial therapy of choice for the treatment of hypotension in septic shock, because most patients with sepsis have inadequate preload due to peripheral vasodilatation. Although exact end points of resuscitation have not been specified, a general goal is a central venous pressure of 8 to 12 mm Hg, a PAOP of 12 to 15 mm Hg, or fluid resuscitation to a point at which additional infusions of fluid are not accompanied by an increase in cardiac output. Additionally, other indicators of adequate tissue perfusion (eg, urine output >0.5 mL/kg per hour, a decrease in the serum level of lactate, and improved mental status) should be assessed.

The issue of crystalloids (including whether to use isotonic sodium chloride solution or lactated Ringer's solution) versus colloids as the resuscitation fluid of choice remains an issue of great debate. This unresolved debate has now shifted to the effects of these various fluids on endothelial inflammation.

Crystalloids Crystalloid solutions include isotonic sodium chloride solution and lactated Ringer's solution. After administration of 1 L of crystalloid solution, approximately 25% of the solution remains in the intravascular space. During the initial 24-hour resuscitation of a patient with septic shock, it is estimated that 10 to 12 L of crystalloids may be infused.[3] Although large-volume fluid resuscitation results in significant tissue edema, no evidence indicates that the edema is associated with impaired tissue perfusion or worse outcomes.[110] However, careful monitoring for pulmonary edema is required.

Currently, the debate is whether isotonic sodium chloride solution (sodium 154 mmol/L, chloride 154 mmol/L) or a balanced salt solution, such as lactated Ringer's solution (sodium 130 mmol/L, chloride 109 mmol/L, lactate 28 mmol/L, potassium 4 mmol/L, calcium 1.5 mmol/L [3 mEq/L]) should be used. Use of a balanced salt solution may reduce the risk of hyperchloremic metabolic acidosis, which can occur with resuscitation with large volumes of isotonic sodium chloride solution, although the clinical effects of the acidosis remain under debate.[111,112]

Colloids Two colloid solutions, hydoxyethyl starch (hetastarch) and albumin, are primarily used for volume resuscitation. Except in cases such as sepsis in which vascular permeability is altered, 50% to 100% of the infused colloid solution remains in the intravascular space. For example, a 1-L infusion of 5% albumin (12.5 g albumin in 250 mL isotonic sodium chloride solution) increases the intravascular volume by 500 to 1000 mL. In contrast, infusion of 100 mL of a 25% solution of albumin requires mobilization of fluid from the extravascular space to cause intravascular volume expansion; a

single 100-mL aliquot of albumin causes a maximum intravascular volume increase of 400 to 500 mL 1 hour after infusion.[3] A smaller intravascular increase may occur if vascular permeability is altered, a situation that allows some of the colloidal solution to leak out of the intravascular space. Thus, for initial fluid resuscitation, 5% rather than 25% albumin is recommended.[3] A 1-L infusion of 6% hetastarch expands the intravascular volume in a manner similar to 5% albumin.

The expansion of the intravascular space beyond the volume infused reflects the effect of the increased colloidal osmotic pressure, which draws fluid from the interstitium and intracellular space into the intravascular space. In instances in which vascular permeability is altered (septic shock), the colloid solution may leak into the interstitium, and the resultant increase in interstitial colloid osmotic pressure may expand the extracellular volume by drawing fluid out of the cells.[113]

Hydroxyethyl starch or 6% hetastarch in isotonic sodium chloride solution (Hespan 6%) is a synthetic colloid. Another 6% solution of hetastarch, Hextend, has the colloid in a buffered salt solution with lactate. Compared with Hextend and lactated Ringer's solution, Hespan can alter fibrin clot formation and the lysis of fibrinogen, changes that decrease coagulation.[114] However, altered coagulation has also been observed with Hextend.[115] All patients receiving a hetastarch solution should be monitored for indications of altered coagulation.

Great debate surrounds the administration of albumin; the results of meta-analyses[116-118] suggest both increased and decreased risk of mortality. The current consensus is that administration of albumin has no effect on mortality and may be associated with decreased length of stay and a reduction in complications (respiratory dysfunction, pulmonary edema).[116,119,120]

Blood Transfusions In patients with septic shock, anemia may develop as a result of fluid resuscitation, inadequate secretion of erythropoietin in response to a decreased hematocrit, and nosocomial anemia due to phlebotomy for laboratory studies.[121] Blood transfusions may be part of a therapeutic plan to optimize hemodynamic status and oxygenation. Although blood transfusions consistently increased Do_2 in patients with septic shock (because of the increase in hemoglobin levels and cardiac output), $\dot{V}o_2$ does not consistently increase, especially in patients with cytopathic hypoxia.[122,123] For example, in one study,[122] 10 patients with sepsis with a hemoglobin level less than 10 g/dL received 1 unit of packed red blood cells. No significant change in hemodynamic indices (eg, heart rate, MAP, mean pulmonary artery pressure, PAOP, cardiac index) occurred after the blood transfusion. Although the increase in the Do_2I was not significant (before transfusion: mean 607 mL/(min · m^2), SD 123; after transfusion: mean 648 mL/ (min · m^2), SD 168), no change occurred in systemic $\dot{V}o_2I$ (before: mean 169 mL /(min · m^2), SD 63; after: mean 163 mL/(min · m^2), SD 68), pHi (before: mean 7.19, SD 0.07; after: mean 7.21, SD 0.16) or lactate level (before: mean 1.8 mmol/L, SD 0.5; after: mean 1.7 mmol/L, SD 0.5).[122] This failure to increase $\dot{V}o_2$ may indicate that for this group of patients, $\dot{V}o_2$ was independent of Do_2.

Factors to assess in determining a patient's need for a transfusion include the patient's ability to increase cardiac output to offset the reduction in oxygen-carrying capacity along with indications of impaired tissue oxygenation (eg, increased serum levels of lactate, decreased $S\bar{v}O_2$). As described earlier, the cardiac index–OER ratio may be a useful indicator of intolerance to anemia due to an inadequate cardiac response.[69] Current hemoglobin levels considered indicators for a blood transfusion are 10 g/dL for patients with significant cardiac disease (ie, myocardial infarction or unstable angina), with a maintenance level of 10 to 12 g/dL, and 8 g/dL for all other patients, with a maintenance level between 8 and 10 g/dL.[3,4,124] These indicators are based on a study[125] that showed that in less acutely ill patients a restrictive transfusion strategy (transfuse when hemoglobin level <7 g/dL and maintain hemoglobin level between 8 and 9 g/dL) was associated with lower mortality rates than was a liberal transfusion strategy (transfuse when hemoglobin level <10 g/dL and maintain hemoglobin level between 10 and 12 g/dL). The only exception to these findings was in patients with significant cardiac disease, who may require more a liberal indicator of the need for transfusion (hemoglobin level <10 g/dL).[126] The debate has now shifted to whether these absolute hemoglobin levels should be used or whether more physiological indicators of the need for a transfusion (ie, $ScvO_2$ <70%) are more appropriate.

Vasopressor Therapy

If adequate fluid therapy does not restore arterial pressure and organ

perfusion, treatment with vasopressors should be started.[3,109] Vasopressors may also be used transiently to maintain the blood pressure until adequate volume resuscitation can be achieved. Potential vasopressors include dopamine, norepinephrine, epinephrine, phenylephrine, and vasopressin (Table 4). The choice of a vasopressor requires an understanding of the expected effects as well as the effects of the medications on regional perfusion and outcomes (eg, end-organ damage, mortality).

The goal of vasopressor therapy is to increase the MAP to at least 60 to 65 mm Hg, or even higher for patients with chronic hypertension, without decreasing the stroke volume.[127] However, an excessive increase in the MAP in an attempt to increase organ perfusion may not be effective, because once the autoregulatory threshold is reached (~60 mm Hg), perfusion remains stable despite variations in pressure. For example, in 10 patients with sepsis who required vasopressor agents to maintain the MAP at more than 60 mm Hg despite volume resuscitation to a PAOP greater than 12 mm Hg, norepinephrine was administered to sequentially increase the MAP from 65 to 85 mm Hg. Despite a progressive increase in cardiac index (from mean 4.7, SD 0.5 at a MAP of 65 mm Hg to mean 5.5, SD 0.6 at a MAP of 85 mm Hg) no increase in urine output or improvement in the $Pico_2$ (indicating improved splanchnic perfusion) occurred.[52] Failure of perfusion indices to improve despite the increase in blood pressure highlights the limitation of using blood pressure as an indicator of perfusion. Therefore, monitoring of other indications of global and regional perfusion may be needed.

Dopamine The effects of dopamine are dose dependent. Low doses of dopamine have traditionally been used because of the dopaminergic effects, which increase blood flow to the kidneys and splanchnic beds. However, recent studies[128,129] have shown that although low doses of dopamine (1-4 µg/kg per minute),

Table 4 Vasopressor agents

Agent, units for dose	Dose	Effect	Notes
Dopamine, µg/kg per minute	<5	Dopaminergic effects (↑ renal/splanchnic flow)	Low doses (<5 µg/kg per minute) no longer recommended for renal protection
	5-10	↑ Heart rate, cardiac index, and contractility (β-adrenergic effects)	First-line drug for pressure support during fluid volume resuscitation (5-15 ug/kg per minute)
	10-20	↑ Blood pressure and cardiac index (α-adrenergic effects)	Dose >20 ug/kg per minute may indicate need to convert to or add another agent (norepinephrine or phenylephrine)
	>20	↑ Right atrial pressure/↑ heart rate	
Norepinephrine, µg/kg per minute	0.01-3.00	↑ Mean arterial pressure (α-adrenergic effects; ↑ systemic vascular resistance) ↑ Splanchnic perfusion (β-adrenergic effect) ↑ Heart rate	Compared with high-dose dopamine in patients who are hypotensive and refractory to fluid resuscitation, improves splanchnic perfusion and is associated with increased survival Combination therapy (norepinephrine plus dobutamine) may further improve splanchnic perfusion
Epinephrine, µg/kg per minute	0.1-0.8	↑ Mean arterial pressure associated with ↑cardiac index and stroke volume ↑ Heart rate ↑ Blood pressure in patients unresponsive to traditional agents	Recommended for patients who are refractory to fluid resuscitation and other vasopressors Decreases splanchnic perfusion Increases serum lactate levels
Phenylephrine, µg/min	40-180	↑ Mean arterial pressure (α-adrenergic effects; ↑ systemic vascular resistance) ↓ Heart rate (compensatory) ↔ Cardiac output	Has rapid onset and short duration Is useful in patients with tachycardia (causes reflex decrease in heart rate) Increases vascular resistance with a decrease in cardiac index, although caution required if used in patients with depressed myocardial function
Vasopressin, U/min)	0.01-0.04	↑ Mean arterial pressure ↑ Urine output ↓ Requirement for other vasopressors	Use supported by results of small clinical trials Dose >0.04 U/min may have adverse effects because of excessive vasoconstriction Randomized control trials required before definitive recommendations can be made

Symbols: ↑, increase; ↓, decrease; ↔, no change.

alone or in conjunction with norepinephrine, increase renal blood flow, they do not have a renal protective effect and are no longer recommended for this purpose. Despite a dopamine-induced increase in blood flow to the splanchnic bed,[130] the gastric pHi may not increase[131] and splanchnic oxygen consumption may decrease, perhaps because of altered hepatosplanchnic cellular metabolism or direct acidification of the mucosal cells.[132] Because of the equivocal findings on the effects of dopamine on splanchnic circulation and oxygenation, no specific recommendations can be made on the selection of a vasoactive agent (eg, dopamine vs norepinephrine vs epinephrine) for maintenance of mucosal blood flow in the gut.[133]

Because of its ability to increase both blood pressure and flow at a dose of 5 to 15 µg/kg per minute, dopamine remains the first-line drug of choice for temporary pressure support during fluid resuscitation.[3] At a dose of 20 µg/kg per minute, dopamine causes increases in right atrial and ventricular pressures and tachycardia, which may indicate a need to add or convert to another agent (norepinephrine or phenylephrine). In patients who remain hypotensive despite adequate volume resuscitation, norepinephrine is superior to high doses of dopamine for reducing end-organ failure and improving survival.[72]

Norepinephrine Currently, norepinephrine is used for its α-adrenergic agonist effects, which increase the MAP due to an increase in peripheral vascular resistance. However, its beneficial effects may also reflect its β-adrenergic effects, which increase splanchnic blood flow.[134] Previously, concerns about norepinephrine's potent vasoconstrictive effects made it the last drug of choice in the treatment of shock. The use of norepinephrine as a late-stage therapy may have contributed to its poor outcomes. However, in patients with septic shock, norepinephrine effectively increases MAP without compromising renal or splanchnic organ function.[135,136] In patients with hyperdynamic septic shock, compared with high doses of dopamine (10-25 µg/kg per minute), norepinephrine (0.5-5.0 µg/kg per minute) was more effective in increasing hemodynamic and oxygenation indices to within normal limits and also was associated with increased survival.[72] Thus, current literature supports the early use of norepinephrine.

Epinephrine Epinephrine has α_1- (vasoconstriction), β_2- (vasodilatation), and β_1- (increased heart rate/contractility) adrenergic effects. Epinephrine is currently recommended for patients who are refractory to volume expansion and other vasopressors.[3] Epinephrine must be used cautiously because it decreases splanchnic perfusion and oxygen consumption, despite unchanged global indicators of tissue hypoxia.[137-139] Additionally, administration of epinephrine increases the serum levels of lactate independent of any signs of tissue hypoxia, thus limiting the use of lactate as an indicator of global oxygenation status.[76,77]

Phenylephrine Phenylephrine is an α_1-adrenergic agonist that has been used in patients with septic shock who have a decrease in MAP and vasodilatation. Phenylephrine may also be useful in patients in septic shock who have tachycardia, because the drug causes a reflex decrease in heart rate.[140] The general dose response is a progressive increase in vascular resistance without a change in cardiac output or pulmonary artery pressures.[141] However, patients should be monitored for decreased cardiac output (particularly patients with indications of myocardial depression) in response to increased vascular resistance.

Vasopressin A decrease in endogenous vasopressin occurs in septic shock, which may contribute to the peripheral vasodilatation.[14] In several small studies[5,14,142] of the effects of a vasopressin infusion (0.01-0.04 U/min) in patients with septic shock who were refractory to standard vasopressor therapy, administration of the drug was beneficial (increased MAP, increased urine output, no indications of decreased end-organ perfusion). Additional clinical trials will be required before recommendations can be made about the use of vasopressin in patients with septic shock.[143,144]

Inotropic Therapy

Patients with septic shock may have myocardial depression. In general, patients who have had adequate volume resuscitation will be in a hyperdynamic state. Despite the hyperdynamic condition, myocardial contractility may still be decreased.[36,145] Awareness of the potential for myocardial depression is important in guiding therapy. For example, a patient with septic shock with hypotension, a low cardiac output, and low PAOP requires volume resuscitation.[146] Myocardial depression should be suspected if despite adequate volume resuscitation, the patient remains refractory (cardiac index <2.5 with a MAP <60 mm Hg).[3] For patients

with myocardial depression, dobutamine is recommended. In patients who are refractory to dobutamine (systolic blood pressure < 90 mm Hg, serum lactate level > 2 mmol/L) with a low systemic vascular resistance, the addition of norepinephrine alone or in combination with the dobutamine can increase the cardiac index, MAP, systemic vascular resistance, and left ventricular stroke work index and decrease the serum lactate level.[147]

Summary

The care of patients with septic shock is exceedingly complex. New therapies and monitoring technologies are being rapidly developed. To create an effective plan of care that integrates these new therapies and technologies, critical care nurses must understand the underlying pathophysiology of septic shock, techniques to accurately monitor patients' status, and the rationale for care.

Case Study

Mr S, a 55-year-old, was brought to the emergency department by his wife because of lethargy during the previous 3 days and a decrease in appetite. He had had a prolonged stay in the surgical intensive care unit after a colectomy and ileostomy but had been discharged 2 weeks before the current visit to the hospital. In the emergency department, he was hypotensive and severely acidotic.

Mr S had a history of coronary artery disease, heart failure, and severe peripheral vascular disease. He was allergic to penicillin. Results of laboratory studies were as follows: potassium 6.6 mmol/L, urea nitrogen 35.0 mmol/L (98 mg/dL), and creatinine 804 µmol/L (9.1 mg/ dL). At a fraction of inspired oxygen (F_{IO_2}) of 1.00, results of arterial blood gas analysis were pH 7.05, P_{CO_2} 22 mm Hg, bicarbonate 5 mmol/L, and P_{O_2} 524 mm Hg. The diagnoses at admission were septic shock, acute renal failure, and hyperkalemia.

While Mr S was still in the emergency department, he was aggressively resuscitated with isotonic sodium chloride solution. Despite volume resuscitation, he remained hypotensive (blood pressure 70/40 mm Hg, MAP 50 mm Hg). Treatment with dopamine was started, and the dose was adjusted to 30 µg/kg per minute.

Comment: The initial therapy for septic shock is to ensure adequate volume resuscitation. If after adequate volume resuscitation (central venous pressure >8 mm Hg or PAOP >12-15 mm Hg) the patient remains hypotensive, use of a vasopressor is recommended. Mr S required high doses of dopamine. Consideration should have been given to adding another vasopressor (eg, norepinephrine).

While in the emergency department, Mr S become confused and was unable to maintain effective oxygenation and ventilation. He was subsequently intubated. A urethral catheter was placed to monitor urine output, but he remained oliguric. He was severely acidemic (pH 7.04), but no ketones were detected in the urine and the serum lactate level was normal. A bicarbonate infusion was started. Urine and blood samples were obtained for culture, and he was treated empirically with levofloxacin (Levaquin), vancomycin, and clindamycin.

Comment: In interpreting the laboratory values, nurses should recall that tissue hypoxia can exist in the presence of a normal serum lactate level, because a lag occurs between the onset of tissue hypoxia and the appearance of increased serum levels of lactate. In Mr S, the hypoxia may have been due to the development of acute respiratory distress syndrome. The acidosis most likely was initially due to worsening renal failure. One of the first priorities in the treatment of patients with septic shock is to identify and eliminate the cause of the septic shock. One of the few interventions that has been consistently associated with decreased mortality in septic shock is the early and appropriate administration of antibiotics.[148,149]

On physical examination, no bowel sounds could be detected. A nasogastric tube was inserted and was connected to low-level continuous suction.

Comment: The physical finding of no bowel sounds highlights the fact that the gastrointestinal tract is highly sensitive to a decrease in perfusion. This perfusion abnormality probably reflects the combined effects of hypotension and the high dose of dopamine, which may impair splanchnic perfusion. Monitoring for development of stress ulcers, ileus, and malabsorption is necessary.

In addition to elevated levels on liver function tests, Mr S also had an elevation in the international normalized ratio (INR), an indication of possible early-stage disseminated intravascular coagulation. A dose of 10 mg of phytonadione (vitamin K) was given subcutaneously to help with reversal of the coagulopathy.

Comment: Coagulopathies in septic shock range from minor alteration in platelet function to disseminated intravascular coagulation. Sepsis induces the release and activation of proinflammatory cytokines, which cause a downregulation of fibrinolysis, leading to the formation of microthrombi, which is manifested as organ dysfunc-

tion. Conversely, consumption of platelets and clotting factors is increased, a situation that causes bleeding.[16,17] *As revealed in the recent PROWESS trial, altered coagulation plays a key role in the morbidity and mortality of patients with septic shock.*[18] *Treatment with new agents, such as drotrecogin alfa (activated), can markedly reduce mortality and end-organ dysfunction due to severe sepsis. Consideration may be given to slow intravenous administration of phytonadione (vitamin K, dilute solution administered at a rate not to exceed 1 mg/mL)*[150] *to reduce the risk of hematoma formation from a subcutaneous injection.*

Mr S was transferred to the medical ICU. His potassium level remained elevated at 6.7 mmol/L, and he had periods of polymorphic ventricular tachycardia. He was treated with intravenous calcium, the bicarbonate infusion was continued, and administration of amiodarone was started. Infusions of insulin and 5% dextrose in water were started to help decrease his potassium level. A renal consultation was scheduled for possible dialysis because of severe acidosis, acute renal failure, and hyperkalemia.

Mr S received 18 L of crystalloids during the first night in the ICU. Vasopressor support was changed to norepinephrine (Levophed). By the following morning, his chest radiograph showed early signs of pulmonary edema. A pulmonary artery catheter was placed to help manage his fluid status (central venous pressure 18 mm Hg, pulmonary artery systolic pressure 44 mm Hg, pulmonary artery end-diastolic pressure 28 mm Hg, PAOP 21 mm Hg).

Comment: Pulmonary artery catheterization is recommended for patients with septic shock who are refractory to initial fluid volume resuscitation. Compared with use of dopamine or epinephrine, use of norepinephrine in patients with septic shock may improve outcomes.

Results of laboratory tests of samples collected that morning were serum pH 7.21 and decreases in hemoglobin level (9.2 g/dL) and hematocrit (0.28). Throughout the day, Mr S's pH and urine ketone levels returned toward normal, and the bicarbonate infusion was tapered off. Two units of packed red blood cells were transfused.

Comment: The current indicator for blood transfusions in patients with septic shock who have significant cardiovascular disease is a hemoglobin level of 10 g/dL, with a maintenance hemoglobin level of 10 to 12 g/dL. Further attempts to increase the hemoglobin level to more than 10 to 12 g/dL to increase Do_2 *have not been beneficial. The current debate is whether to use these standardized indicators or physiological indicators of the need for blood (ie,* $Scvo_2$ *or the cardiac index–OER ratio).*

Results of subsequent laboratory tests revealed that Mr S had had had an acute myocardial infarction: serum creatine kinase concentration 4000 U/L and serum troponin I level 4.0 µg/L. The myocardial infarction was thought to be related to oxygen supply-and-demand mismatch caused by the severe hypotension.

Comment: In addition to myocardial ischemia and infarction due to the severe hypotension that occurs in septic shock, patients with septic shock may sustain myocardial injury (as indicated by increased troponin levels) from inflammatory mediators. The presence of myocardial dysfunction, regardless of the cause, should be considered when the effects of vasoactive medications on the cardiac output are evaluated.

By the time of discharge 5 weeks later, Mr S's condition was stabilized with his oral cardiac medications. His oxygen saturation was 100% on room air. Even though he had had oliguric renal failure at the time of admission, he had responded well to intravenous fluids. The acute tubular necrosis had resolved and was thought to be due to hypotension/hypovolemia related to septic shock. After initial correction with fluids and the bicarbonate infusion, the serum pH had remained stable. Bowel function had returned, and at the time of discharge, findings on abdominal examination were normal. Mr S had no evidence of disseminated intravascular coagulation, and his coagulation profile was stable at the time of discharge. By the time of discharge, cultures were negative and findings on computed tomography were normal.

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CE Test Form

Cardiovascular Aspects of Septic Shock: Pathophysiology, Monitoring, and Treatment

Objectives:

1. Describe the primary effects of septic shock on the cardiovascular system
2. Recognize the role of various monitoring modalities in the patient with septic shock
3. Identify current recommendations for treatment of septic shock

Mark your answers clearly in the appropriate box. There is only 1 correct answer. You may photocopy this form.

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❑b	❑b	❑b	❑b	❑b	❑b	❑b	❑b	❑b	❑b	❑b	❑b
❑c	❑c	❑c	❑c	❑c	❑c	❑c	❑c	❑c	❑c	❑c	❑c
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CE Test Questions

Cardiovascular Aspects of Septic Shock: Pathophysiology, Monitoring, and Treatment

1. Which of the following categories best describes septic shock?
   a. Obstructive shock
   b. Hypovolemic shock
   c. Cardiogenic shock
   d. Distributive shock

2. Which of the following is characteristic of hypotension associated with septic shock?
   a. The hypotension is poorly responsive to adequate fluid resuscitation and accompanied by hypoperfusion and organ dysfunction.
   b. The hypotension is highly responsive to fluid resuscitation.
   c. The hypotension is responsive to high doses of inotropic agents.
   d. The hypotension is rarely accompanied by hypoperfusion and organ dysfunction.

3. Which of the following is *not* a common pathophysiologic manifestation seen in patients with septic shock?
   a. Myocardial depression
   b. Maldistribution of blood flow
   c. Increase in systemic vascular resistance
   d. Tissue hypoxia secondary to decreased oxygen delivery

4. Which coagulation system is primarily affected in septic shock?
   a. Tissue plasminogen activator cascade
   b. Extrinsic tissue factor pathway
   c. Alteration in platelet function
   d. Intrinsic tissue factor pathway

5. Which of the following are beneficial effects of endogenous activated protein C?
   a. Profibrinolytic effects
   b. Anti-inflammatory effects
   c. Antithrombotic effects
   d. All of the above

6. Which of the following is *not* 1 of the 3 primary goals in the treatment of septic shock?
   a. Identify and eliminate cause of infection
   b. Maintain adequate mean arterial pressure
   c. Systemic anticoagulation to avoid disseminated intravascular coagulation
   d. Interruption of the pathogenic process leading to septic shock

7. What is the initial therapy of choice for the treatment of hypotension is septic shock?
   a. Vasopressor agents
   b. Inotropic agents
   c. Fluid resuscitation
   d. Vasodilator agents

8. What is the primary manner in which myocardial depression is manifested in patients with septic shock who have been adequately fluid resuscitated?
   a. Ventricular dilatation, flattening of the Frank-Starling curve, and decreased ejection fraction
   b. Increased cardiac output and increased systemic vascular resistance
   c. Decreased cardiac output and increased systemic vascular resistance
   d. Altered myocardial compliance and peaking of the Frank-Starling curve

9. Which of the following is true regarding the standard indices of hemodynamic stability in patients with septic shock?
   a. Blood pressure, heart rate, and urine output may be normal despite continued tissue hypoxia.
   b. Invasive blood pressure monitoring will consistently demonstrate hypotension in patients in septic shock.
   c. Blood pressure and urine output will always be decreased in patients with septic shock.
   d. Lactate levels will be consistently decreased in patients in septic shock.

10. Which of the following is true regarding splanchnic perfusion in hypoperfused patients?
    a. Elevated lactate levels often precede splanchnic hypoperfusion.
    b. Decreased splanchnic perfusion often precedes overt signs and symptoms of shock.
    c. Decreased gastric intramucosal pH in patients with decreased splanchnic perfusion is predictive of survival.
    d. Hypotension in hypoperfused patients is often followed by decreased splanchnic perfusion.

11. What is the inotrope of choice in patients who have undergone volume replacement, have a normal pulmonary artery wedge pressure, a cardiac index < 2.5, and a mean arterial pressure < 60 mm Hg?
    a. Dopamine
    b. Phenylephrine
    c. Dobutamine
    d. Epinephrine

12. In patients with septic shock who have been adequately fluid resuscitated and who continue to be hypotensive with a low systemic vascular resistance despite addition of dobutamine, which of the following is recommended?
    a. Addition of epinephrine
    b. Addition of dopamine
    c. Additional fluid resuscitation
    d. Addition of norepiniphrine