

Approach to Hemodynamic Shock and Vasopressors

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Hemodynamic shock (HS) is a clinical syndrome that is commonly observed in hospitalized patients. Prompt recognition and intervention are the cornerstones of mitigating the dire consequences of HS. Untreated HS usually leads to death. Unlike other types of clinical syndromes (*e.g.*, chest pain), for which a clinical diagnosis is made before treatment is initiated in earnest, the treatment of shock often occurs concurrently or ahead of the diagnostic process. The maintenance of end-organ perfusion is critical to prevent irreversible organ injury and failure, and this frequently requires the use of fluid resuscitation and vasopressors. A complete review of all of the signs and symptoms, diagnosis, and treatment of HS has been reviewed in detail elsewhere (1). This article provides a concise summary of how to approach the patient in HS, diagnostic and therapeutic decision making, and the use of vasopressors. In addition, the effects of vasopressors on end organs with particular focus on renal hemodynamics is reviewed.

Clinical Manifestations and Recognition of Hemodynamic Shock

HS is classically described as “an acute clinical syndrome initiated by ineffective perfusion, resulting in severe dysfunction of organs vital to survival” (1). As clinicians, we take great pains to teach our trainees that shock is not just hypotension, but that shock represents hypoperfusion of end organs. This rationale leads to the common refrain: “Normotensive patients can often suffer from shock.” The clinical manifestations of HS are related directly to the end organs that are not receiving adequate perfusion and can be categorized on the basis of the organ affected. Besides hypotension, the classic signs and symptoms of HS are tachycardia, relative hypotension (a decrease in baseline BP of 40 mmHg), tachypnea, cool and clammy extremities, oliguria, dysglycemia, and delirium (1). Patients who are hypotensive (systolic BP <90 mmHg in patients whose baseline BP is usually low) but show no signs or symptoms of shock should have their BP rechecked. An in-

dwelling arterial catheter or Doppler may be necessary to resolve a false low BP reading (1). In the absence of hypotension, the diagnosis of HS can be more challenging and will require the clinician to increase his or her scrutiny of the patient and either rule in or rule out HS with further clinical investigations. For patients who are normotensive, the measurement of serum lactate will often reveal the presence of HS in a patient whose clinical evaluation is equivocal. This entity of a normotensive patient with some clinical signs of HS with an elevated lactate is often referred to as “cryptic shock.” In this condition, the patient is not yet in critical condition but cannot meet their body’s oxygen demand, resulting in evidence of significant anaerobic metabolism. Previous trials showed that presence of HS and a serum lactate concentration of >4.0 mmol/L are associated with a mortality of 30 to 45% (2).

Once HS is recognized, interventions to restore tissue perfusion are mandatory. Three important questions should be asked immediately: (1) Does the patients need to be intubated? (2) Is there an obvious cause of shock that needs to be addressed without delay (*e.g.*, tension pneumothorax, pericardial tamponade)? (3) Is the patient hypotensive? If the patient is hypotensive, then the first step must be to restore an adequate BP. For all patients, volume should initially be infused intravenously, and the clinician should be not be afraid to “bridge” the patient with a vasopressor (dopamine, phenylephrine, or norepinephrine) while volume is being infused to maintain an adequate BP. The use of vasopressors to bridge hypotensive patients should even be done in patients with “pure” hypovolemic shock because progressive hypotension can lead to decreased coronary perfusion, further worsening cardiac function, hypotension, and myocardial ischemia. In the case of hypovolemic shock, vasopressors can be titrated off as the treating team catches up to the volume deficit. First responders (the first health care professional to see the patient in HS) are the key personnel who must make the intervention of defending the BP. This is a critical step in breaking the cycle of poor perfusion leading to worsening perfusion.

Classification of HS

The most widely accepted classification system organizes shock into four broad categories: (1) Hypovolemic, (2) cardiogenic, (3) obstructive, and (4) distributive (1). Patients who are in HS

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often have overlap between these categories, but determining which form shock is primarily involved is helpful for further diagnosis and treatment. Akin to the classic approach to acid-base disorders, the primary disorder should be identified. Table 1 outlines the causes of shock within the Weil and Shubin classification system (3).

Hypovolemic Shock

Hypovolemic shock can be caused by any disorder that causes volume depletion of the intravascular space. Typical causes are hemorrhage, acute volume losses (*e.g.*, diarrhea, vomiting), capillary leak causing “third spacing,” and burns. Patients with hypovolemic shock initially are able to compensate for the decreased stroke volume with compensatory increases in heart rate and systemic vascular resistance. This leads to the characteristic findings of tachycardia, flattened neck veins, cool clammy extremities, and oliguria.

Cardiogenic Shock

Cardiogenic shock is typically caused by disorders that affect myocardial contractility. The most common causes are acute myocardial infarction and arrhythmias. Other, less common causes include cardiomyopathy, valvular disease (*e.g.*, acute mitral valve regurgitation), acute decompensation of chronic heart failure, myocarditis, and conduction defects (1). The clinical picture of patients with cardiogenic shock is often similar to that of hypovolemic shock. Tachycardia, oliguria, and cool clammy extremities are usual prominent. In contrast to hypovolemic shock, cardiogenic shock usually features jugular venous distension and pulmonary edema.

Obstructive Shock

Obstructive shock is associated with any extracardiac process that impedes forward circulatory flow. The two main types of obstructive shock are those that block cardiac filling (*e.g.*, tension pneumothorax, cardiac tamponade) and those that cause increased cardiac (right or left sided) afterload (*e.g.*, aortic dissection, massive pulmonary embolus) (1). Certain causes of obstructive shock must be considered at the onset of the recognition of HS, because the window of opportunity to intervene may only be a few minutes. The critical three diagnoses that should be considered in all patients with obstructive shock at the outset are tension pneumothorax, cardiac tamponade,

and massive pulmonary embolus. Because obstructive shock impedes forward flow, cardiac output is greatly diminished, and the clinical signs and symptoms can resemble those of hypovolemic and cardiogenic shock, depending on the specific cause. Because the causes of obstructive shock are heterogeneous, there are no specific signs and symptoms for this category of shock. Once the three immediately reversible causes of reversible shock are ruled out, a structured diagnostic approach (see the Initial Therapy and Diagnostic Approach section) should be initiated to make the diagnosis.

Distributive Shock

Distributive shock is a form of HS that is associated with a hyperdynamic state with a high cardiac output and low systemic vascular resistance. The most common cause of distributive shock is the systemic inflammatory response syndrome, which is most often due to sepsis. Other causes of systemic inflammatory response syndrome include pancreatitis, trauma, and significant tissue injury. Distributive shock can also be caused by endocrine dysfunction (*e.g.*, thyrotoxicosis, adrenal insufficiency), spinal cord injury, anaphylaxis, and liver failure. Despite the decreased vascular resistance, the absence of cool, clammy extremities and absence of pulmonary edema cannot be used with certainty to distinguish distributive shock from other forms of shock. Because the causes of distributive shock are so varied, a full diagnostic work-up is often required to confirm the specific diagnosis.

Initial Therapy and Diagnostic Approach

As mentioned previously, once HS is recognized, certain immediate steps should be undertaken while the cause of HS is determined.

1. If the patient's airway, oxygenation, or ventilation is not effective, then the patient should be intubated.
2. Large-bore intravenous access should be established.
3. Any arrhythmias should be addressed per standard advanced cardiac life support protocols.
4. A trial of at least 1.0 L of crystalloid should be infused to treat hypotension; the fear of pulmonary edema should not preclude the use of volume in a patient who is not perfusing adequately. In cardiogenic shock this fluid challenge will not be as harmful as compared to sustained hypotension.

Table 1. Weil/Shubin shock classification^a

Type of Shock	Common Causes
Hypovolemic	Hemorrhage, vomiting, diarrhea, burns, polyuria (diabetic ketoacidosis)
Cardiogenic	MI, cardiomyopathy, drugs (overdose β blocker), valvular dysfunction, arrhythmias
Obstructive	Tension pneumothorax, pulmonary embolism, air embolism, pericardial tamponade, aortic dissection,
Distributive	SIRS related: Sepsis, pancreatitis, trauma, burns Neurogenic: Spinal cord injury, Endocrine related: Adrenal insufficiency, thyroid disease Anaphylactic

^aMI, myocardial infarction; SIRS, systemic inflammatory response syndrome.

5. If the BP remains low, then a vasopressors should be initiated to maintain BP.
6. The diagnosis of acute myocardial infarction, tension pneumothorax, pericardial tamponade, and massive pulmonary embolus should be considered on the basis of the available information. If any of these diagnoses is being considered, then targeted diagnostic and therapeutic interventions should proceed while more formal diagnostic investigations occur concurrently.

Once the patient is stabilized, the cause of the patient's HS can be safely assessed. In certain instances, the clinical situation may point to an obvious cause, in which case the treatment should be initiated for that cause of shock (e.g., antibiotics for septic shock); however, given the myriad causes of HS, a structured diagnostic approach should still be conducted because of the ability of certain types of shock to masquerade as one another and for multiple types of shock to coexist. The key to distinguishing distributive shock from the other categories of shock is an objective assessment of cardiac function. An echocardiogram, a pulmonary artery catheter, or an indwelling arterial line cardiac output assessment should be conducted as soon as possible. This cardiac assessment should occur while other targeted diagnostic investigations are ongoing, but even if the type of shock seems obvious and certain, the objective cardiac output measurement will ensure that an atypical presentation of one form of shock is not being mistaken for another form of HS. The atypical presentation of pulmonary embolus or cardiac tamponade can masquerade as sepsis and has fooled many seasoned clinicians; therefore, the next steps for the diagnostic work-up for a patient who is in HS should be as follows:

7. Complete blood count, complete serum chemistry, serum lactate, arterial blood gas, cardiac enzymes, electrocardiogram, chest radiograph, random serum cortisol, and coagulation assessment.
8. Echocardiogram, pulmonary artery catheter, or an indwelling arterial line cardiac output measurement.

On the basis of the results of these investigations, a picture of the cause of the HS will emerge. In general, in hypovolemic and distributive shock, the patient is volume responsive. Volume responsive means that as volume is infused, the cardiac index (CI) increases significantly. In the case of hypovolemic shock, if volume is replaced faster than volume is being lost, then both BP and CI will increase proportionately. In patients with distributive shock, the CI will respond significantly to volume, but the BP will often remain low as the hyperdynamic state evolves. Usually, the CI will increase to a zenith, at which point volume no longer improves the CI yet the patient remains hypotensive, requiring the use of vasopressors. If the patient's CI is <2.0 despite volume resuscitation, then obstructive or cardiogenic shock must be considered. At this point, echocardiography is mandatory.

Brief Review of Common Vasopressors and Inotropes

The four major adrenergic receptors are the α_1 , α_2 , β_1 , and β_2 receptors. In the cardiovascular system, activation of the α_1 -adrenergic receptor induces vasoconstriction, whereas activation of the α_2 -adrenergic receptor reduces norepinephrine release at the synaptic end plate, thus mildly decreasing BP and being mildly negatively dromotropic. Activation of the β_1 receptor, conversely, increases cardiac output by its positive chrono-, dromo-, and inotropic action, whereas activation of the β_2 receptor results in vasodilation (4).

The receptor selectivity of various catecholamines and vasopressors can be dosage dependent. For instance, both dopamine and epinephrine have varying effects on adrenergic and dopaminergic receptors on the basis of dosage (4).

Epinephrine

Epinephrine is a potent mixed α - and β -adrenergic agonist. Because of its mixed properties, epinephrine increases both mean arterial BP by vasoconstriction (α_1 -adrenergic effect) and cardiac output (β_1 -adrenergic effect); however, excessive vasoconstriction may be undesirable in states of low cardiac output. Low-dosage epinephrine infusions primarily stimulate β receptors. For this reason, epinephrine at a dosage of <4.0 $\mu\text{g}/\text{min}$ is often considered to be a "pure" inotrope dosage, and this low level of epinephrine infusion is commonly encountered in patients after cardiac surgery. At first blush, epinephrine seems to be an ideal inotrope and pressor; however, epinephrine is associated with a host of adverse effects. Epinephrine is associated with the induction of pulmonary hypertension, tachyarrhythmia, myocardial ischemia, lactic acidosis, and hyperglycemia (5). Lactic acidosis and hyperglycemia are caused by epinephrine-induced hypermetabolism, suppression of insulin release, and glycolysis. In addition, epinephrine can compromise hepatosplanchnic perfusion, oxygen exchange, and lactate clearance, especially in septic shock (6,7). In animal models, these adverse effects are dosage related and more pronounced as compared with norepinephrine or vasopressin (6,7).

Epinephrine is the first-line catecholamine in cardiopulmonary resuscitation and anaphylactic shock. As a vasopressor and as an inotrope, epinephrine is usually considered a second-line agent.

Norepinephrine

Norepinephrine is an endogenous catecholamine that has potent α_1 - and β_1 -adrenergic effects. The primary vasoactive effect of norepinephrine is arterial and venous vasoconstriction. The inotropic properties of norepinephrine are usually offset by increases in afterload. Because of its marked vasoconstrictive characteristics, norepinephrine seems the logical drug of choice in distributive forms of shock, increasing mean arterial pressure (MAP), effective circulating blood volume, and venous return and preload, with minimal increase of heart rate or stroke volume. Norepinephrine is more potent than dopamine and is commonly considered the first-choice vasopressor to reverse hypotension in vasodilatory shock (8). Some clinicians

fear that the use of norepinephrine will cause severe vasoconstriction in visceral and renal microperfusion, yet norepinephrine seems to improve parameters of visceral microperfusion when hypotension is reversed in septic shock, compared with epinephrine or dopamine (9–11). This may explain why norepinephrine therapy was associated with some survival benefit in septic shock, compared with high-dosage dopamine and epinephrine (12). In comparison with epinephrine, norepinephrine demonstrates many fewer metabolic adverse effects; however, the use of norepinephrine is not advisable in forms of shock exclusively with low cardiac output.

Dopamine

Dopamine is a α - and β -adrenergic agonist that also stimulates dopaminergic receptors DA₁ and DA₂. DA₁ stimulation causes renal and visceral vasodilation in healthy animals and humans; DA₂ stimulation inhibits norepinephrine reuptake at the synapse. In healthy humans, the effects of dopamine are dosage dependent. At lower dosages (1 to 3 $\mu\text{g}/\text{kg}$ per min), it dominates the dopaminergic, at medium dosages (3 to 10 $\mu\text{g}/\text{kg}$ per min) the β_1 -adrenergic, at higher dosages (10 to 20 $\mu\text{g}/\text{kg}$ per min) the mixed α_1 - and β_1 -adrenergic, and at highest dosages (>20 $\mu\text{g}/\text{kg}$ per min) the α_1 -adrenergic effect (4); however, these dosage-dependent effects vary by individual and have not been reproduced in critically ill patients (4). The α - and β -adrenergic effects of dopamine are generally weaker compared with epinephrine or norepinephrine. Dopamine is used as a vasoconstrictor in vasodilatory shock and as an inotrope in low cardiac output. Dopamine's niche indication is vasodilatory shock associated with bradycardia, both of which can be corrected with this agent.

Despite the theoretical beneficial effect of dopamine on splanchnic perfusion by stimulation of DA₁ receptors, this has not been reproduced in critically ill patients. Published data in sepsis suggest that dopamine may impair hepatosplanchnic perfusion and metabolism (9,12,13). Tachycardia, another adverse effect of dopamine, together with vasoconstriction can lead to increased cardiac oxygen demand and decreased oxygen delivery and may trigger myocardial ischemia and arrhythmias.

Dopamine should not be considered a "mild" catecholamine. When used in dosages to achieve adequate BP and cardiac output targets, dopamine is a vasopressor and like other vasopressors at high dosage may become harmful. Recent guidelines consider both norepinephrine and dopamine as first-choice vasopressors to correct hypotension in septic shock (14).

Dobutamine

Dobutamine is a synthetic catecholamine with predominately β -adrenergic and only limited α -adrenergic effects. As a result of β_1 receptor-mediated, positive inotropic, and β_2 -receptor-mediated vasodilatory action, dobutamine increases cardiac output and decreases systemic and pulmonary vascular resistance. Dobutamine is the preferred vasoactive agent to treat cardiogenic shock with low output and increased afterload. In combination with norepinephrine, dobutamine is used in septic shock with myocardial dysfunction. In septic shock, dobut-

amine also increases splanchnic blood flow and oxygen delivery and decreased endogenous glucose production (15). As with all catecholamines with a β -adrenergic effect, dobutamine may cause a mismatch of myocardial oxygen delivery and requirement.

Dopexamine

Dopexamine, another synthetic catecholamine with predominately β_2 -adrenergic effects, also activates dopaminergic receptors. Besides marked general vasodilation and decrease of afterload, inhibition of norepinephrine reuptake in sympathetic neurons may contribute to the positive inotropic actions of dopexamine. Animal and human data on the use of dopexamine are limited and somewhat conflicting. Dopexamine results in improved or impaired visceral microperfusion by its general, β_1 receptor-mediated, and mesenteric DA₁ receptor-mediated vasodilation (16–18). Most data, however, suggest increased blood flow in major visceral arteries by dopexamine, which is not passed down to the microcirculation, possibly as a result of shunting (16–18); therefore, the proposed improvement of hepatosplanchnic microperfusion by dopexamine is questionable, as previously reviewed (5,19). In contrast to dopamine, dopexamine does not suppress pituitary function (20). Despite all expectations raised for dopexamine, there seems to be no advantage over dobutamine. In conclusion, the indications for dopexamine are those described for dobutamine, but its use is limited because it is not widely available.

Phenylephrine and Metaraminol

Phenylephrine and metaraminol are α_1 -adrenergic agonists. Both are commonly used as initial and temporal treatment to restore MAP, systemic vascular resistance, and central venous pressure in hypotension with vasodilation and adequate cardiac output until more definite therapies are instituted. They restore BP with a decrease of cardiac output. Metaraminol also inhibits norepinephrine reuptake, thus mimicking norepinephrine effects. Metaraminol has also been in use for a long time to maintain MAP during subarachnoid anesthesia. Only recently, the effect of metaraminol was compared with norepinephrine in patients with septic shock (21). Because both agents perform similarly well in maintaining MAP, metaraminol could potentially be used as a salvage therapy in norepinephrine-resistant septic shock. Because of their potential to reduce hepatosplanchnic perfusion and the lack of evidence-based data on their continuous use, phenylephrine and metaraminol are predominately used as temporary vasoconstrictors.

Nonadrenergic Vasoactive Drugs

Calcium Channel Sensitizer

Levosimendan and pimobendan are the clinically used agents of this novel drug class. Calcium channel sensitizers have a positive inotropic effect by increasing the sensitivity of cardiac myofilaments to calcium, a vasodilatory effect by stimulation of ATP-sensitive potassium channels, and inhibit phosphodiesterase (PDE) III, as recently reviewed (22). Calcium channel sensitizers exert strong inotropic and vasodilating effects, possibly stronger than dobutamine, with less potential for myocardial

ischemia. The main indication for calcium channel sensitizers is severe low-output heart failure as acutely decompensated chronic heart failure. The recently published, large, randomized, double-blind "Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support" (SURVIVE) trial, however, did not demonstrate a difference in 6-mo survival in acute decompensated heart failure comparing levosimendan and dobutamine (23). Studies also indicated that calcium channel sensitizers may be beneficial in septic myocardial insufficiency (24). Levosimendan has been associated with an increased proarrhythmic risk. This may be prevented by cautious, concurrent β blocker therapy, which inhibits levosimendan-induced sympathetic hyperreactivity.

Nesiritide

Nesiritide, a recombinant human brain natriuretic peptide, belongs to a family of structurally related peptides that regulate sodium and volume homeostasis. They consist further of atrial and C-type natriuretic peptide. Increased wall stress of the cardiac atria and ventricles is followed by the release of these natriuretic peptides, and they are markedly elevated in left ventricular dysfunction. Furthermore, the release of atrial natriuretic peptide and brain natriuretic peptide might be triggered by IL-6 and endotoxin in critical illness. Nesiritide enhances natriuresis and diuresis, causes peripheral vasodilation, and inhibits the renin-angiotensin system (25). Because nesiritide decreases systemic vascular resistance and augments cardiac output, it improves hemodynamics in acutely decompensated chronic heart failure; however, two recent meta-analyses of randomized, controlled trials (RCT) suggested that nesiritide either increased 30- and 180-d mortality or did not improve mortality compared with nitroglycerin or dobutamine in acutely decompensated heart failure (26). Nesiritide seems not to have proarrhythmic effects. Severe hypotension and cardiogenic shock are the major contraindications to nesiritide use. It is a potential second-line drug for the treatment of acutely decompensated chronic heart failure, although, in clinical practice, it is more liberally used.

PDE III Inhibitors

This class of drugs incorporates amrinone, enoximone, milrinone, and olprinone, of which milrinone, the strongest and shortest acting with the best control, is the most commonly used in intensive care medicine. By selectively inhibiting PDE III, these agents mobilize intracellular calcium. In consequence, PDE inhibitors have vasodilatory and inotropic actions and improve diastolic ventricular relaxation. PDE inhibitors improve cardiac output in cardiogenic shock and are used as second-line drugs for this indication. The exact evidenced-based role of PDE inhibitors in shock treatment still needs to be defined. As is true for inotropic catecholamines, PDE inhibitors can cause intracellular calcium overload, leading to disadvantageous increase in myocardial oxygen demand and consecutively to significant ventricular tachyarrhythmias, myocardial cell injury, and ultimately cell death. Because of their substantial vasodilatory action, PDE inhibitors frequently require the addition of vasopressors.

Vasopressin, Ornipressin, and Terlipressin

Vasopressin is a stress hormone that is released during shock. Septic shock is associated with a vasopressin deficiency (27). Administration of vasopressin reverses vasodilation in vasopressor-resistant shock by activation of vasopressin₁ receptors, inhibition of ATP-sensitive potassium channels and nitric oxide, and amplification of vasoconstrictive catecholamine effect, as previously reviewed (27). Vasopressin and its analogues decrease cardiac output and redistribute cardiac output to the hepatosplanchnic microcirculation, improving visceral perfusion relatively safely and effectively in septic shock in dosages of 0.01 to 0.04 U/min; however, longer continuous infusions, especially with dosages >0.04 U/min, should be used with great care because these dosages may severely compromise perfusion of the visceral microvasculature (4). Vasopressin is a second-line agent in septic shock or refractory hypotension that is unresponsive to norepinephrine (or epinephrine). Recently, the Vasopressin in Septic Shock Trial (VASST) comparing the use of vasopressin and norepinephrine in septic shock was completed. From preliminary data, only patients with previous administration of low-dosage norepinephrine demonstrated improved survival with vasopressin. In general, there was no survival benefit with vasopressin over norepinephrine. The role of vasopressin in septic shock should be more clearly defined when the full results of the VASST are published. Terlipressin and ornipressin both are synthetic vasopressin analogues with longer half-life and duration of action. This may be disadvantageous in shock therapy, because their effects are less controllable compared with vasopressin. In noncontrolled, small-sized septic shock studies, addition of terlipressin to norepinephrine increased MAP and visceral perfusion, but these data are still preliminary (28).

Effects of Catecholamines and Vasoactive Agents on Renal Function and Acute Kidney Injury

Hypotension and decreased cardiac output are significant modifiable risk factors for the development of acute kidney injury (AKI). In established AKI, renal autoregulation may be lost, which can aggravate AKI *via* relative hypotension because when autoregulation is not functioning appropriately, renal perfusion is determined by MAP (29). The region of the kidney most vulnerable to impaired microperfusion is the outer medulla, which is critical in the development of renal injury in AKI (30); therefore, it seems logical that optimization of MAP and cardiac output should increase renal perfusion, thereby preventing and/or treating AKI. Some investigators have postulated that the target MAP should be increased beyond 65 mmHg to increase renal perfusion. However, increasing the MAP beyond 65 mmHg has not been associated with improved renal outcomes. In humans, studies that increased the target MAP from 65 to 85 mmHg were associated with no improvement in creatinine clearance and urine output (10,31). Given the available evidence, there are no data to support the widespread use of vasopressors to increase the MAP beyond 65 to 70 mmHg. Patients with chronically highly elevated MAP may be exceptions to this recommendation.

Table 2. Summary of the data on effects of catecholamines and vasoactive agents on renal function in critical ill humans^a

Substance	AKI Prevention	AKI Treatment	Renal Perfusion	GFR	Urine Output
Dopamine (<3 μg/kg per min)	∅	∅	∅	∅	↑
Dopamine (≥3 μg/kg per min)	Unknown	Unknown	↑	↑	↑
Fenoldopam	∅ to +	Unknown	↑	↑	↑
Norepinephrine	Unknown	Unknown	↑	∅ to ↑	∅ to ↑
Epinephrine	Unknown	Unknown	↓	∅ to ↑	↑
Dobutamine	Unknown	Unknown	↑	∅ to ↑	↑
Dopexamine	Unknown	Unknown	∅ to ↑	∅ to ↑	∅ to ↑
Levosimendan	Unknown	Conflicting results	∅	↑	↑
Nesiritide	Conflicting results	Unknown	↑	Unknown	↑
Milrinone	Unknown	Unknown	Unknown	↓	Unknown
Vasopressin	Unknown	∅ to +	↓ to ↑	↑	↑

^aAKI, acute kidney injury; ∅, no effect; +, positive effect; ↑, increase; ↓, decrease.

With the exception of low-dosage dopamine, studies examining vasopressor use for nephrocentric outcomes in humans are derived from a small number of studies that are either underpowered or based on inference (Table 2). There is now ample evidence from a large, double-blind, prospective, RCT and a meta-analysis that low-dosage dopamine does not affect the risk for development of AKI or the need for renal replacement therapy but may compromise myocardial or visceral perfusion (32,33). As a consequence, the use of low-dosage dopamine for renoprotection or for the treatment of AKI should be abandoned.

Fenoldopam, a synthetic DA₁ receptor agonist, has also been studied in AKI. Numerous studies have failed to demonstrate any benefit of fenoldopam in the treatment of AKI (34–36). A recent meta-analysis suggested a reduction of AKI associated with fenoldopam in critically ill patients, but the studies included were mostly heterogeneous and of variable quality, which limits this conclusion (37). Fenoldopam may have a role in the prevention of AKI in patients with sepsis; however, larger validation studies are still required (38).

Norepinephrine used to be a vasopressor of last resort because of its vasoconstrictive properties. Despite the fear that norepinephrine could severely constrict renal microvasculature, norepinephrine has been shown to improve renal function as measured by increased renal medullar blood flow, creatinine clearance, and urine flow in experimental and human septic shock (39–41). These data suggest that the increase in the MAP and tissue perfusion by norepinephrine can offset its vasoconstrictive effect. In another small RCT in septic shock, norepinephrine was superior to high-dosage dopamine in maintaining adequate MAP and increasing diuresis (8); however, this effect has not been shown to translate consistently into improved creatinine clearance and urine output (42). In conclusion, data suggest a beneficial effect of norepinephrine on renal function in septic shock as compared with dopamine.

Nesiritide, in two double-blind, placebo-controlled trials, was associated with improved renal function after cardiac sur-

gery in patients with impaired left ventricular function and chronic kidney disease (43,44). Conversely, in another randomized, double-blind, placebo-controlled study, nesiritide failed to lower the incidence of AKI in patients with acute decompensated heart failure and chronic kidney disease (45). In a recent retrospective analysis and a meta-analysis, the administration of nesiritide was associated with a significantly increased risk for AKI and of increased mortality in those patients who developed AKI (46,47). Given the contradictory nature of the available studies, large RCT will be required to determine whether there is a role for nesiritide for renal specific outcomes.

Conclusions

Norepinephrine is considered the first-line vasopressor in vasodilatory shock, dobutamine the first-line inotrope in shock associated with decreased cardiac output, and their combination in vasodilatory shock with decreased cardiac output. Epinephrine is the first-line catecholamine in cardiopulmonary resuscitation and also as second line in shock that is unresponsive to other catecholamines. Vasopressin is emerging as a therapy in resistant vasodilatory shock. The use of other catecholamines and modern nonadrenergic vasoactive drugs in shock remains with little evidence. In general, results of large, high-quality trials of catecholamines and vasoactive agents for shock are urgently required to provide data for evidence-based guidelines for their use. Similarly, conclusive evidence is needed on the effect of catecholamines and vasoactive agents to prevent and treat AKI, except for low-dosage dopamine, which is ineffective and potentially harmful for these indications.

Disclosures

None.

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