

Use of vasopressor agents in critically ill patients

John A. Kellum, MD, and Michael R. Pinsky, MD

Distributive shock is a common problem in intensive care. Systemic hypotension is a medical emergency and will cause end-organ injury if not reversed. There are relatively few medications available to treat distributive shock. Catecholamines are most widely used for this indication and work by stimulating α - and/or β -adrenergic receptors. Vasopressin and corticosteroids may have a role in reversing refractory shock and work primarily through nonadrenergic mechanisms. Shock is difficult to define using hemodynamic criteria, because the same hemodynamic values can be normal in one patient, yet represent shock in another. Thus, the appropriate therapeutic endpoints for vasopressor therapy are not uniform for all patients. Similarly, the available evidence comparing vasopressor agents in terms of safety and efficacy is limited. When used at doses necessary to reverse distributive shock, less potent vasoconstrictors (eg, dopamine) do not appear to be safer than more potent ones (eg, norepinephrine) and do not appear to be as effective. *Curr Opin Crit Care* 2002, 8:236–241 © 2002 Lippincott Williams & Wilkins, Inc.

Departments of Anesthesiology and Critical Care Medicine and Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA.

Correspondence to John A. Kellum, MD, 606c Scaife Hall, Division of Critical Care Medicine, 3550 Terrace St, Pittsburgh, PA 15261, USA; e-mail: kellumja@ccm.upmc.edu

Current Opinion in Critical Care 2002, 8:236–241

Abbreviations

MAP mean arterial pressure
Pco₂ partial pressure of carbon dioxide

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Pathophysiology of shock

Systemic hypotension is a medical emergency. Sustained acute hypotension–induced end-organ ischemia can cause cerebral infarction and myocardial failure if not reversed. Vasopressor agents are used clinically in the treatment of arterial hypotension in shock states. *Shock* is best defined as inadequate blood flow to meet the metabolic needs of the tissues. The most common reasons for shock are (1) the cardiac output is low relative to the global demand, despite increased O₂ extraction by the tissues; or (2) perfusion pressure is inadequate such that blood flow distribution to metabolically active tissues is inadequate, despite an otherwise adequate cardiac output. Thus, ineffective tissue blood flow—not absolute cardiac output or perfusion pressure—defines shock. Accordingly, the treatment of shock must focus not merely on maintaining a given arterial blood pressure or cardiac output but on tissue blood flow. In this regard, the physician has a few pharmacologic options available to achieve this goal, all of which have their specific strengths and weaknesses. Their use should be based on the known mechanisms of action of these drugs and the underlying mechanism inducing and sustaining the shock state.

Cardiac output is determined by left ventricular stroke volume and heart rate. Stroke volume is determined by venous return and ventricular function. Venous return may be decreased as a result of inadequate circulatory volume (*ie*, hypovolemic shock); loss of vascular tone (vasomotor shock); or, less commonly, increased extracardiac pressure (*eg*, positive intrathoracic pressure, tamponade). Ventricular function may be abnormal as a result of decreased ventricular muscle function to valvular dysfunction or to outflow obstruction (*eg*, pulmonary embolism) [1]. Importantly, myocardial dysfunction can be caused by low coronary perfusion (*eg*, coronary artery disease or profound hypotension), drugs, metabolic disturbances, or structural changes (*eg*, myocardial infarction, fibrosis).

Under normal conditions, if cardiac output should decrease independent of metabolic demands, then peripheral vasomotor tone increases via baroreceptor reflex arcs to maintain constant mean arterial pressure (MAP). Usually, this results from a combined α - (increased tone) and β -adrenergic (tachycardia and increased inotropy) response classically seen in hemorrhagic shock [2]. Tissue blood flow may be impaired for reasons other than reduced cardiac output. Shock often exists despite a nor-

mal or even increased cardiac output. Because the primary mechanism by which local blood flow increases is local vasodilation, it is axiomatic that this mechanism will only be effective if perfusion pressure is adequate to allow an increase in flow. Although most organs normally attempt to maintain a constant blood flow by inversely altering their vasomotor tone to changes in MAP, flow becomes pressure-limited below some minimal pressure. Thus, hypotension alone impairs auto-regulation of blood flow distribution. Furthermore, in many systemic disease states, a generalized inflammatory response develops that activates the synthesis of inducible nitric oxide synthase in the vascular endothelium, causing a nitric oxide-induced generalized vasodilation [3]. This condition, which includes septic shock, pancreatitis, and severe burns, is referred to as distributive shock. In this condition, arterial vasomotor tone decreases, and, thus, arterial pressure is less for the same cardiac output. Because, in systemic hypotension, all vascular beds are perfused in a pressure-dependent fashion and not primarily because of their metabolic requirements, regional blood flow is impaired relative to metabolic demand. The net effect is an initial decrease in both arterial pressure and cardiac output (because of an increase in total vascular capacitance) and, following fluid resuscitation, a hyperdynamic, hypotensive state (resulting from a combined increase in venous return and reduced left ventricular afterload). The maldistribution of blood flow associated with the increase in cardiac output and impaired regulation of blood flow distribution results in a reduced O_2 extraction and an increase in venous oxygen saturation. Thus, vasopressors are often needed for the treatment of hypotensive distributive shock.

Importantly, pressure-dependent vascular beds with minimal α -adrenergic receptors, such as in the cardiac and cerebral circulation, will increase blood flow if arterial pressure is increased by pharmacologic means. Similarly, other vital visceral beds, such as the gut and kidney, that can vasoconstrict in response to α -adrenergic stimulation usually increase their flow in response to α -adrenergic receptor-induced increased MAP as long as the pressure increases to some minimal level. However, increasing vasomotor tone even further will often result in vasoconstrictor-induced gut ischemia and renal hypoperfusion. Thus, two primary principals of vasopressor management emerge from these considerations: (1) maintaining at least a minimal MAP is imperative in insuring vital organ blood flow; and (2) excessive vasopressor therapy, although occasionally necessary to sustain cardiac and cerebral blood flow, may compromise vital visceral organ blood flow.

Pharmacotherapy for shock

There are relatively few medications available to treat distributive shock. Catecholamines are used primarily for this indication and work by stimulating α - and/or β -ad-

renergic receptors. Vasopressin and corticosteroids may have a role in reversing refractory shock and work primarily through nonadrenergic mechanisms.

Catecholamines reverse shock through their effects on inotropy (β -adrenergic receptors), vasoconstriction (α -adrenergic receptors), or both. Catecholamines vary in the degree to which they stimulate α - and β -adrenergic receptors. Table 1 summarizes the differential effects of common catecholamines on adrenergic receptors. Given these effects, norepinephrine, epinephrine, phenylephrine, and dopamine are all considered to be vasopressors. However, in order of potency, epinephrine, dopamine, and norepinephrine are all inotropic agents as well. Given the complex hemodynamic effects of sepsis, a combination vasopressor-inotropic agent would seem beneficial, but little comparative data exist. In this review, four aspects of catecholamine therapy for distributive shock will be discussed.

- (1) The therapeutic goal of resuscitation in distributive shock is to maintain adequate organ perfusion, not pressure or total blood flow.
- (2) Increasing perfusion pressure by a balanced increase in circulating blood volume and vasopressor therapy is the primary mechanism for increasing organ blood flow.
- (3) When all other vasopressors fail, use epinephrine.
- (4) "Renal dose" dopamine has no place in the management of patients in shock.

The use of vasopressin and steroids as adjuncts to catecholamine therapy will also be discussed.

Global and regional perfusion

Because tissue blood flow is difficult to measure, shock is difficult to define using hemodynamic criteria. The same hemodynamic values can be normal in one patient, yet represent shock in another. For example, a MAP of 65 mm Hg may define severe hypotension in a patient with long-standing untreated hypertension, whereas it may be above resting baseline in a well-conditioned athlete. Similarly, a cardiac index of 2.0 L/min/m² would be very low in this same athlete during exercise, yet it would represent "normal" function for many elderly patients

Table 1. Relative effects of common vasoactive medications on adrenergic receptors

Agent (typical dosages)	β -1	β -2	α -1
Isoproterenol (0.01–0.1 μ g/kg/min)	+++	+++	O
Norepinephrine (0.05–1 μ g/kg/min)	++	O	+++
Epinephrine (0.05–2 μ g/kg/min)	+++	++	+++
Phenylephrine (0.5–5 μ g/kg/min)	O	O	+++
Dopamine* (1–20 μ g/kg/min)	+(+++)	+	+(+++)
Dobutamine (2.5–20 μ g/kg/min)	+++	+	+

*Dopamine effects at "high-dose," which are typically greater than 3 to 5 μ g/kg/min, are shown in parentheses. O, no effect; +, minimal effect; ++, moderate effect; +++, substantial effect.

with mild to moderate left ventricular dysfunction. Markers of cellular metabolism (*eg*, lactate) and organ function are often used as surrogates for the adequacy of tissue blood flow, because the consequence of shock is cellular injury. Unfortunately, there are no indices specific to shock, and organ dysfunction and derangement in cellular metabolism may occur (particularly in sepsis) in the absence of tissue blood flow abnormality. Markers of regional perfusion, such as urine output and gastric mucosal partial pressure of carbon dioxide (PCO₂), have not yet been shown to be superior to markers of global perfusion. Urine output is affected by numerous physiologic conditions and pharmacologic agents, which limit its positive and negative predictive value as a measure of renal perfusion. Gastric tonometry–derived measures of mucosal PCO₂ show promise as accurate markers of mesenteric perfusion. However, the specific operating characteristics (*eg*, sensitivity, specificity) in patients with distributive shock have yet to be determined, and at least one recent study demonstrated that changes in gastric tonometric measures did not follow changes in splanchnic regional blood flow in postoperative surgical patients [4•]. Thus, it appears that the integration of physical examination findings (*eg*, delayed capillary refill, oliguria, confusion), hemodynamic variables (*eg*, MAP, cardiac index, mixed venous oxygen saturation), and metabolic parameters (*eg*, arterial base excess, lactate, glucose) reflects the present-day approach to diagnose shock and monitor its response to therapy. Unfortunately, physical examination findings alone are insensitive in the diagnosis of shock and poorly predict circulating blood volume. Many patients will require invasive hemodynamic monitoring to classify the cause of shock and to assure adequacy of treatment.

If sustaining blood flow to regional vascular beds in distributive shock may require excessive blood flow to less metabolically active tissues, should total blood flow be increased to supraphysiologic levels? Early studies suggested that the answer to this question might be yes [5,6], whereas the results of recent, large, randomized clinical trials have clearly demonstrated that hyperresuscitation of critically ill patients (*eg*, to achieve a cardiac index > 4.5 L/min/m²) is not only not associated with improved outcome [7] but may actually increase mortality [8]. Presumably, the increase in mortality is related to the side effects of the resuscitative efforts, which usually include the infusion of very high doses of catecholamines. This observation may even be the cause of the observed increased mortality from the use of the pulmonary artery catheter in one recent observational cohort study [9].

Increasing perfusion pressure

Perfusion pressure is a function of total flow and vasomotor tone. In distributive shock, venous pooling of blood and capillary leak result in an initial and continu-

ing intravascular fluid requirement. Although fluid resuscitation alone often restores perfusion pressure in mild distributive shock, its primary role is to sustain cardiac output. Thus, fluid resuscitation should be targeted to a specific cardiac output or left ventricular preload rather than to a specific MAP. Because vasopressors also decrease peripheral vascular capacitance, they can transiently increase cardiac output in hypovolemic states while reducing blood flow to some tissues (especially the kidney and the gut). Thus, vasopressor therapy should not be instituted unless circulating blood volume is deemed adequate. Realistically, in the profoundly hypotensive patient, combined vasopressor therapy and fluid resuscitation are simultaneously used. In general, vasopressor management is indicated to sustain a MAP greater than 60 to 65 mm Hg in the fluid resuscitated patient to sustain blood flow regulation [10•]. However, certain caveats are important. Patients with atherosclerotic disease and patients with longstanding hypertension may need higher levels of MAP to maintain pressure-independent flow.

The choice of vasopressors is dependent on the underlying pathophysiologic process and patient-specific responses. However, some generalities are supported by the literature. Norepinephrine and dopamine are excellent first line α -adrenergic agents (vasopressors) of similar efficacy with an associated lesser degree of β -adrenergic activity (inotropic agents). Few direct comparison studies exist. However, studies have found that patients with septic shock often respond better to norepinephrine [11], and one recent retrospective study documented that norepinephrine treatment was associated with a survival advantage as compared with all other forms of vasopressor therapy when patients with similar illness severity were compared [12••]. Many clinicians are concerned about the potential for norepinephrine to impair renal and mesenteric perfusion. However, there is no evidence that reversing hypotension with norepinephrine compromises mesenteric or renal blood flow. Indeed, animal data show an increase in renal blood flow when norepinephrine is used to reverse septic shock [13], and human studies have shown an improvement in gastric mucosal PCO₂ when hypotension was reversed with norepinephrine [14].

Both norepinephrine and dopamine have the ability to increase peripheral vasomotor tone while providing additional increased inotropy to minimize the afterload-increasing effects on reducing cardiac output. Dopamine has additional side effects, such as tachycardia (which can be useful in patients with bradycardia, but detrimental in patients with coronary artery disease) and immunosuppression [15]. All vasopressors, if used in high enough doses, will induce ischemic vasoconstriction. The gut mucosa and liver appear to be especially sensitive to this side effect, whereas renal vasoconstriction

tends to develop only at higher infusion rates [16]. Table 1 lists infusion ranges for presently available catecholamines. The pure α -adrenergic agent phenylephrine is a secondary choice in the management of distributive shock because it does not also increase inotropy. In generalized inflammatory shock states, which comprise a majority of patients with distributive shock, baseline cardiac depression also occurs. Restoring MAP without increasing inotropy in these states is usually associated with a decrease in cardiac output. Phenylephrine is primarily used in selective vasomotor shock (*eg*, spinal cord shock, anesthesia-induced loss of vasomotor tone) or as an immediate temporizing measure while more definitive therapies, such as those described above, are being instituted.

Crisis resuscitation principals

Profound hypotension (MAP < 50 mm Hg) is associated with a pressure-dependent decrease in coronary and cerebral blood flow and can rapidly induce myocardial depression and cerebral ischemia. In patients in whom rapid fluid infusion and norepinephrine/dopamine therapies have failed to restore organ perfusion pressure and in whom emergent increases in MAP are required, epinephrine is the catecholamine of last resort. Epinephrine is both a potent inotropic agent and vasopressor. Epinephrine produces venoconstriction that will increase the effective circulating blood volume, thereby increasing venous return. Although some increased peripheral edema formation will occur, anasarca is not a life-threatening condition, unlike hypotension. Additional disadvantages of epinephrine are its associated pulmonary hypertension and metabolic effects. Epinephrine induces hypermetabolism and glycolysis, resulting in lactic acidosis and hyperglycemia. Although these effects generally resolve quickly when epinephrine is discontinued, they can result in important clinical problems and make management more difficult.

Other therapeutic options for patients who are unresponsive to catecholamines include vasopressin infusion [17,18] and the administration of “stress” doses of corticosteroids [19,20]. Vasopressin induces vasoconstriction by stimulating vasopressin receptors and by potentiating the actions of catecholamines. Vasopressin can be effective in reversing shock when catecholamines are ineffective, particularly in sepsis [18,21] and after cardiac surgery [22•]. For this indication, the dosage of vasopressin is low: 0.05 to 0.1 U/min achieves blood levels of approximately 150 pg/mL [23]. However, even in this range, vasopressin reduces mesenteric and renal blood flow. There are no randomized, controlled trials comparing catecholamines to vasopressin or catecholamines plus vasopressin in terms of clinical outcome. Finally, in patients with peripheral vascular collapse who are unresponsive to catecholamines, consideration must be given

to adrenal cortical insufficiency as either the underlying etiology or as a complication of the stress state. Accordingly, stress dosages of corticosteroids (approximately 300 mg/d of hydrocortisone) are indicated when there is suspicion of adrenal insufficiency in patients with persistent cardiovascular collapse despite appropriate fluid resuscitation and high-dose vasopressor therapy. Recent studies have emphasized the lack of predictive value of the adrenocorticotrophic hormone stimulation test in predicting which patients will respond to corticosteroid replacement [19].

Low-dose dopamine

Because α -adrenergic agonists increase MAP by decreasing blood flow to certain tissues, there is concern about the potential for injury of certain organs, most notably the kidneys and the gut. For this reason, there is reluctance among some clinicians to use these vasoconstrictors for fear of renal or mesenteric injury. Furthermore, many clinicians attempt to vasodilate the renal vasculature with dopaminergic agents either to preserve flow during concomitant use of vasoconstrictors or in an effort to provide renal protection in a wide variety of clinical conditions. In evaluating these agents, it is important to appreciate that increased urine output or increased renal blood flow are not important clinical endpoints in themselves. This is both because these endpoints have not been shown to be correlated with survival and because the increase in urine output secondary to dopamine is largely a result of the inhibition of sodium-potassium ATPase at the tubular epithelial cell level, which increases sodium excretion and, hence, diuresis [24]. Evidence of clinical effectiveness should, instead, include outcome measures of clinical significance (*eg*, mortality, need for hemodialysis) or biochemical evidence of organ function (serum creatinine or creatinine clearance), which are sustained following the maneuver.

A systematic review using the effectiveness criteria outlined previously was recently published [25••]. Until the end of 1999, a total of 58 clinical trials had been published, both for prevention and treatment of acute renal failure. However, of these, only 24 used outcomes other than surrogate markers (*eg*, urine output, renal blood flow), and only 17 of these were randomized, clinical trials. Analysis of the randomized trials showed that dopamine did not prevent mortality, onset of renal failure, or need for dialysis in any subgroup [25••]. Furthermore, in the largest study to date ($n = 323$), dopamine failed to reduce the incidence of acute renal failure, the need for hemodialysis, or mortality [26••]. Although renal blood flow (but not glomerular filtration rate) has been shown to decrease in normotensive healthy volunteers given norepinephrine and reversed with dopamine [27], these investigators correctly point out that the effects of these

drugs in patients with shock may be quite different. Thus, there is no evidence that dopamine provides any benefit to patients with impending or existing renal failure or in the setting of vasoconstrictor therapy.

Conclusions

The use of vasopressor agents in critically ill patients should be directed by knowledgeable clinicians with an understanding of the pathophysiology of shock and the pharmacology of the agents used to treat it. All vasopressors have the potential to induce tissue ischemia and, thus, should be used with caution. When used at doses necessary to reverse distributive shock, less potent vasoconstrictors (*eg*, dopamine) are no safer than more potent ones (*eg*, norepinephrine). Although little comparative data exist, we recommend the following for patients with distributive shock.

- (1) Fluid resuscitation should be assured before (or, in severe cases, at same time as) the initiation of vasopressors. It is rare that intravascular fluid volume will be optimized with a right atrial pressure less than 10 mm Hg. Often, fluid resuscitation will need to be guided by pulmonary artery catheterization.
- (2) For patients with a cardiac index greater than or equal to 3.0 L/min/m², norepinephrine is the agent of choice. Alternatively, phenylephrine may be considered when the duration of vasodilatation is expected to be short and no cardiac dysfunction is likely to be present.
- (3) For patients with a cardiac index greater than 3.0 L/min/m², cardiac function is likely to be impaired, and re-evaluation of preload is encouraged. If cardiac index is less than 3.0 L/min/m², despite optimal preload, a greater proportion of inotropic support is probably required, and either dopamine or norepinephrine plus dobutamine should be used.
- (4) If patients are refractory to the agents listed previously, epinephrine should be used. Alternatively, or in addition, vasopressin should be considered, especially in patients with sepsis or those recovering from cardiac surgery.
- (5) Adrenal insufficiency may present as or complicate distributive shock. Hydrocortisone should be used to treat adrenal insufficiency. Adrenocorticotropic hormone stimulation tests may not predict which patients will respond to corticosteroid replacement.
- (6) Dopamine is not effective in reversing or preventing renal or mesenteric dysfunction and/or injury and should not be used for this indication either alone or in the setting of vasopressor therapy.

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