Inotrope and Vasopressor Therapy of Septic Shock

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KEYWORDS

• Sepsis • Septic shock • Vasopressor • Inotrope • Dopamine
• Norepinephrine • Epinephrine • Vasopressin

Septic shock results when infectious agents or mediators induced by these agents circulate in the bloodstream and produce hemodynamic decompensation. Its pathogenesis involves a complex interaction between pathologic vasodilation, relative and absolute hypovolemia, myocardial dysfunction, and altered blood flow distribution caused by the inflammatory response to infection; even after the restoration of intravascular volume, microcirculatory abnormalities may persist and lead to maldistribution of cardiac output.[1,2] About half of the patients who succumb to septic shock die of multiple organ system failure, and most other nonsurvivors have progressive hypotension with low systemic vascular resistance refractory to vasopressor agents.[1] Although myocardial dysfunction is not uncommon, death from myocardial failure is rare.[3]

The initial priority in managing septic shock is to maintain a reasonable mean arterial pressure and cardiac output to keep the patient alive while the source of infection is identified and addressed, and measures to interrupt the pathogenic sequence leading to septic shock are undertaken. While these latter goals are being pursued, adequate organ system perfusion and function must be maintained, guided by cardiovascular monitoring.

This article focuses on vasopressor and inotropic support for patients with septic shock. Hemodynamic therapy of sepsis can be conceptualized in three broad categories: (1) fluid resuscitation, (2) vasopressor therapy, and (3) inotropic therapy. Although many vasoactive agents have both vasopressor and inotropic actions, the distinction is made on the basis of the intended goals of therapy; vasopressor actions raise blood pressure, whereas inotropic actions raise cardiac output. This conceptualization is not intended to minimize the importance of assessing the effects of vasoactive agents on perfusion, as is made clear from the following discussion.

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GENERAL APPROACH

Septic shock requires early, vigorous resuscitation. An integrated approach directed at rapidly restoring systemic oxygen delivery and improving tissue oxygenation has been shown to improve survival significantly in septic shock.[4] Although the specific approach that is used may vary, certain critical elements should be incorporated in any resuscitative effort. Therapy should be guided by parameters that reflect the adequacy of tissue and organ perfusion. Fluid infusion should be vigorous and titrated to clinical end points of volume repletion. Systemic oxygen delivery should be supported by ensuring arterial oxygen saturation, maintaining adequate levels of hemoglobin, and by using vasoactive agents directed to physiologic and clinical end points.

In shock states, estimation of blood pressure using a cuff may be inaccurate; use of an arterial cannula provides a more appropriate and reproducible measurement of arterial pressure.[5–7] Arterial catheters also allow beat-to-beat analysis so that decisions regarding therapy can be based on immediate and reproducible blood pressure information, facilitating the administration of large quantities of fluids and potent vasopressor and inotropic agents to critically ill patients.[1]

Although patients with shock and mild hypovolemia may be treated successfully with rapid fluid replacement alone, hemodynamic monitoring may be useful to provide a diagnostic hemodynamic assessment in patients with moderate or severe shock. In addition, because hemodynamics can change rapidly in sepsis, and because noninvasive evaluation is frequently incorrect in estimating filling pressures and cardiac output, hemodynamic monitoring is often useful for monitoring the response to therapy.

Changes in systolic arterial pressure or pulse arterial pressure caused by positive pressure ventilation can predict which patients respond to fluid loading (increased preload) with an increase in their cardiac output.[8] Echocardiography can also provide information on left ventricular size and systolic performance, right ventricular size and function, and valvular and pericardial abnormalities; and echo Doppler allows for estimation of stroke volume, pulmonary systolic pressure, the severity of valvular stenosis or regurgitation, and diastolic function. This information can be useful to assess myocardial function, cardiac output, and fluid status in patients with septic shock, and is complementary to hemodynamic assessment.

Goals and Monitoring of Vasopressor Therapy

When fluid administration fails to restore an adequate arterial pressure and organ perfusion, therapy with vasopressor agents should be initiated.[6] The ultimate goals of hemodynamic therapy in shock are to restore effective tissue perfusion and to normalize cellular metabolism. In septic shock, tissue hypoperfusion may result not only from decreased perfusion pressure attributable to hypotension but also from abnormal shunting of a normal or increased cardiac output.[1] Cellular alterations may also occur. Hemodynamic support of sepsis requires consideration of both global and regional perfusion.

Arterial pressure is the end point of vasopressor therapy, and the restoration of adequate pressure is the criterion of effectiveness. Blood pressure, however, does not always equate to blood flow, and the precise level of mean arterial pressure to aim for is not necessarily the same in all patients. Animal studies suggest that below a mean arterial pressure of 60 mm Hg, autoregulation in the coronary, renal, and central nervous system vascular beds is compromised, and flow may become linearly dependent on pressure.[9,10] Loss of autoregulation can occur at different levels in different organs, however, and the degree to which septic patients retain intact autoregulation is uncertain. Some patients (especially those with pre-existing hypertension) may require higher blood pressures to maintain adequate perfusion.

The precise blood pressure goal to target in septic shock remains uncertain. Most experts agree, largely on the basis of the animal studies cited previously and on physiologic reasoning, that in septic patients with evidence of hypoperfusion, mean arterial pressure should be maintained above 60[6] or 65 mm Hg.[11] There are no data from randomized clinical trials that demonstrate that failure to maintain blood pressure at this level worsens outcome, but it seems unlikely that such a clinical trial will be conducted soon. It should be recognized that individual patients may have blood pressures somewhat lower than these thresholds without hypoperfusion; it is clinical shock in the presence of hypotension that merits vasopressor support.

Higher blood pressure targets may be warranted in some patients. The renal circulation may be especially sensitive to perfusion pressure, and vasopressor therapy to augment renal perfusion pressure has been shown to increase urine output or creatinine clearance in a number of open-label clinical series; the targeted mean blood pressure varied, but was as high as 75 mm Hg.[12–19] Improvements in renal function with increased perfusion pressure, however, have not been demonstrated in prospective, randomized studies. Randomized trials comparing norepinephrine titrated to either 65 or 85 mm Hg in patients with septic shock have found no significant differences in metabolic variables or renal function.[20,21]

It is important to supplement end points, such as blood pressure, with assessment of regional and global perfusion. Bedside clinical assessment provides a good indication of global perfusion. Indications of decreased perfusion include oliguria, clouded sensorium, delayed capillary refill, and cool skin. Some caution is necessary in interpreting these signs in septic patients, however, because organ dysfunction can occur in the absence of global hypoperfusion. Clinical assessments can be supplemented by other measures, such as serum lactate levels and mixed venous oxygen saturation. Elevated lactate in sepsis may result from global hypoperfusion or from cellular metabolic alterations that may or may not represent tissue hypoxia,[22] but its prognostic value, particularly of the trend of lactate concentrations, has been well established in septic shock patients.[23–25] Mixed venous oxyhemoglobin saturation (SvO_2) reflects the balance between oxygen delivery and consumption, and can be elevated in septic patients because of maldistribution of blood flow, so values must be interpreted in the context of the wider hemodynamic picture. Low values, however, suggest increased oxygen extraction and potentially incomplete resuscitation. A recent study showed that monitoring of central venous oxygen saturation ($ScvO_2$) can be a valuable guide to early resuscitation.[4] The correlation between $ScvO_2$ and SvO_2 is reasonable,[26] but may not always be reliable.[27]

Adequacy of regional perfusion is usually assessed clinically.[1] Methods of measuring regional perfusion more directly have been under investigation, with a focus on the splanchnic circulation, which is especially susceptible to ischemia and may drive organ failure.[28] Measurements of oxygen saturation in the hepatic vein have revealed oxygen desaturation in a subset of septic patients, suggesting that hepatosplanchnic oxygen supply may be inadequate in some patients, even when more global parameters seem adequate.[29] Direct visualization of the sublingual circulation[30] or sublingual capnometry[31] may be useful to monitor the restoration of microvascular perfusion in patients with sepsis.

ADRENERGIC AGENTS

There has been longstanding debate about whether one catecholamine vasopressor agent is superior to another. These discussions may be enlightening in that they tend to highlight differences in pharmacology among the agents, but sometimes

the arguments tend to focus on the agents themselves when the therapeutic strategy is actually what differs. Different catecholamine agents have different effects on α- and β-adrenergic receptors, as shown in **Fig. 1**. The hemodynamic actions of these receptors are well known, with α-adrenergic receptors promoting vasoconstriction, β_1-adrenergic receptors increasing heart rate and myocardial contractility, and β_2-adrenergic receptors causing peripheral vasodilation.

The result of these differential effects on adrenergic receptors is that the different agents have different effects on pressure and flow, as shown in **Fig. 2**. Conceived in these terms, the argument about which catecholamine is best in a given situation is transformed into a discussion about which agent is best suited to implement the therapeutic strategy chosen. This may or may not make the choice easier, but it does emphasize the need to define the goals and end points of therapy and to identify how those end points will be monitored.

INDIVIDUAL VASOPRESSOR AGENTS

Dopamine

Dopamine, the natural precursor of norepinephrine and epinephrine, has distinct dose-dependent pharmacologic effects. At doses less than 5 μg/kg/min, dopaminergic receptors are activated, leading to vasodilation in the renal and mesenteric beds.[32] At doses of 5 to 10 μg/kg/min, β_1-adrenergic effects predominate, increasing cardiac contractility and heart rate. At doses above 10 μg/kg/min, α_1-adrenergic effects predominate, leading to arterial vasoconstriction and an increase in blood pressure. There is a great deal of overlap in these effects, particularly in critically ill patients.

Dopamine increases mean arterial pressure and cardiac output, primarily by an increase in stroke volume, and to a lesser extent by an increase in heart rate.[33–43] In open-label trials, dopamine (median dose, 15 μg/kg/min) increased mean arterial pressure by 24% in septic patients who remained hypotensive after optimal fluid resuscitation.[33–43] Dopamine has been shown to increase oxygen delivery, but its effects on calculated or measured oxygen consumption have been mixed, suggesting that tissue oxygenation may not always be improved, perhaps because of failure to

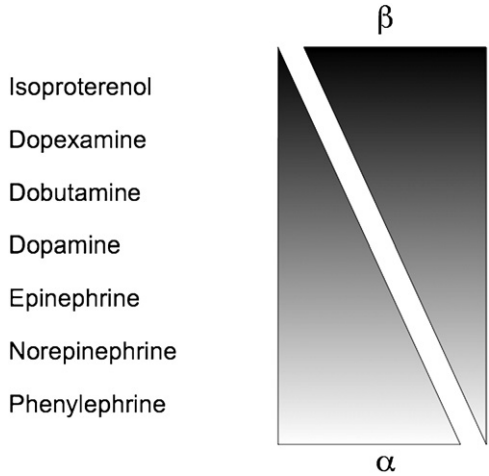

Fig. 1. α- and β-adrenergic effects of vasoactive catecholamines.

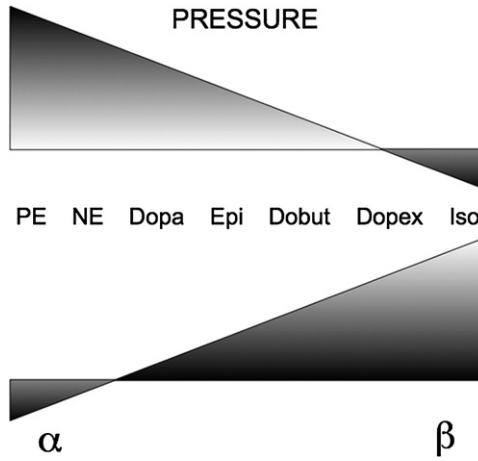

Fig. 2. Effects of vasoactive catecholamines on pressure and blood flow.

improve microcirculatory flow.[34,35,44,45] The effect of dopamine on splanchnic perfusion has also been mixed. Increases in splanchnic blood flow have been reported, but have not always been associated with increases in splanchnic oxygen consumption, beneficial effects on gastric intramucosal pH, or improvement in hepatosplanchnic energy balance.[33,34,36,46–48]

Low doses of dopamine increase renal blood flow and glomerular filtration rate in laboratory animals and healthy volunteers, supporting the idea that dopamine can reduce the risk of renal failure in critically ill patients by increasing renal blood flow. This notion has now been put to rest by a definitive clinical trial that randomized 328 critically ill patients with early renal dysfunction to low (''renal'') dose dopamine (2 μg/kg/min) or placebo.[49] No difference was found in either the primary outcome (peak serum creatinine); other renal outcomes (increase in creatinine, need for renal replacement, urine output); or secondary outcomes (survival to either ICU or hospital discharge, ICU or hospital stay, arrhythmias).[49]

Dopamine effectively increases mean arterial pressure in patients who remain hypotensive after optimal volume expansion, largely as a result of increasing cardiac index, so it may be chosen in patients with compromised cardiac function or cardiac reserve. Its major side effects are tachycardia and arrhythmogenesis, both of which are more prominent than with other vasopressor agents. Safety concerns have also been raised concerning extracardiac side effects. Dopamine has the potential to decrease prolactin release, favoring lymphocyte apoptosis with consequent immunosuppression.[50,51]

Dopamine use was associated with increased mortality in patients with shock in an observational cohort study of 198 European ICUs, and remained a significant predictor after multivariate analysis.[52] Another, similarly sized observational cohort of 17 Portuguese ICUs showed decreased mortality in septic shock patients treated with dopamine compared with norepinephrine, however, a finding that also persisted after multivariate analysis.[53] These observational studies have known limitations. A large prospective randomized clinical trial comparing dopamine with norepinephrine in 1603 pressor-dependent patients with septic shock has recently been completed, and presented but not yet published.[54] No significant difference in mortality between use of dopamine and norepinephrine was observed, although there were more arrhythmias in the dopamine group.[54]

Norepinephrine

Norepinephrine, the endogenous mediator of the sympathetic nervous system, is a potent α-adrenergic agonist with less pronounced β-adrenergic agonist effects. Norepinephrine increases mean arterial pressure by vasoconstriction, with a small (10%–15%) increase in cardiac output and stroke volume.[12–14,18,55,56] Filling pressures are either unchanged[12–14,18,57] or modestly increased (1–3 mm Hg).[17,19,34,36,38]

Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in septic shock patients. In open-label trials, norepinephrine at doses ranging from 0.01 to 3.3 μg/kg/min has been shown to increase mean arterial pressure in patients who remained hypotensive after fluid resuscitation and dopamine.[13,14,18,19,36,56–59] The large doses of the drug required in some patients may be caused by α-receptor down-regulation in sepsis.[60]

In the only randomized trial comparing vasopressor agents, 32 volume-resuscitated septic patients were given either dopamine or norepinephrine to achieve and maintain normal hemodynamic and oxygen transport parameters for at least 6 hours. Dopamine was successful in only 31% of patients, whereas norepinephrine administration (1.5 ± 1.2 mg/kg/min) was successful in 93% ($P<.001$). Of the 11 patients who did not respond to dopamine, 10 responded when norepinephrine was added. Serum lactate levels were also decreased, suggesting that norepinephrine improved tissue oxygenation.[38]

The vasoconstrictive effects of norepinephrine can have detrimental effects on renal hemodynamics in patients with hypotension and hypovolemia, with the potential for renal ischemia.[61–63] The situation may differ in adequately resuscitated, hyperdynamic septic shock.[17] Norepinephrine has a greater effect on efferent than afferent renal arteriolar resistance and increases the filtration fraction. Several studies have shown increases in urine output and renal function in patients with septic shock treated with norepinephrine alone or norepinephrine added to dobutamine.[12,15,17,19,34,38,39,57,64]

Results of studies of the effects of norepinephrine on splanchnic blood flow in patients with septic shock have been mixed. Effects of norepinephrine on both splanchnic blood flow and oxygen consumption have been unpredictable both among patients and within groups.[33,36] Comparisons between norepinephrine and other vasoactive agents have also been variable. One pilot study found that gastric mucosal pHi was significantly increased during a 3-hour treatment with norepinephrine but significantly decreased during treatment with dopamine.[34] A more recent study compared the effects of norepinephrine, epinephrine, and dopamine in 20 patients with septic shock.[65] In the 10 patients with moderate shock, no differences in splanchnic blood flow or gastric-arterial P_{CO_2} difference were observed. In the 10 with severe shock, the effects of norepinephrine and dopamine were similar: epinephrine increased cardiac index more than norepinephrine but splanchnic blood flow was lower despite this higher cardiac index.[65]

Norepinephrine can increase blood pressure in patients with septic shock without causing deterioration in cardiac index and organ function. Although the effect of the drug on oxygen transport variables and splanchnic parameters has varied in different studies, other clinical parameters of peripheral perfusion, such as urine flow and lactate concentration, are significantly improved in most studies. In a recent multivariate analysis including 97 septic shock patients, mortality was favorably influenced by the use of norepinephrine; use of high-dose dopamine, epinephrine, or dobutamine had no significant effect.[66]

Controlled data comparing norepinephrine with other catecholaminergic agents were limited to one small randomized study[38] until completion of the large randomized

trial comparing dopamine with norepinephrine.[54] This trial showed no difference in mortality, but fewer arrhythmias with norepinephrine.[54] Because randomized data do not suggest large differences in overall outcomes across broad populations, individualization of vasopressor agents based on clinical and hemodynamic factors still seems warranted.

Phenylephrine

Phenylephrine, a selective α_1-adrenergic agonist, increases blood pressure by vasoconstriction. Its rapid onset, short duration, and primary vascular effects make it an attractive agent in the management of hypotension associated with sepsis, but there are concerns about its potential to reduce cardiac output in these patients.

Data concerning the use of phenylephrine in hyperdynamic sepsis are sparse. Phenylephrine has been shown to increase blood pressure when given to normotensive hyperdynamic septic patients at doses of 0.5 to 8 μg/kg/min, with little change in cardiac output or stroke volume.[67,68] A small 13-patient study in hypotensive septic patients showed that phenylephrine added to either low-dose dopamine or dobutamine increased mean arterial pressure and cardiac index without a change in heart rate.[69] Recently, a crossover pilot study compared systemic hemodynamics, gastric tonometry, and renal function in 15 patients with septic shock changed from norepinephrine to phenylephrine titrated to maintain a similar blood pressure, and then back again.[70] Systemic hemodynamics were similar (although heart rate, as expected, was slightly lower), but indices of hepatosplanchnic perfusion and function were decreased with phenylephrine, as was renal function.[70] A 32-patient randomized control trial comparing phenylephrine with norepinephrine for initial support of patients with septic shock by the same group, however, showed no significant difference in global or regional hemodynamics, or in renal function, which might suggest potential differences between delayed and early administration.[71]

The limited information available with phenylephrine suggests that this drug can increase blood pressure modestly in fluid-resuscitated septic shock patients, and may be a good option when tachyarrhythmias limit therapy with other vasopressors.[6]

Epinephrine

Epinephrine, which is synthesized, stored, and released from the chromaffin cells of the adrenal medulla, is a potent α- and β-adrenergic agent that increases mean arterial pressure by increasing both cardiac index and peripheral vascular tone.[16,72–74] Epinephrine increases oxygen delivery, but oxygen consumption also may be increased.[72–76] Lactate levels can be increased after use of epinephrine in sepsis, although whether this results from excess vasoconstriction and compromised perfusion or increased lactate production remains uncertain.[58,72,76]

The main concern with the use of epinephrine in sepsis is the potential to decrease regional blood flow, particularly in the splanchnic circulation.[58,77–79] In a recent study of patients with severe septic shock, epinephrine increased global oxygen delivery and consumption but caused a lower absolute and fractional splanchnic blood flow and lower indocyanine green clearance, validating the adverse effects of epinephrine alone on the splanchnic circulation.[65] Another group has reported improved gastric mucosal perfusion with epinephrine compared with norepinephrine-dobutamine combination,[80] but the same group subsequently reported superiority of a norepinephrine-dopexamine combination over epinephrine.[81]

A randomized clinical trial comparing epinephrine with norepinephrine in 280 critically ill patients with shock found no difference in time to achieve arterial pressure goals, 28-day mortality, or 90-day mortality, although 13% of the patients in the

epinephrine group were withdrawn from the study because of lactic acidosis or tachycardia.[82] When a prespecified analysis of the 158 patients with septic shock was performed, results were similar, with no differences in hemodynamics or mortality.[82]

Another fairly large (N = 330) randomized clinical trial compared epinephrine with norepinephrine with or without dobutamine, with drugs titrated to maintain a mean arterial pressure above 70 and a cardiac index above 2.5 L/min, in patients with septic shock.[83] Metabolic abnormalities were transient in this trial, and no patients were withdrawn for this reason. There was no significant difference in time to hemodynamic success, vasopressor withdrawal, or mortality at 28 days in the ICU or in the hospital between epinephrine and norepinephrine with dobutamine.[83]

Epinephrine can increase blood pressure in patients unresponsive to traditional agents. It increases heart rate and has the potential to induce tachyarrhythmias, ischemia, and hypoglycemia. Because of its effects on gastric blood flow and its propensity to increase lactate concentrations, epinephrine has been considered a second-line agent whose use should be considered in patients failing to respond to traditional therapies.[6] Recent clinical trials, however, have cast some doubt on whether epinephrine is inferior to other agents.

Vasopressin

Vasopressin is a peptide hormone synthesized in the hypothalamus and then transported to and stored in the pituitary gland. Released in response to decreases in blood volume, decreased intravascular volume, and increased plasma osmolality, vasopressin constricts vascular smooth muscle directly by V1 receptors and also increases responsiveness of the vasculature to catecholamines.[84,85] Vasopressin may also increase blood pressure by inhibition of vascular smooth muscle nitric oxide production[86] and K^+-ATP channels.[85,87]

Normal levels of vasopressin have little effect on blood pressure in physiologic conditions[84] but vasopressin helps maintain blood pressure during hypovolemia,[88] and seems to restore impaired hemodynamic mechanisms and also inhibit pathologic vascular responses in shock.[85] Increased levels of vasopressin have been documented in hemorrhagic shock,[89] but a growing body of evidence indicates that this response is abnormal or blunted in septic shock. One study found markedly increased levels of circulating vasopressin in 12 patients with cardiogenic shock, but much lower levels in 19 patients with septic shock, levels that were hypothesized to be inappropriately low.[90] One potential mechanism for this relative vasopressin deficiency is depletion of pituitary stores, possibly in conjunction with impaired synthesis. Depletion of vasopressin stores in the neurohypophysis evaluated by MRI has been described in a small group of septic shock patients.[91] A recent prospective cohort study of patients with septic shock found that vasopressin levels were almost always elevated in the initial hours of septic shock and decreased afterward; one third of patients developed relative vasopressin deficiency as defined by the investigators.[92]

Given this theoretical rationale, observational studies demonstrated that the addition of a low dose of vasopressin (0.01–0.04 U/min) to catecholamines can raise blood pressure in patients with pressor-refractory septic shock.[93–95] Several small randomized studies comparing vasopressin with norepinephrine have demonstrated that initiation of vasopressin decreases catecholamine requirements,[96,97] and one showed improved renal function.[96] Similar data are available for terlipressin, a synthetic vasopressin analog.[98] There is concern, however, that vasopressin infusion in septic patients may either decrease splanchnic perfusion or redistribute blood flow away from the splanchnic mucosa.[99,100] Vasopressin should be thought of as replacement therapy for relative deficiency rather than as a vasopressor agent to be titrated to effect.

A large randomized clinical trial (VASST) has now been completed comparing vasopressin with norepinephrine in 776 patients with pressor-dependent septic shock.[101] Patients were randomized to vasopressin (0.03 U/min) or 15 μg/min norepinephrine in addition to their original vasopressor infusion; the primary end point was 28-day mortality; a prespecified subgroup analysis was done on patients with less severe (NE 5–14 μg/min) and more severe (NE >15 μg/min) septic shock. For the group as a whole, there was no difference in mortality, but vasopressin seemed to be better in the less severe subgroup.[101]

Vasopressin (0.03 U/min) added to norepinephrine seems to be as safe and effective as norepinephrine in fluid-resuscitated patients with septic shock. Vasopressin may be more effective in patients on lower doses of norepinephrine than when started as rescue therapy, although what to do in patients with high vasopressor requirements despite vasopressin infusion remains uncertain.

INOTROPIC THERAPY

Background

The broad outlines of myocardial dysfunction in patients with septic shock have been well defined. Despite the fact that cardiac output is usually normal or high, there is evidence that myocardial contractility may be impaired in a subgroup of septic patients. In the initial report, performed with serial radionuclide scans, left ventricular ejection fraction was decreased, and the left ventricle was dilated, so stroke volume was preserved.[102] Subsequent reports using echocardiography found a similarly decreased ejection fraction in a subset of septic patients, but less prominent ventricular dilation, and some of these patients were reported to have low stroke volumes.[103,104] In reports from both groups, myocardial depression developed 24 to 48 hours after the onset of septic shock and was reversible in survivors. In addition to depressed left ventricular ejection fraction, some studies in septic patients have suggested abnormalities in ventricular responses to fluid loading, with lower increases in left ventricular performance (measured by left ventricular stroke work index) increased less in septic shock patients than in controls.[105]

The reversibility of myocardial dysfunction in sepsis suggests the involvement of circulating mediators, but the precise mechanisms of myocardial dysfunction remain unclear. A role for inflammatory cytokines has been suggested by studies showing that tumor necrosis factor,[106] interleukin-1,[107] and other inflammatory cytokines, either alone or in combination,[108] depress contractility of isolated cardiac myocytes. The time course of myocardial depression in large animal models and in patients with sepsis, with onset between 24 and 48 hours, along with evidence for its induction by cytokines, suggests the possibility of cytokine-inducible nitric oxide synthase as a mediator.[108] Studies have implicated both nitric oxide production and reactive oxygen species in cytokine-induced myocardial depression, and have further suggested a role for peroxynitrite.[109] Other studies have implicated decreased myocyte myofilament calcium responsiveness, possibly mediated by abnormal protein kinase A phosphorylation.[110] Regardless of the mechanism, the reversibility of myocardial depression in septic patients suggests the feasibility of a strategy of inotropic support while awaiting recovery.

The challenge in interpreting myocardial dysfunction in sepsis is that the most important physiologic parameter is cardiac output, not ejection fraction. Some patients, especially those with pre-existing cardiac dysfunction, may have decreased cardiac output, and those patients are clearly candidates for inotropic therapy to improve cardiac performance. For other patients, the clinical issue is not so much

how to optimize cardiac systolic performance, but how to determine whether cardiac output is adequate to meet physiologic needs.

Goals and Monitoring of Inotropic Therapy

Tissue perfusion is a function of both pressure and flow. The challenge in titrating therapy to a cardiac output is to determine when that output is adequate. Because of the complexity of assessment of clinical parameters in septic patients, direct measurement of cardiac output in patients receiving inotropic therapy is advisable, but other end points of global perfusion also should be followed. When global hypoperfusion is manifested by decreased mixed venous oxygen saturation, this measure may be used as a guide to the adequacy of inotropic therapy. Similarly, a fall in blood lactate concentrations concomitant with increased cardiac output is a good prognostic sign.

Early and late inotropic therapy in sepsis may well be different. In the study by Rivers and coworkers[4] of early goal-directed resuscitation for patients presenting with septic shock, if central venous oxygen saturation remained low despite resuscitation with fluids and vasopressors and packed red blood cells if necessary, patients received inotropic therapy; 13.7% of patients in the intervention group were given dobutamine, compared with 0.8% in the standard treatment group. In this setting, low central venous oxygen saturation provided presumptive evidence for inadequate oxygen delivery. Precisely which components of the resuscitation bundle were responsible for improved outcomes in this trial, however, remains uncertain, and is the subject of ongoing trials.

After initial resuscitation, what to do is less clear. More is known about what not to do than what to do in this respect. Some critically ill septic patients are hypermetabolic and may require high levels of oxygen delivery to maintain oxidative metabolism.[111] Accordingly, it has been hypothesized that such patients would benefit from therapeutic measures to increase oxygen delivery to "supranormal" levels. Retrospective analyses showed that achievement of cardiac index greater than 4.5 L/min/m^2, oxygen delivery greater than 600 mL/min/m^2, and oxygen consumption greater than 170 mL/min/m^2 correlates with improved survival.[112] Two large randomized studies to test the hypothesis that routinely increasing oxygen delivery to these predefined levels in all critically ill patients, however, did not show improved outcomes,[113,114] and mortality in the treatment arm was higher than control in one of the studies, a trial that allowed very high doses of dobutamine in some patients.[114] A strategy of routinely increasing oxygen delivery to predetermined elevated end points of cardiac index and oxygen delivery is not recommended in the guidelines.[6,115]

Nonetheless, some patients may have improved tissue perfusion with inotropic therapy aimed at increasing oxygen delivery. Because the goal of such therapy is to increase cardiac output, is seems logical that such therapy is best guided by monitoring of cardiac output, but this should be supplemented by clinical measures of perfusion. When global hypoperfusion is manifest by decreased venous oxygen saturation, its monitoring can be helpful to guide response to therapy. Similarly, although lactate production in sepsis is complex, a fall in blood lactate levels during inotropic therapy is a good prognostic sign.[116] In addition, assessment of the adequacy of regional or microcirculatory perfusion may also be useful in selected patients.[6]

INDIVIDUAL INOTROPIC AGENTS

Dobutamine

Dobutamine is a racemic mixture of two isomers, a D isomer with β_1- and β_2-adrenergic effects, and an L isomer with β_1- and α_1-adrenergic effects; its predominant

effect is inotropic by stimulation of β_1 receptors, with a variable effect on blood pressure. A number of studies have investigated the effect of dobutamine on cardiac function during sepsis or septic shock at doses ranging from 2 to 28 μg/kg/min.[56,117–121] In these studies, increases in cardiac index ranged from 12% to 61%. Heart rate increases, however, often significantly (9%–23%). Two studies reported that left ventricular stroke work index increased by 23% to 58% at mean dobutamine doses of 5 to 12 μg/kg/min.[117,119] Similar increases in right ventricular stroke work were also observed in these studies.

Despite a paucity of randomized data demonstrating its efficacy, dobutamine is the first-choice inotropic agent for patients with measured or suspected low cardiac output in the presence of adequate filling pressures.[6,115] Although dobutamine does not influence the distribution of blood flow, therapy is often aimed at increasing blood flow to organs, such as the gut or the kidneys.

Dopamine

Dopamine has β-adrenergic activity, usually at doses greater than 5 μg/kg/min. At doses of 5 to 10 μg/kg/min vasopressor effects caused by α-adrenergic stimulation occur and become predominant at higher doses. Dopamine also causes the release of norepinephrine from nerve terminals, contributing to its cardiac effects. The pharmacokinetics of dopamine in critically ill patients is highly variable.

In patients with severe sepsis or septic shock, dopamine increases cardiac index, largely because of an increase in stroke volume, but to a lesser extent by increasing heart rate.[33–43] Patients receiving dopamine at rates greater than 20 μg/kg/min show increases in right heart pressures and in heart rate, and doses should not usually exceed 20 μg/kg/min, at least not without adequate hemodynamic monitoring. Dopamine may be used when both cardiac output and blood pressure are low, a setting in which its vasopressor effect may be desirable. Concerns about extracardiac immunosuppressive effects[50,51] have limited enthusiasm for its use as a first-line inotropic agent.

Epinephrine

Epinephrine stimulates both α and β receptors. At low doses, the β-adrenergic effects predominate. Studies examining its hemodynamic effects in septic shock at doses ranging from 0.1 to 0.5 μg/kg/min have shown increases in cardiac index ranging from 24% to 54%.[73,74,76] This increase in oxygen delivery may be accompanied by metabolic effects,[58,72,76] the significance of which is uncertain in view of trials showing no difference in outcome between epinephrine and other catecholamines.[82,83] Epinephrine does seem to be more arrhythmogenic than other catecholamines.

Combination and Comparative Catecholamine Studies

Most studies investigating catecholamine combinations have been limited by lack of standardized infusion protocols, limiting the robustness of their conclusions. Patients who do not respond to dopamine with an increase in cardiac index may reach the desired end point with a dopamine-norepinephrine combination.[38] Epinephrine seems to be as good if not better at improving cardiac performance than dopamine or a dobutamine-norepinephrine combination.[58,76] In several studies, dopamine increased cardiac index and stroke volume index to a greater extent than norepinephrine but increases in left and right ventricular stroke volume index were about the same with the two agents, and tachycardia was less prominent with norepinephrine.[34,57]

Table 1
Consensus recommendations for vasopressor support in sepsis

#	ACCM Practice Parameters	Level	#	Surviving Sepsis Campaign	Level
	When fluid administration fails to restore an adequate arterial pressure and organ perfusion, therapy with vasopressor agents should be initiated. Vasopressor therapy may also be required transiently to maintain perfusion in the face of life-threatening hypotension, even when adequate cardiac filling pressures have not yet been attained.	None (text)	1	—	—
	Arterial cannulation should be performed in patients with shock to provide a more accurate measurement of intra-arterial pressure and to allow beat-to-beat analysis so that decisions regarding therapy can be based on immediate and reproducible blood pressure information.	None (basic principle)	6	All patients requiring vasopressors should have an arterial catheter placed as soon as practical if resources are available.	D
Vasopressors					
				Mean arterial pressure (MAP) be maintained above 65 mm Hg	C
1	Dopamine and norepinephrine are both effective for increasing arterial blood pressure. It is imperative to ensure that patients are adequately fluid resuscitated. Dopamine raises cardiac output more than norepinephrine, but its use may be limited by tachycardia. Norepinephrine may be a more effective vasopressor in some patients.	C	1	Norepinephrine or dopamine as the first-choice vasopressor agent to correct hypotension in septic shock (administered through a central catheter as soon as one is available).	C
2	Phenylephrine is an alternative to increase blood pressure, especially in the setting of tachyarrhythmias. Epinephrine can be considered for refractory hypotension, although adverse effects are common, and epinephrine may potentially decrease mesenteric perfusion.	D	2/3	Phenylephrine, epinephrine, or vasopressin not be administered as the initial vasopressor in septic shock. Epinephrine be the first alternative agent in septic shock that is poorly responsive to norepinephrine or dopamine.	C B

3	Administration of low doses of dopamine to maintain renal function is not recommended.	B	5	Low-dose dopamine not be used for renal protection.	A
5	Low doses of vasopressin given after 24 hours as hormone replacement may be effective in raising blood pressure in patients refractory to other vasopressors, although no conclusive data are yet available regarding outcome.	D	2	Vasopressin, 0.03 units, may be added to norepinephrine subsequently with anticipation of an effect equivalent to norepinephrine alone.	—
Inotropes					
1	Dobutamine is the first choice for patients with low cardiac index or low mixed venous oxygen saturation and an adequate mean arterial pressure following fluid resuscitation. Dobutamine may cause hypotension or tachycardia in some patients, especially those with decreased filling pressures.	C	1	A dobutamine infusion be administered in the presence of myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output.	C
2	In patients with evidence of tissue hypoperfusion, addition of dobutamine may be helpful to increase cardiac output and improve organ perfusion. A strategy of routinely increasing cardiac index to predefined "supranormal" levels (more than 4.5 L/min/m^2) has not been shown to improve outcome.	B	2	Use of a strategy to increase cardiac index to predefined supranormal levels is not recommended.	B
3	A vasopressor, such as norepinephrine, and an inotrope, such as dobutamine, can be titrated separately to maintain both mean arterial pressure and cardiac output.	C	—	—	—

Strength of recommendation levels: A, supported by at least two level I investigations; B, supported by only one level I investigation; C, supported only by level II investigations; D, supported by at least one level III investigation; E, supported only by level IV or level V investigations.
Strength of evidence: Level I, large, randomized trials with clear-cut results, low risk of false-positive (α) error or false-negative (β) error; Level II, small, randomized trials with uncertain results, moderate to high risk of false-positive (α) error or false-negative (β) error; Level III, nonrandomized, contemporaneous controls; Level IV, nonrandomized, historical controls and expert opinion; Level V, case series, uncontrolled studies, and expert opinion.

Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors increase intracellular cyclic AMP and have inotropic effects independent of β-adrenergic receptors. In view of recent data suggesting the potential for decreased myocardial adrenergic responsiveness in septic shock,[122] their use might be considered in some settings. Most of the available case series are confounded by concomitant use of adrenergic agents, but one small randomized trial of 12 pediatric patients was able to demonstrate increased cardiac output with milrinone in sepsis.[123] Phosphodiesterase inhibitors have vasodilatory effects that might exacerbate hypotension in sepsis, mandating caution in their use, especially given their relatively long half-lives. The decision to use this drug in septic shock patients to increase cardiac output is expected to increase vasopressor requirements.

Levosimendan

Levosimendan is a novel agent that increases cardiac myocyte calcium responsiveness and also opens ATP-dependent potassium channels, giving the drug both inotropic and vasodilatory properties. Levosimendan has been most extensively studied in acute heart failure, but given the potential role for abnormal calcium handling in sepsis-induced myocardial depression, its use also has been proposed in sepsis. Studies in animal models of endotoxin infusion have suggested that levosimendan can improve myocardial performance with relatively modest decreases in arterial pressure.[124] One clinical trial randomized 30 patients with septic shock and ejection fraction less than 45% to dobutamine or levosimendan, with norepinephrine used to maintain blood pressure.[125] Levosimendan improved ejection fraction, stroke volume, and cardiac index and also improved urine output and gastric mucosal PO_2 compared with dobutamine.[125] Another trial by the same group randomized 35 patients with septic shock and acute respiratory distress syndrome to levosimendan or placebo.[126] Levosimendan improved right ventricular performance, and mixed venous oxygen saturation also was improved, suggesting that its effects on cardiac function translated into a systemic effect.[126]

Levosimendan is not currently approved for use in the United States. Despite a reasonable rationale for its use, and some experimental data suggesting some beneficial effects, larger randomized trials with patient-centered end points, such as survival and length of stay, are needed before it can be considered for widespread use as an inotropic agent in sepsis.

COMPLICATIONS OF VASOPRESSOR THERAPY

All of the catecholamine agents can cause significant tachycardia, especially in patients who are inadequately volume resuscitated. In patients with significant coronary atherosclerosis, catecholamine-induced coronary artery constriction may precipitate myocardial ischemia and infarction; this is of particular concern in patients treated with vasopressin. In the presence of myocardial dysfunction, excessive vasoconstriction can decrease stroke volume, cardiac output, and oxygen delivery. Should this occur, the dose should be lowered, or the addition of an inotropic agent should be considered.[56] Excessive doses of vasopressors can also cause limb ischemia and necrosis.

Administration of vasopressor agents may potentially impair blood flow to the splanchnic system, and this can be manifested by stress ulceration, ileus, malabsorption, and even bowel infarction.[58,76] Gut mucosal integrity occupies a key position in the pathogenesis of multiple organ failure, and countercurrent flow in splanchnic microcirculation gives the gut a higher critical threshold for oxygen delivery than other

organs. It makes sense to avoid episodes of intramucosal acidosis, which might be detected either by a fall in gastric mucosal pHi or an increase in gastric mucosal P_{CO_2}. Whether to monitor these parameters routinely is less certain, because pHi or gastric P_{CO_2}-directed care has not been shown to reduce mortality in patients with septic shock in prospective randomized controlled trials.

At inotropic doses, catecholamines can trigger tachyarrythmias, including supraventricular tachycardias, atrial fibrillation, and ventricular tachycardia. The phosphodiesterase inhibitors and levosimendan also have the potential to produce hypotension, especially in patients with inadequate fluid resuscitation. As such, monitoring stroke volume and cardiac output with these agents, so as to obtain the desired therapeutic effect at the minimal dosage, is advisable. Patients in septic shock may manifest severe clinical manifestations of disseminated intravascular coagulation including loss of digits and extremities. These patients may also be on significant doses of vasopressors, leading to a false conclusion that the limb loss is caused by the vasopressors.

CONSENSUS RECOMMENDATIONS

Consensus recommendations regarding vasopressor support in patients with septic shock have been put forth by the American College of Critical Care Medicine[6] and the Surviving Sepsis campaign[11]; these recommendations differ more in wording than in substance, and are compiled in **Table 1**. The Surviving Sepsis campaign will likely amend the vasopressin section to take the VASST trial results under consideration.

SUMMARY

The ultimate goals of hemodynamic therapy in shock are to restore effective tissue perfusion and to normalize cellular metabolism. In sepsis, both global and regional perfusion must be considered. In addition, mediators of sepsis can perturb cellular metabolism, leading to inadequate use of oxygen and other nutrients despite adequate perfusion; one would not expect organ dysfunction mediated by such abnormalities to be corrected by hemodynamic therapy.

Despite the complex pathophysiology of sepsis, an underlying approach to its hemodynamic support can be formulated that is particularly pertinent with respect to vasoactive agents. Both arterial pressure and tissue perfusion must be taken into account when choosing therapeutic interventions and the efficacy of hemodynamic therapy should be assessed by monitoring a combination of clinical and hemodynamic parameters. It is relatively easy to raise blood pressure, but somewhat harder to raise cardiac output in septic patients. How to optimize regional blood and microcirculatory blood flow remains uncertain. Specific end points for therapy are debatable and are likely to evolve. Nonetheless, the idea that clinicians should define specific goals and end points, titrate therapies to those end points, and evaluate the results of their interventions on an ongoing basis remains a fundamental principle. The practice parameters were intended to emphasize the importance of such an approach so as to provide a foundation for the rational choice of vasoactive agents in the context of evolving monitoring techniques and therapeutic approaches.

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