

Vasoactive Drugs in Circulatory Shock

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Shock occurs when failure of the cardiovascular system compromises tissue perfusion. When fluid administration fails to restore adequate arterial pressure and organ perfusion in patients with shock, therapy with vasoactive agents should be initiated. The key to selecting among vasoactive agents is to make the choice in the context of the goals of therapy. The ultimate goals of hemodynamic therapy in shock are to restore effective tissue perfusion and to normalize cellular metabolism. The clinician needs to consider ways of achieving those goals and the mechanisms of action of potential therapies. Armed with this knowledge, it becomes easier to match the mechanism of action of a particular agent to the goals of therapy. When this is done, differences among various agents are seen primarily as differences in mechanisms of action, and discussions about which agent is “best” are transformed into consideration of which agent is best suited to implement the therapeutic strategy that has been selected in a given clinical context. Despite the complex pathophysiology of shock, use of vasoactive agents for hemodynamic support of patients with shock can be guided by an underlying approach in which clinicians define specific goals and end points, titrate therapies to those end points, and evaluate the results of their interventions on an ongoing basis.

Keywords: shock; vasopressor; inotropic; dopamine; norepinephrine

Shock is the syndrome that results from failure of the cardiovascular system to maintain adequate tissue perfusion (1). The initial priority is to maintain reasonable hemodynamics while the etiology of shock is identified and its pathogenesis is addressed. Hemodynamic therapy can be conceptualized in three broad categories: fluid resuscitation, vasopressor therapy, and inotropic therapy. Fluid resuscitation is usually the first step, but has been well described elsewhere (2), and is considered here only peripherally; this review focuses on use of vasoactive agents for patients with shock. When fluid administration fails to restore adequate arterial pressure and organ perfusion in patients with shock, therapy with vasoactive agents should be initiated. Although many vasoactive agents have both vasopressor and inotropic actions, a distinction is made on the basis of the intended goals of therapy; vasopressor actions raise blood pressure, whereas inotropic actions raise cardiac output. As becomes clear, this distinction should not minimize the importance of assessing the effects of vasoactive agents on perfusion.

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perfusion and to normalize cellular metabolism. The clinician needs to consider ways of achieving those goals and the mechanisms of action of potential therapies. Armed with this knowledge, it becomes easier to match the mechanism of action of a particular agent to the goals of therapy. When this is done, differences among various agents are seen primarily as differences in mechanisms of action, and discussions about which agent is “best” are transformed into consideration of which agent best addresses the physiological abnormalities in a given clinical context. It also becomes less surprising that trials of drugs per se do not often show big differences, because these trials often include heterogeneous populations with heterogeneity in the goals of therapy. Nonetheless, vasoactive therapy should be guided not only by mechanisms of actions but also by the best available clinical trial evidence.

The use of mechanisms of action to guide therapy can be illustrated with catecholamines as an example. Although debates about whether one catecholamine agent is superior to another can be enlightening in that they tend to highlight differences in pharmacology among the agents, sometimes the arguments tend to focus on the agents themselves when it is actually the therapeutic strategy that differs. Different catecholamine agents have different effects on α - and β -adrenergic receptors, as shown in Figure 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 Figure 2. Conceived in these terms, choosing among catecholamines in a given situation becomes a discussion more about effects than about agents, with the choice dictated by which agent is best suited to implement the therapeutic strategy selected. 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.

ASSESSMENT OF THERAPEUTIC GOALS

Although it is recognized that many vasoactive agents have both vasopressor and inotropic actions, distinction between the two is useful for the purpose of defining goals and end points of therapy. The end point of vasopressor therapy is arterial pressure, and restoration of adequate pressure is the criterion of effectiveness, but blood pressure does not always equate to blood flow. The end point of inotropic therapy is increased cardiac output, but how to determine whether cardiac output is adequate in patients with shock remains a thorny problem. Despite the complex pathophysiology of shock, an underlying approach to its hemodynamic support can be formulated that takes both pressure and perfusion into account when choosing therapeutic interventions.

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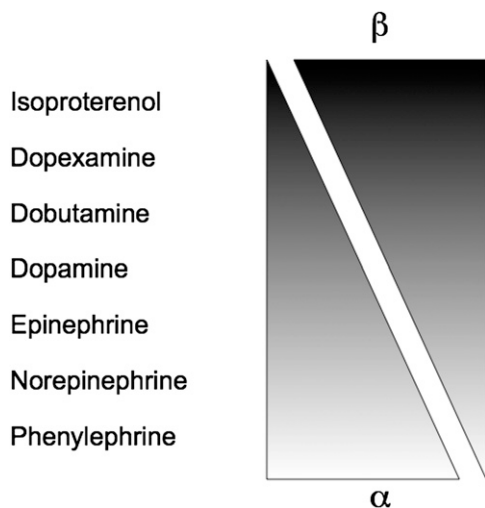


Figure 1. α -Adrenergic and β -adrenergic effects of vasoactive catecholamines. Adapted by permission from Reference 95.

Tissue hypoperfusion in shock may result not only from decreased perfusion pressure attributable to hypotension but also from abnormal **shunting** of blood flow within organs (1, 3). Cellular alterations resulting in inability to use delivered substrate appropriately may also **occur** (4). Such alterations would not be expected to respond to therapies aimed at global hemodynamics. Thus, defining the adequacy of resuscitation requires attention to both **global** and **regional** perfusion. In addition, measuring the determinants of perfusion, that is, perfusion pressure and flow, is **more straightforward** than assessing the **adequacy** of perfusion.

Bedside clinical assessment provides a good indication of the adequacy of global perfusion. Indications of insufficient perfusion include oliguria, clouded sensorium, delayed capillary refill, and cool skin. Some **caution** is necessary in interpreting these signs, 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** may result **from global hypoperfusion** or **from cellular metabolic** alterations that may

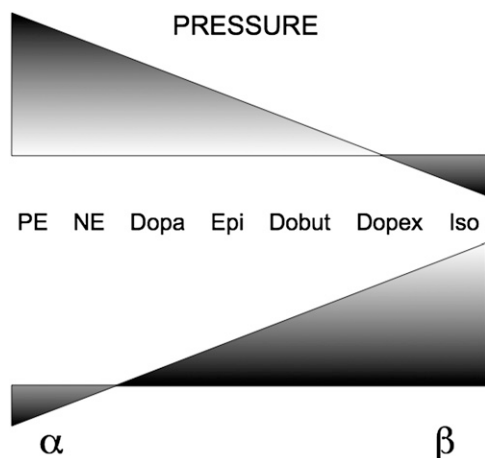


Figure 2. Effects of vasoactive catecholamines on pressure and blood flow. Dobut = dobutamine; Dopa = dopamine; Dopex = dopexamine; Epi = epinephrine; Iso = isoproterenol; NE = norepinephrine; PE = phenylephrine. Adapted by permission from Reference 95.

or **may not** represent tissue **hypoxia** (5), but its **prognostic** value, particularly the utility of trending lactate concentrations, has been **well established** (6–8). Mixed venous oxyhemoglobin saturation reflects the balance between oxygen delivery and consumption. Low values indicate increased oxygen extraction and therefore potentially incomplete resuscitation. **One study showed** that monitoring of **central venous oxygen saturation** can be a **valuable guide to early resuscitation** (9). The correlation between central venous oxygen saturation and mixed venous oxyhemoglobin saturation is reasonable (10), but may not always be reliable (11).

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 (12). In sepsis, measurements of oxygen saturation in the hepatic vein have revealed oxygen desaturation in a subset of patients, suggesting that **hepatosplanchnic** oxygen supply may be **inadequate** in some patients, **even** when more global parameters appear **adequate** (13). Direct visualization of the sublingual circulation has shown microcirculatory perturbation in patients with cardiogenic (14) and septic shock (15). These techniques are better measures of the degree of microcirculatory perfusion than its adequacy, but changes appear to track the clinical course (16, 17). **Sublingual capnometry** correlates with microcirculatory findings (18), and other techniques under investigation, such as near-infrared spectroscopy, may potentially address the adequacy of microcirculatory flow.

Hemodynamic therapies for shock are usually (and appropriately) targeted at the determinants of perfusion. It is important to supplement those assessments with clinical and other parameters indicative of the adequacy of perfusion.

GENERAL APPROACH

Shock can be categorized by underlying pathophysiology as hypovolemic, cardiogenic, **extracardiac obstructive**, or **distributive**, a **classification** that is useful because it has therapeutic implications (19). In hypovolemic, cardiogenic, and extracardiac obstructive shock, decreased tissue perfusion results primarily **from inadequate cardiac output**. In distributive shock, perfusion defects relate to **both** hypotension resulting from decreased systemic vascular resistance and **maldistribution** of blood flow.

For hypovolemic, obstructive, and distributive shock, fluid resuscitation is the first step in management. **Fluid administration** should be considered **even in cardiogenic shock** resulting from myocardial infarction; patients are commonly diaphoretic, and relative hypovolemia may be present (20). Resuscitation should be early and vigorous. An integrated approach directed at rapidly restoring systemic oxygen delivery and improving tissue oxygenation has been demonstrated to improve survival significantly in septic shock (9). Although the specific approach that is used may vary, there are critical elements that should be incorporated in any resuscitative effort. Therapy should be titrated to clinical end points of volume repletion and guided by parameters that reflect the adequacy of tissue and organ perfusion. Systemic oxygen delivery should be supported by ensuring arterial oxygen saturation, maintaining adequate levels of hemoglobin, and by using vasoactive agents directed to physiological and clinical end points.

A useful concept to guide fluid resuscitation is the concept of **preload responsiveness**. Preload is a key component of myocardial function and represents the load present before contraction has started. Preload is provided by venous return and can be manipulated by fluid resuscitation. From a therapeutic standpoint, however, what is important is not so much preload as

preload responsiveness, which represents the degree to which stroke volume can be improved by fluid administration (21). Full consideration of methods to assess preload responsiveness is beyond the scope of this review, but the key concept is that fluid challenges should be administered, with preference given to dynamic assessment of response to those challenges over reliance on static parameters that reflect either pressure or volume at only one time point (2, 21).

In shock states, estimation of blood pressure with a cuff, especially an automated measurement system, may be inaccurate. Use of an arterial cannula provides a more appropriate and reproducible measurement of arterial pressure (22, 23) and also allows beat-to-beat analysis so that decisions regarding therapy can be based on immediate and reproducible blood pressure information (1).

Although patients with shock and mild hypovolemia may be treated successfully with rapid fluid replacement alone, hemodynamic monitoring is often useful to provide a diagnostic hemodynamic assessment in patients with moderate or severe shock, one that may lead to reassessment of either the underlying etiology or of the therapeutic strategy. In addition, because hemodynamics can change rapidly, and because noninvasive evaluation is frequently incorrect in estimating filling pressures and cardiac output, hemodynamic monitoring is commonly useful to assess the response to therapeutic interventions.

VASOPRESSORS

When fluid administration fails to restore adequate arterial pressure and organ perfusion, therapy with vasopressor agents should be initiated (23). Vasopressor therapy may be required even while cardiac filling pressures are not yet adequate, to maintain perfusion in the face of life-threatening hypotension. Potential vasopressors include norepinephrine, dopamine, epinephrine, phenylephrine, and vasopressin. Table 1 summarizes the relative potency of the cardiac and peripheral vascular effects of various vasoactive agents. The principal use of vasopressor agents is in vasodilatory shock, the most common cause of which is sepsis, but they may be needed in other forms of shock as well. In cardiogenic shock, hypotension may exacerbate myocardial ischemia by reducing the driving force for coronary perfusion, and vasopressors may be administered to maintain adequate coronary perfusion pressure. In other forms, such as hypovolemic and obstructive shock, vasopressors may be used to temporize and maintain perfusion pressure until definitive therapy is accomplished.

Arterial pressure is the end point of vasopressor therapy, and the restoration of adequate pressure is thus the criterion of effectiveness. Below a certain blood pressure, autoregulation in vascular beds is compromised, and flow is dependent on pressure. Loss of autoregulation can occur at different levels in different organs, however, and the degree to which patients with shock retain intact autoregulation is uncertain. Some patients (especially those with preexisting hypertension) may require higher blood pressures to maintain adequate perfusion. The precise blood pressure goal to target in septic shock remains uncertain. Animal studies suggest that below a mean arterial pressure of 60 mm Hg, autoregulation is compromised in the coronary, renal, and central nervous system vascular beds (24, 25). In sepsis, guidelines recommend that mean arterial pressure (MAP) should be maintained above 60 mm Hg (23) or 65 mm Hg (26), and several randomized trials that increased MAP to 75 or 85 mm Hg in patients with septic shock found no significant differences in metabolic variables or renal function (27, 28). There are no data from randomized clinical trials that demonstrate that failure to maintain MAP at 60–65 mm Hg

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 the scenario of hypotension with shock that merits vasopressor support. As noted previously, it is important to support end points such as blood pressure with assessment of the adequacy of perfusion.

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 (29, 30). Filling pressures are either unchanged (29, 31) or modestly increased (1–3 mm Hg) (32–36).

Norepinephrine is a potent vasoconstrictor when titrated to effect. The range of doses required is wide (from 0.01 to 3.3 $\mu\text{g/kg/min}$) (30, 31, 34, 35, 37), possibly due to down-regulation of α -receptors in some settings (38). Its vasoconstrictive effects have the potential to decrease renal, splanchnic, or peripheral blood flow, particularly in patients who are not adequately volume resuscitated (23). Nonetheless, most studies have found that norepinephrine can increase blood pressure in patients with septic shock without causing deterioration of the cardiac index and organ function (39, 40).

Randomized data comparing norepinephrine with other catecholamines have previously been limited to one small trial in which norepinephrine was compared with dopamine in 32 volume-resuscitated septic patients, and proved better at achieving and maintaining normal hemodynamic and oxygen transport parameters (36). A more recent multicenter trial randomized 1,679 patients with shock to either dopamine or norepinephrine as first-line therapy, and found no significant difference in the primary end point of 28-day mortality (41). Interestingly, in a prespecified analysis of patients by etiology of shock, mortality was lower with the use of norepinephrine than dopamine in the subgroup of patients with cardiogenic shock (41). These data are likely to remain the definitive comparison between these two agents for some time, and suggest that norepinephrine should be regarded as a first-line vasopressor for patients with shock.

Dopamine

Dopamine, the natural precursor of norepinephrine and epinephrine, has distinct dose-dependent pharmacological effects. At doses less than 5 $\mu\text{g/kg/minute}$, dopaminergic receptors are activated, leading to vasodilation in the renal and mesenteric beds (42). At doses of 5 to 10 $\mu\text{g/kg/minute}$, β_1 -adrenergic effects predominate, increasing cardiac contractility and heart rate. At doses above 10 $\mu\text{g/kg/minute}$, 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 due to an increase in stroke volume, and to a lesser extent to an increase in heart rate (32, 35, 36). Effects on splanchnic perfusion have been mixed (32, 35, 43, 44). Low doses of dopamine increase renal blood flow and the 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 $\mu\text{g/kg/min}$) or placebo (45). No difference was found in either the primary outcome (peak serum creatinine), other renal outcomes, survival, or hospital stay.

TABLE 1. RELATIVE POTENCY OF COMMONLY USED VASOACTIVE AGENTS

	Dose	Cardiac		Peripheral Vasculature		
		Heart Rate	Contractility	Vasoconstriction	Vasodilation	Dopaminergic
Norepinephrine	2–40 µg/min	+	++	++++	0	0
Dopamine	1–4 µg/kg/min	+	+	0	+	++++
	4–20 µg/kg/min	++	++–+++	++–+++	0	++
Epinephrine	1–20 µg/min	++++	++++	++++	+++	0
Phenylephrine	20–200 µg/min	0	0	+++	0	0
Vasopressin	0.01–0.03 U/min	0	0	++++	0	0
Dobutamine	2–20 µg/kg/min	++	+++–++++	0	++	0
Milrinone	0.375–0.75 µg/kg/min	+	+++	0	++	0
Levosimendan	0.05–0.2 µg/kg/min	+	+++	0	++	0

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Observational cohort studies examining mortality after dopamine administration have been conflicting. Dopamine use was associated with increased mortality in patients with shock in an observational cohort study of 198 European intensive care units (ICUs), and remained a significant predictor after multivariate analysis (46). On the other hand, another, similarly sized observational cohort of 17 Portuguese ICUs showed decreased mortality in patients with septic shock treated with dopamine compared with norepinephrine, a finding that also persisted after multivariate analysis (47). These observational studies have known limitations. A large randomized trial comparing dopamine with norepinephrine showed no difference in overall mortality, although more arrhythmic events occurred in patients treated with dopamine (41). The propensity for tachycardia and arrhythmias is common to all catecholamines, but appears to be more prominent with dopamine than some other agents such as norepinephrine or phenylephrine. With the use of dopamine there is also concern about the potential for decreased prolactin release, lymphocyte apoptosis, and consequent immunosuppression (48, 49).

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 the cardiac index and peripheral vascular tone (50–53). Epinephrine increases oxygen delivery, but oxygen consumption may be increased as well (51–55). Lactate levels can be increased, although the degree to which this results from excess vasoconstriction and compromised perfusion or increased metabolic lactate production is not entirely certain (37, 51, 55).

The chief concern with the use of epinephrine in sepsis is the potential to decrease regional blood flow, particularly in the splanchnic circulation (37, 56–58). In a study of patients with severe septic shock, epinephrine increased global oxygen delivery and consumption but caused lower absolute and fractional splanchnic blood flow and lower indocyanine green clearance, thus suggested that epinephrine may affect the splanchnic circulation (40). Another group has reported improved gastric mucosal perfusion with epinephrine compared with a norepinephrine–dobutamine combination (59), but subsequently the same group reported superiority of a norepinephrine–dopexamine combination over epinephrine (60).

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 (61). Another fairly large (n =

330) randomized clinical trial compared epinephrine with norepinephrine with or without dobutamine, with the drugs titrated to maintain a mean arterial pressure above 70 mm Hg and a cardiac index above 2.5 L/minute, in patients with septic shock (62). Metabolic abnormalities were transient in this trial, and no patients were withdrawn for this reason. There was no significant difference between epinephrine and norepinephrine–dobutamine in time to hemodynamic success, vasopressor withdrawal, and either 28-day, ICU, or hospital mortality.

Epinephrine can increase blood pressure in patients unresponsive to traditional agents. It increases the 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 (23).

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, but there are concerns about its potential to reduce cardiac output.

Phenylephrine can raise blood pressure in patients with vasodilatory shock, although trial data are fairly sparse. 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 (63). 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. 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 (64). The limited information available for phenylephrine suggests that this drug can increase blood pressure modestly in fluid-resuscitated patients with septic shock, but studies with hard end points are lacking, and so phenylephrine is regarded as a second-line agent in this setting. Phenylephrine can be useful in other settings of systemic vasodilation, including spinal shock and vasoplegia after cardiac bypass, which is associated with both protamine administration and previous angiotensin-converting enzyme therapy. Phenylephrine, either in addition to other agents or as an alternative, may also be a good option when tachyarrhythmias limit therapy with other vasopressors.

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 via V_1 receptors and also increases responsiveness of the vasculature to catecholamines (65, 66). Vasopressin may also increase blood pressure by inhibition of vascular smooth muscle nitric oxide production and K^+ -ATP channels (66).

Normal levels of vasopressin have little effect on blood pressure under physiological conditions (65), but vasopressin helps maintain blood pressure during hypovolemia (67), and seems to restore impaired hemodynamic mechanisms and also inhibit pathological vascular responses in shock (66). Increased levels of vasopressin have been documented in hemorrhagic shock (68), 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 (69), which results from depletion of pituitary stores (70), possibly in conjunction with impaired synthesis. A 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 (71).

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 (72–74), and initiation of vasopressin decreases catecholamine requirements (75, 76). Similar data are available for terlipressin, a synthetic vasopressin analog (77). There is concern, however, that vasopressin infusion in septic patients at high doses may either decrease splanchnic perfusion or redistribute blood flow away from the splanchnic mucosa (78, 79).

A multicenter clinical trial (Vasopressin and Septic Shock Trial, VASST) randomized 776 patients with pressor-dependent septic shock to vasopressin (0.03 U/min) or norepinephrine (15 μ g/min) in addition to their original vasopressor infusion (80). The primary end point was 28-day mortality; a prespecified subgroup analysis was done on patients with less severe (NE, 5–14 μ g/min) and more severe (NE, >15 μ g/min) septic shock. For the group as a whole, there was no difference in mortality, but vasopressin appeared to be better in the subgroup with less severe septic shock (80).

Vasopressin (0.03 U/min) added to norepinephrine appears to be as safe and effective as norepinephrine in fluid-resuscitated patients with septic shock, and may be more effective in patients receiving lower doses of norepinephrine than when started as rescue therapy. In this context, vasopressin should be thought of as replacement therapy for relative deficiency rather than as a vasopressor agent to be titrated to effect, and should be used only at low doses. What to do for patients with high vasopressor requirements despite vasopressin infusion remains uncertain.

Complications of Vasopressor Therapy

All of the catecholamine vasopressor agents can cause significant tachycardia, especially in patients who are inadequately volume resuscitated. Tachyarrhythmias can occur as well. In patients with significant coronary atherosclerosis, vasopressor-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 of vasopressor should be lowered, or the addition of an inotropic agent such as dobutamine should be considered (30). Excessive doses of vasopressors can also cause limb ischemia and necrosis.

Administration of vasopressors may potentially impair blood flow to the splanchnic bed, and this can be manifested by stress ulceration, ileus, malabsorption, and even bowel infarction (37, 55). 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. This, it makes sense to avoid episodes of intramucosal acidosis, which might be detected by either a fall in gastric mucosal pH (pHi) or an increase in gastric mucosal PCO_2 , if possible. Whether to monitor these parameters routinely is less certain, as pHi- or gastric PCO_2 -directed care has not been shown to reduce mortality in prospective controlled trials.

INOTROPES

Inotropic therapy is used to refer to pharmacological treatment aimed at improving myocardial contractility and thus increasing cardiac output. The effects of inotropic therapy are best monitored by measuring responses of cardiac output, something both easier and more relevant than assessing contractility, because flow is one of the determinants of perfusion. The challenge in titrating therapy to cardiac output is to determine when that output is adequate. Because of the complexity of assessment of clinical parameters in patients with shock, direct measurement of cardiac output in patients receiving inotropic therapy is advisable, but other end points of global perfusion should be monitored as well. 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.

Although many of the catecholamine agents have both vasopressor and inotropic effects, it is conceptually useful for the clinician to define their intended use in one or both of these categories. It should be recognized, however, that pressure is proportional to flow divided by resistance, and so if vascular resistance does not change, then an increase in cardiac output will produce an increase in blood pressure. In practice, sorting out inotropic from vasopressor effects may require careful hemodynamic assessment, something that can clarify a complex clinical situation.

In cardiogenic shock, impaired tissue perfusion is indicative of inadequate cardiac output, and so initiation of inotropic therapy is usually warranted until the underlying cause can be addressed. As noted previously, vasopressor therapy may also be needed in some situations to maintain coronary perfusion pressure, which can be accomplished by either using one agent with both vasopressor and inotropic properties, or by adding a vasopressor to an inotrope. In other forms of shock the indications for inotropic therapy are less clear-cut. Myocardial dysfunction occurs in a subset of patients with septic shock, but cardiac output is usually preserved by ventricular dilation and tachycardia (81). In this setting, more is known about what not to do than what to do. It is clear that routinely increasing cardiac output to predetermined “supranormal” levels in all patients does not improve outcomes (23, 82, 83). Some patients, however, may have improved tissue perfusion with inotropic therapy aimed at increasing oxygen delivery. Monitoring the response of indices of perfusion to measured increases in

cardiac output is the best way to surmount the challenge of identifying these patients (23).

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 via stimulation of β_1 receptors, with a variable effect on blood pressure. Dobutamine increases cardiac output by increasing both contractility and heart rate, to a different extent in different patients.

In cardiogenic shock, dobutamine is the initial agent of choice in patients with a low-output syndrome with reasonable blood pressure (84). Dobutamine may improve blood pressure in some hypotensive patients, but this response is unreliable, as dobutamine is an inotrope but not a vasopressor. Norepinephrine or dopamine, either as an alternative or added to dobutamine, may be preferable in this setting. Dobutamine increases heart rate and thus myocardial oxygen demand, which can exacerbate ischemia in patients with cardiogenic shock; hemodynamic monitoring can help titrate dosages to maximize effect while minimizing toxicity.

Dobutamine is also the first-line inotropic agent for the relatively small subset of patients with septic shock and low cardiac output in the presence of adequate filling pressures (23, 85). 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. Addition of dobutamine to norepinephrine can increase both cardiac output and blood pressure in this setting.

Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors increase intracellular cyclic AMP and thus have inotropic effects independent of β -adrenergic receptors. They also tend to have fewer chronotropic and arrhythmogenic effects than catecholamines, but increases in cyclic AMP in vascular smooth muscle cells can cause vasodilation, which can exacerbate hypotension.

Milrinone has been used to treat acute heart failure. Its use in this setting is most logical in systolic heart failure when hypoperfusion is compromising organ function, and some patients will respond with increased perfusion. Milrinone has the potential to cause hypotension, and so most clinicians eschew a loading dose in patients with marginal blood pressure. Registry data, however, suggest that milrinone is not always used in this fashion (86). The OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) trial compared milrinone with digoxin in patients without evidence of inadequate end-organ perfusion, on the theory that increasing cardiac output would result in more rapid resolution of symptoms and facilitate institution of neurohormonal therapies, thus decreasing length of stay and rehospitalization (87). It does not seem surprising that there were no benefits with the use of milrinone in this study. Both arrhythmias and the incidence of hypotension were increased, and subsequent analysis suggested worsened outcomes in patients with ischemic cardiomyopathy, although patients with shock were not included in the OPTIME-CHF trial (88). In cardiogenic shock, milrinone is usually considered only after other agents have proven ineffective, because it has a long half-life and the potential to worsen hypotension (20). Milrinone is a more potent pulmonary vasodilator than dobutamine, and so is often preferred in cases of predominant right heart failure.

Data concerning the use of milrinone in other forms of shock are sparse. In septic shock, case series are usually 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 (89).

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 does not appear to increase myocardial oxygen consumption, and has been most extensively studied in acute heart failure. Several relatively small studies have shown hemodynamic benefits with levosimendan in cardiogenic shock after myocardial infarction (90), one suggesting a better hemodynamic effect than dobutamine (91), but survival benefits with the use of levosimendan have not been shown in either cardiogenic shock or acute heart failure (92). Levosimendan has the potential to cause hypotension and thus should be used with some caution in patients with cardiogenic shock, but the current data suggest that it is no worse than dobutamine, and there is as much or more evidence for its safety and efficacy as for any other intravenous inotropic or vasodilator agent.

Given the potential role for abnormal calcium handling in sepsis-induced myocardial depression, use of levosimendan has been proposed in septic shock as well. In a clinical trial randomizing 30 patients with septic shock and ejection fraction less than 45% to dobutamine or levosimendan, with norepinephrine used to maintain blood pressure, levosimendan improved ejection fraction, stroke volume, and cardiac index, and also improved urine output and gastric mucosal perfusion compared with dobutamine (93). Another trial by the same group randomized 35 patients with septic shock and acute respiratory distress syndrome to levosimendan or placebo (94). Levosimendan improved right ventricular performance, and mixed venous oxygen saturation was improved as well, suggesting that its effects on cardiac function translated into a systemic effect.

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 will be needed before it can be considered for widespread use as an inotropic agent.

Complications of Inotropic Therapy

All of the catecholamine vasopressor agents can cause significant tachycardia, with the potential to precipitate or exacerbate ischemia. At inotropic doses, catecholamines can trigger tachyarrhythmias, 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.

CONCLUSIONS

The ultimate goals of hemodynamic therapy in shock are to restore effective tissue perfusion and to normalize cellular metabolism. The pathophysiology of organ dysfunction in shock is complex; some cellular abnormalities can result in inadequate use of oxygen and other nutrients despite adequate perfusion, and one would not expect organ dysfunction mediated by such abnormalities to be corrected by hemodynamic therapy. It is easier to raise blood pressure than cardiac output, and how to optimize regional blood and microcirculatory blood flow remains uncertain.

Despite this complexity, use of vasoactive agents for hemodynamic support of patients with shock can be guided by an underlying approach that takes both arterial pressure and tissue perfusion into account when choosing therapeutic interventions. The efficacy of hemodynamic therapy should be assessed by monitoring a combination of clinical and hemodynamic parameters. 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.

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