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EM Critical Care

UNDERSTANDING AND CARING FOR CRITICAL ILLNESS IN EMERGENCY MEDICINE

The Use Of Vasoactive Agents In The Management Of Circulatory Shock

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Abstract

Circulatory shock is frequently encountered in the emergency department, and prompt and aggressive resuscitation improves patient outcomes. Vasoactive agents are commonly used to optimize end-organ perfusion and oxygen delivery, and an understanding of the pathophysiology of different shock states and relevant pharmacology can aid in the selection of appropriate vasoactive agents. For septic shock, norepinephrine is the first-line agent, and in patients with anaphylactic shock, knowledge of dosing of epinephrine is key in preventing potentially fatal errors during administration. In patients with cardiogenic or obstructive shock, norepinephrine and dobutamine may be of benefit until definitive therapy can be achieved. This review discusses the most important principles of management of each type of shock, along with information regarding the preparation, dosing, administration, and possible adverse effect of key vasoactive agents. The endpoints of resuscitation are reviewed, including mean arterial pressure, serum lactate levels, and central venous oxygen saturation. Recent high-quality clinical trials that provide better evidence for the use of vasoactive agents are reviewed, and recommendations for critical care management are given.

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CME Objectives

Upon completion of this article, you should be able to:

1. Describe physical examination findings that help differentiate shock due to low cardiac output versus shock due to low systemic vascular resistance.
2. Identify the mechanisms of action, dosing, and routes of administration for commonly used vasoactive agents.
3. Select the appropriate vasoactive agent for different categories of shock using physiologic rationale and evidence from clinical trials.
4. Discuss endpoints of resuscitation when titrating vasoactive agents.

Prior to beginning this activity, see "Physician CME Information" on the back page.

Case Presentation

At the start of your Sunday morning shift, your colleague signs out a case to you. The patient is a 74-year-old female with a history of hypertension and diabetes who presented with 2 days of lethargy, fevers, and chills. Her initial vitals are: temperature, 39°C; heart rate, 110 beats/min; blood pressure, 80/30 mm Hg; respiratory rate, 24 breaths/min; and oxygen saturation, 97% on room air. Chest x-ray was normal. Labs demonstrate a WBC count of 18,000 with 12% bands, HCT of 34%, serum lactate of 5 mmol/L, and > 50 WBC/HPF and bacteria on urinalysis. Cultures of her urine and blood were sent and broad-spectrum antibiotics started. Your colleague placed a central line and started early goal-directed therapy for septic shock from a urinary source. Despite 5 L of crystalloid and a central venous pressure of 10 cm H_20, her blood pressure remained low and your colleague started a norepinephrine infusion. "I signed her out to the ICU, but it's going to be a while before the bed is ready," said your colleague as he heads home after an exhausting shift. Just then, the patient's nurse calls to you, "Hey doc, I'm going to need some help in here!" As you walk into the room, you glance up at the monitor and note that her blood pressure reads 70/30 mm Hg despite 10 mcg/min of norepinephrine. "She's on a lot of norepi. Do you want to add something else?" the nurse asks. You usually start dopamine for patients with septic shock, and you wonder why your colleague chose norepinephrine. Should you just keep titrating up the norepinephrine? Should you switch to a different vasoactive agent? Should you add a second agent? As you ponder your options for vasopressor management, the ICU team arrives to evaluate the patient.

Introduction

Circulatory shock is defined as a state of inadequate tissue perfusion, which can lead to multisystem organ dysfunction and death if it is not treated in a timely fashion. Emergency physicians frequently treat patients with shock of different etiologies and pathophysiology. Hypotension in the emergency department (ED) independently predicts inhospital mortality, and the risk of death increases when hypotension is severe (systolic blood pressure [SBP] < 80 mm Hg) or sustained (> 60 min).[1,2] Hypotension also predicts mortality in specific conditions commonly encountered in the ED, including pulmonary embolism, myocardial infarction, traumatic brain injury, and sepsis.[3-6] Early and aggressive resuscitation in the ED improves patient outcomes, particularly in severe sepsis and septic shock.[7]

The management of circulatory shock involves 2 major considerations: (1) identification and treatment of the underlying cause, and (2) maintaining perfusion and oxygen delivery to vital organs. Fluid resuscitation is often the initial therapy, but up to one-half of critically ill patients with poor tissue perfusion will not respond to a fluid challenge.[8] In a subset of such cases, vasoactive agents may help improve organ perfusion and oxygen delivery. Although vasoactive agents have been employed to treat shock for over 70 years, evidence for their use has rested primarily on expert opinion and animal studies.[9] Only in recent years have high-quality trials compared clinical outcomes with different vasoactive agents. In this issue of *EM Critical Care,* we perform an evidence-based review of the use of vasoactive agents in the management of shock.

Critical Appraisal Of The Literature

A literature search was performed using Ovid MEDLINE® and PubMed. Search terms included: *shock, circulatory shock, distributive shock, hypovolemic shock, obstructive shock, cardiogenic shock, septic shock, neurogenic shock, anaphylactic shock, norepinephrine, epinephrine, phenylephrine, dopamine, dobutamine, vasopressin,* and *milrinone.* The search terms were combined with *obstetrics, pregnancy,* and *pediatrics.* Relevant articles were reviewed and used to identify other articles. The Cochrane Database of Systematic Reviews and the National Guideline Clearinghouse (www.guideline.gov) were also utilized. In general, the use of specific vasoactive agents for the treatment of circulatory shock is supported by several high-quality randomized trials; however, when examining specific categories of shock, the quality of evidence varies considerably. For example, several large randomized trials provide evidence for the use of specific vasoactive agents in septic shock, but the use of vasoactive agents in other categories of shock (such as anaphylactic or neurogenic shock) are generally supported by observational studies and case series.

Etiology And Pathophysiology Of Shock

Shock can be classified into 1 of 4 categories: (1) hypovolemic, (2) distributive, (3) cardiogenic, or (4) obstructive.[10] **(See Table 1.)** The appropriate selec-

Table 1. Categories Of Shock And Their Causes

Category	Common Causes
Hypovolemic	Hemorrhage, fluid loss, third-spacing of fluid
Cardiogenic	Myocardial infarction, arrhythmias, valvular defects, cardiomyopathy
Obstructive	Pulmonary embolism, tension pneumothorax, cardiac tamponade
Distributive	Sepsis, neurogenic causes, anaphylaxis, adrenal crisis

tion of vasoactive agents depends on the etiology of shock and a bedside assessment of the patient's hemodynamics and volume status. Not all patients with shock will require vasoactive agents, and treating the underlying cause (eg, pericardiocentesis, in the case of cardiac tamponade) is of paramount importance.

Mean arterial pressure (MAP) is determined by the product of cardiac output (CO) and systemic vascular resistance (SVR).

$$MAP = CO \times SVR$$

Cardiac output is the product of heart rate (HR) and stroke volume (SV).

$$CO = HR \times SV$$

Stroke volume is the amount of blood ejected from the heart during ventricular contraction. It follows that the hypotensive patient can be thought of as having either a reduction in stroke volume (low output state) or a reduction in systemic vascular resistance (vasodilatory state). Clinically, the stroke volume can be assessed by evaluating the pulse pressure:

Pulse pressure = systolic – diastolic blood pressure

For example, a hypotensive patient with a narrow pulse pressure likely has a reduction in stroke volume. **(See Table 2.)** Patients with hypotension due to a reduction in stroke volume typically have a decrease in either preload (hypovolemic shock) or contractility (cardiogenic or obstructive shock). A central venous pressure (CVP) or evaluation of the jugular venous pressure may help differentiate these 2 abnormalities: low CVP is observed when the heart is "empty" (hypovolemia) and high CVP when the heart is "full" (cardiogenic and obstructive shock). In patients with low stroke volume and high CVP, vasoactive agents with inotropic properties (increased cardiac contractility) are often used to augment stroke volume. In contrast, when hypotension results from a reduction in systemic vascular resistance (as in distributive shock), a compensatory increase in stroke volume will help to maintain mean arterial pressure. In this case, a large stroke volume will be evidenced by a wide pulse pressure. In cases of reduced systemic vascular resistance, vasoactive agents with more potent vasopressor properties (vasoconstricting) are often used to augment MAP. This description of shock states provides a framework for the initial assessment of a patient with undifferentiated hypotension; however, it bears mentioning that many patients will have a mixed picture with more than 1 etiology of shock simultaneously (eg, cardiogenic and septic shock). Furthermore, physical examination findings and CVP monitoring have significant limitations in the diagnosis of shock. Bedside ultrasound provides a rapid and noninvasive method of improving diagnostic accuracy in shock.[11] **(See Table 2.)**

Pharmacology

Receptor Location And Function

Vasoactive agents agonize both adrenergic and nonadrenergic receptors to exert their effects. Adrenergic receptors include alpha and beta, whereas dopaminergic and vasopressin receptors comprise key nonadrenergic binding sites.[13] Receptor location, density, and action as well as the drug dose determine the effects of vasoactive agents. **(See Table 3, page 4.)** Alpha-1 receptors located in vascular smooth muscle cause constriction of arteries and veins.[13] Activation of beta-1 receptors in the heart improves heart rate, contractility, and cardiac conduction. Agonism of beta-2 receptors in smooth muscle, including the lining of blood vessels and bronchioles, causes vasodilation and bronchodilation. The relative alpha

Table 2. Etiology Of Shock Classified By A Reduction In Stroke Volume Or A Reduction In Systemic Vascular Resistance[11,12]

Category of Shock	Pulse Pressure	Diastolic Blood Pressure	Extremity Temperature	Capillary Refill	Central Venous Pressure	Ultrasound Findings
Reduced Stroke Volume						
Hypovolemic	Narrow	Preserved	Cool	Delayed	Low	• Small inferior vena cava with respiratory collapsibility
Cardiogenic	Narrow	Preserved	Cool	Delayed	High	• Poor left ventricle contractility
Obstructive	Narrow	Preserved	Cool	Delayed	High	• Tamponade: Pericardial effusion • Massive pulmonary embolism: Right ventricle dilation • Tension pneumothorax: Absence of "lung sliding"
Reduced Systemic Vascular Resistance						
Distributive	Wide	Reduced	Warm	Brisk	Normal	• Hyperdynamic left ventricle

and beta effects of adrenergic agents are depicted in **Figure 5.** Dopaminergic (D) receptors play a small therapeutic role, as dopamine exerts most of its clinically relevant effects on alpha and beta receptors. Agonism of D_4 receptors in the heart can increase heart rate and stroke volume, whereas D_1 and D_2 agonism in the kidney induces natriuresis.[14] Vasopressin receptor subtypes include V_1 and V_2. Agonism of V_1 receptors located in vascular smooth muscle leads to vasoconstriction.[15,16] At high doses, V_1 agonism can lead to decreased cardiac output and heart rate through coronary vasoconstriction and changes in vagal and sympathetic tone.[13]

Norepinephrine

Norepinephrine exhibits potent alpha agonism and less pronounced beta agonism.[13] Consequently, norepinephrine produces vasoconstriction and a modest increase in heart rate and contractility.[18,19] **(See Table 3.)** Norepinephrine is a more potent vasoconstrictor than dopamine and phenylephrine, and it is more effective at reversing hypotension. Norepinephrine appears to improve end-organ perfusion in patients with distributive shock after adequate fluid resuscitation, and it selectively increases renal and coronary blood flow.[20,21,22,23] Although norepinephrine can occasionally cause tachyarrhythmias due to modest beta agonism, this effect occurs less commonly than with more potent beta agonists (such as dopamine).[24]

Dopamine

Dopamine binds dopamine, alpha receptors, and beta receptors, leading to the release of norepinephrine. Experimental data suggest that at doses < 5 mcg/kg/min, D_1 agonism leads to renal, mesenteric, cerebral, and coronary vasodilation and increased urine output.[25] At 5 to 10 mcg/kg/min, predominant beta-1 agonism increases heart rate and stroke volume. Beyond 10 mcg/kg/min, primary alpha-1 effects cause vasoconstriction.[26] Although dopamine demonstrates dose-dependent effects, precise dosages at which particular effects predominate vary among patients, especially in the critically ill. Thus, the dose should be titrated to clinical effect rather than attempting to rely on dose-dependent observations for titration of dopamine. Dopamine is a less-potent vasoconstrictor than epinephrine or norepinephrine, and the increase in MAP results mainly from increased stroke

Table 3. Vasoactive Agent Effects And Dosing[30]

Vasoactive Agent	Primary Receptor	Relative Effects	Typical IV Adult Dosing	Common Adverse Effects	Rate of Titration
Dopamine	Dopamine Beta-1 Alpha-1	Natriuresis ↑↑HR ↑↑SV ↑SVR	Dose-dependent effects: 1-5 mcg/kg/min - natriuresis 5-10 mcg/kg/min - ↑↑HR, ↑↑SV 10-20 mcg/kg/min - ↑SVR	• Tachyarrhythmias	2-5 min
Norepinephrine	Beta-1 Alpha-1	↑HR ↑SV ↑↑SVR	1-40 mcg/min	• Tachyarrhythmias	2-5 min
Phenylephrine	Alpha-1	↑SVR ↓HR	20-200 mcg/min	• Reflex bradycardia	2-5 min
Epinephrine	Beta-1 Alpha-1 Beta-2	↑↑↑HR ↑↑↑SV ↑↑↑SVR Bronchodilation	Dose-dependent effects: 1-10 mcg/min - ↑↑↑HR, ↑↑↑SV 10-20 mcg/min - ↑↑↑SVR	• Tachyarrhythmias • Splanchnic ischemia • Myocardial ischemia • ↑Serum lactate	2-5 min
Vasopressin	V_1	↑SVR ↓HR	0.03 or 0.04 units/min	• Limb ischemia • Bradycardia • Myocardial ischemia (at higher doses than typically used)	Fixed dose (do not titrate)
Dobutamine	Beta-1 Beta-2	↑↑HR ↑↑↑SV ↓SVR	2-20 mcg/kg/min	• Tachyarrhythmias • Hypotension • Myocardial ischemia	2-5 min
Milrinone	PDE-3 inhibitor	↑HR ↑↑↑SV ↓SVR	• Normal renal function: 0.25-0.75 mcg/kg/min • Creatinine clearance < 50 mL/min: reduce infusion rate	• Tachyarrhythmias • Hypotension • Myocardial ischemia	2 h; slower titration in renal failure

Abbreviations: IV, intravenous; HR, heart rate; PDE-3, phosphodiesterase 3; SV, stroke volume; SVR, systemic vascular resistance.

volume.[21] Dopamine can cause tachyarrhythmias, which is often severe enough to require a change to another agent with less beta-1 agonism, such as norepinephrine or phenylephrine.

Epinephrine

Epinephrine, the most potent vasopressor used in clinical practice, is an endogenous catecholamine synthesized from norepinephrine that is released from the adrenal medulla. It agonizes alpha and beta receptors and exhibits dose-dependent effects.[27,28] **(See Table 3.)** The use of epinephrine is limited by the potential for tachyarrhythmias, cardiac ischemia, and splanchnic vasoconstriction.[24,29] Although epinephrine should be used with caution in patients with coronary artery disease, clinical trials have not demonstrated worsened outcomes with this agent. Epinephrine causes increased serum lactate levels, but this occurs primarily as a result of increased glycolysis and glycogenolysis within skeletal muscle rather than from tissue hypoperfusion.[18]

Phenylephrine

Phenylephrine functions as a selective alpha-1 agonist, causing vasoconstriction without direct effects on the heart.[28,31] Use of phenylephrine can also lead to baroreceptor-mediated reflex bradycardia.[32] Pure alpha-1 agonism makes phenylephrine useful for treatment of vasodilatory shock, particularly when other vasoactive agents (such as norepinephrine or dopamine) precipitate tachyarrhythmias. Phenylephrine appears to be a less potent vasoconstrictor than norepinephrine, as evidenced by higher dosages required to achieve the same goal MAP.[44] In patients with depressed left ventricular function, unopposed alpha-1 effects may lead to decreased cardiac output or myocardial ischemia.[30] However, clinical trials have failed to demonstrate these adverse effects when phenylephrine is used within the clinically appropriate dose range.[32,33]

Vasopressin

Vasopressin is a hormone released from the pituitary in response to decreased blood pressure, and it acts on V_1 receptors to cause vasoconstriction and increased sensitivity to catecholamines in patients with shock.[32,34] The increased sensitivity to catecholamines may be due, in part, to the observation that metabolic acidosis reduces the potency of alpha-adrenergic agents but not vasopressin.[35] A trend toward higher rates of peripheral ischemia has been observed with vasopressin when it is compared to norepinephrine.[24] In addition, vasopressin-induced increases in afterload have led some to question its use in cardiogenic shock and in patients with depressed left ventricular function. These adverse effects are dose-dependent, and therefore, doses higher than 0.03-0.04 units/min are not recommended.[18]

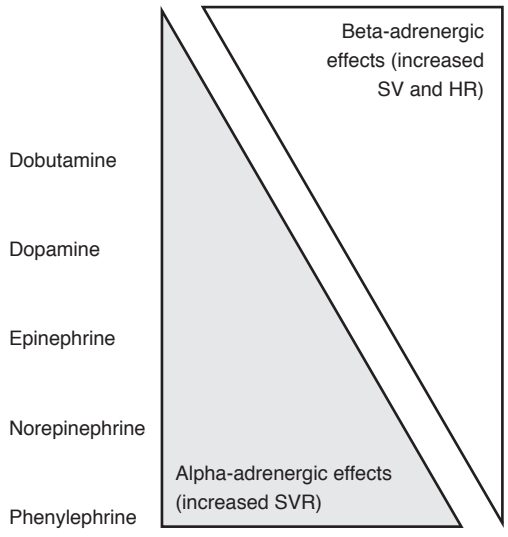
Dobutamine

Dobutamine, a synthetic catecholamine with potent beta-1 agonism, increases heart rate and contractility and is used primarily as an inotropic agent.[36] Dobutamine may cause hypotension as a result of beta-2 agonism, especially in hypovolemic patients and at higher doses, where beta-2 effects become more pronounced. Hypotension may be treated by using an alpha-agonist in conjunction with dobutamine. Beta-1 agonism may cause tachyarrhythmias and increased myocardial oxygen demand, but beta-2 agonism tends to balance myocardial oxygen demand by reducing afterload and increasing contractility.[37]

Milrinone

Milrinone is a phosphodiesterase-3 inhibitor that increases cyclic adenosine monophosphate in cardiac myocytes and vascular smooth muscle, thus increasing heart rate and stroke volume while decreasing systemic vascular resistance.[38] Although milrinone can cause tachyarrhythmias, the incidence is lower than with dobutamine. Hypotension can also occur due to cyclic adenosine monophosphate-induced vasodilation. Because it has a half-life of approximately 2 hours and is cleared renally, milrinone can cause hypotension, especially in patients with hypovolemia or renal failure.[39] A loading dose may be considered when starting milrinone, but the risk of hypotension often outweighs the benefit in patients who are not hypertensive. Milrinone causes pulmonary vasodilation, making it an attractive option when treating right ventricular failure.[40]

Figure 1. Relative Alpha And Beta Effects Of Commonly Used Vasoactive Agents



Abbreviations: HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance.

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Principles Of Management

Septic Shock

Severe sepsis affects over 750,000 people per year in the United States, and approximately 500,000 of these patients are initially treated in the ED.[41,42] One quarter of patients will suffer from circulatory failure and may require vasoactive agents.[41] **(See Table 4.)** In the 2008 Surviving Sepsis® Campaign guidelines, dopamine and norepinephrine were given equal weight as first-line agents in the treatment of septic shock. However, in a meta-analysis of 6 randomized trials published in 2012, dopamine was associated with an increased risk of death when compared to norepinephrine (relative risk [RR], 1.12; confidence interval [CI], 1.01-1.20; $P = .035$).[43] Furthermore, when compared to dopamine, norepinephrine appears to be less arrhythmogenic and a more potent vasopressor.[24,43,44] As a result, the 2012 Surviving Sepsis® Campaign guidelines recommended norepinephrine as the vasopressor of choice.[18] Although norepinephrine should be used preferentially, the chronotropic effects of dopamine make this vasopressor a reasonable alternative in patients with septic shock and relative bradycardia.

In patients requiring moderate doses of norepinephrine (5-15 mcg/min), the addition of vasopressin may be beneficial. In the early phases of septic shock, vasopressin levels initially increase, followed by a rapid decline to inappropriately low levels.[45] When used in high doses as a single agent for septic shock, vasopressin appears less effective than norepinephrine at maintaining MAP and may increase complications and mortality.[18,46] In the Vasopressin and Septic Shock Trial, patients with septic shock who were receiving at least 5 mcg/min of norepinephrine were randomized to norepinephrine alone or norepinephrine plus vasopressin at a low fixed dose of 0.03 units/min. Although there was no difference in mortality in the intent-to-treat population, a subgroup analysis suggested that patients with lower norepinephrine requirements (< 15 mcg/min of norepinephrine at randomization) had a lower mortality when treated with vasopressin (26.5% vs 35.7%, $P = 0.05$). Vasopressin had a catecholamine-sparing effect, as evidenced by a lower norepinephrine requirement in the treatment group. Vasopressin did not increase the rate of serious adverse events compared to norepinephrine alone. In addition, vasopressin has been associated with a reduction in heart rate in septic shock and may be of benefit in patients prone to tachyarrhythmias from norepinephrine.[46-48]

There are limited clinical studies examining phenylephrine in the treatment of septic shock. In 2 small randomized trials, patients with septic shock who were administered phenylephrine had a similar increase in systemic vascular resistance and stroke volume compared to patients receiving norepinephrine.[49,50] However, other studies have shown phenylephrine to be less effective in reversing sepsis-induced hypotension than norepinephrine.[50] The pure alpha-adrenergic effect of phenylephrine may adversely affect myocardial performance in patients with sepsis-induced myocardial dysfunction by excessively increasing afterload without positively affecting cardiac contractility.[51] There appears to be no difference in splanchnic perfusion between phenylephrine and norepinephrine.[50] Current evidence does not support the routine use of phenylephrine in the management of septic shock. Phenylephrine may be considered as an alternative agent in the case of tachyarrhythmias or it can be added to norepinephrine in the case of refractory hypotension.

Although sepsis is generally thought of as a hyperdynamic state, left ventricular dysfunction commonly occurs.[52] In patients with evidence of low cardiac output despite adequate fluid resuscitation, agents with potent inotropic effects (such as dobutamine or epinephrine) may be used to optimize cardiac function.[7] Dobutamine causes vasodilation, and it is typically used in conjunction with a vasoconstrictor (such as norepinephrine) in septic shock. Alternatively, epinephrine can be used as a single agent, owing to its dual inotropic and vasoconstricting effects. In a multicenter randomized trial examining epinephrine versus combination treatment with dobutamine and norepinephrine for septic shock, there was no difference in mortality (40% vs 34%, $P = 0.31$).[53] The time to hemodynamic stabilization was similar between groups. Surprisingly, epinephrine was not associated with an

Table 4. Guidelines For The Use Of Vasoactive Agents In Septic Shock[18]

Vasoactive Agent	Indication
Norepinephrine	Vasopressor of choice for septic shock
Vasopressin	Use in conjunction with norepinephrine
Epinephrine	May be used as an alternative to norepinephrine, especially in patients with evidence of low cardiac output despite fluid resuscitation. Use as additional/substitute agent to maintain blood pressure in refractory shock
Dopamine	Alternative to norepinephrine in patients with bradycardia
Phenylephrine	Alternative when norepinephrine causes tachyarrhythmias. Use as additional agent in refractory shock when cardiac output is known to be high
Dobutamine	Low cardiac output* despite achieving adequate intravascular volume and blood pressure

*May be evidenced by central venous oxygen saturation ($ScVO_2$) < 70%.

increase in severe arrhythmias, myocardial events, or limb ischemia; however, the epinephrine group had significantly higher lactate concentrations. As mentioned previously, epinephrine causes increased serum lactate levels through changes in metabolism in skeletal muscle rather than from tissue hypoperfusion. The increase in lactate concentration may nevertheless confound endpoints of resuscitation when using epinephrine for the treatment of septic shock. In addition, there is some evidence that epinephrine may have deleterious effects on splanchnic perfusion when compared to norepinephrine and dobutamine.[54,55]

Anaphylactic Shock

Up to 40% of patients with anaphylaxis require the administration of vasoactive agents.[56,57] Potent alpha and beta adrenergic properties of epinephrine cause vasoconstriction, reduction of mucosal edema, bronchodilation, and increased myocardial contractility. Thus, epinephrine treats all 3 life-threatening processes of anaphylaxis: laryngeal edema, bronchospasm, and shock.[58] Epinephrine also suppresses leukotriene and histamine release. There are no prospective randomized trials examining epinephrine for the treatment of anaphylaxis.[59] Despite case reports of the successful use of vasopressin, alpha agonists, and other vasoactive agents, epinephrine remains the first-line treatment for anaphylaxis, based primarily on expert opinion.[58-62] Although physicians are often reluctant to administer epinephrine out of fear of precipitating myocardial ischemia, epinephrine is safe and effective when administered appropriately. Furthermore, delayed administration of epinephrine has been associated with death from anaphylaxis,[63-65] and untreated anaphylaxis may precipitate myocardial ischemia.[66]

Lack of physician knowledge about dosing and administration, as well as inadequate communication between physicians and nurses with regard to the dose, route of administration, and drug concentration, contribute to fatal dosing errors with epinephrine.[67] Peak plasma concentrations of epinephrine are higher with intramuscular injection in the lateral thigh compared to either intramuscular or subcutaneous injection in the deltoid.[68] In adults, 0.3-0.5 mg of 1:1000 (1 mg/mL) solution should be administered intramuscularly in the lateral thigh as the preferred route for treatment of anaphylaxis. One to 2 additional intramuscular doses can be repeated every 5 minutes, if necessary. In cases refractory to intramuscular epinephrine or in the case of impending circulatory collapse, 1:10,000 (0.1 mg/mL) solution of epinephrine can be administered intravenously at a rate of 1 to 20 mcg/min and titrated to achieve an adequate MAP. Beta-adrenergic blockers may be associated with more severe anaphylaxis by antagonizing the effects of both endogenous and exogenous epinephrine.

There are case reports of the efficacy of glucagon in treating anaphylaxis in patients on beta blockers.[69] Glucagon has a specific receptor on the cardiac myocyte that is separate from beta-adrenergic receptors, which increases heart rate and contractility when stimulated. Intravenous glucagon can be given in a dose of 1 to 5 mg in cases refractory to epinephrine.

Neurogenic Shock

Neurogenic shock occurs with relative frequency, affecting 13% to 78% of patients with cervical spinal cord injuries.[70-72] A cervical spinal cord injury may result in complete loss of cardiac and vasomotor sympathetic tone and intact parasympathetic function. Thus, neurogenic shock characteristically includes vasodilation with warm distal extremities and the absence of compensatory tachycardia (and often the presence of bradycardia). These features may help to differentiate neurogenic shock from other causes of shock in the trauma patient. Goals of treatment are twofold: (1) reversing systemic hypotension, and (2) preventing secondary injury to the spinal cord from ischemia. Multiple small case series show modest improvement in neurologic outcome (presumably from increased spinal cord perfusion) when MAP is maintained between 85 and 90 mm Hg with the use vasopressors.[73,74] Bradycardia accompanies hypotension in many patients with neurogenic shock and has even been described as occurring "universally."[71] Not surprisingly, many studies of neurogenic shock use dopamine as a first-line agent owing to its chronotropic effects.[75] Although phenylephrine and norepinephrine have also been used, there are no randomized controlled trials comparing the safety and efficacy of different vasoactive agents in neurogenic shock. Phenylephrine can cause reflex bradycardia, and this should be taken into consideration prior to using this agent in patients with spinal cord injury-related bradycardia.

Cardiogenic Shock

Cardiogenic shock results from primary cardiac dysfunction, most commonly due to acute myocardial infarction. In patients with cardiogenic shock from myocardial infarction, the condition is apparent on presentation to the ED in 15% of cases.[76] Although mechanical complications of myocardial infarction (papillary muscle or ventricular septal rupture) may cause cardiogenic shock, left ventricular dysfunction remains the most common cause, accounting for almost 80% of cases.[77] Vasoactive agents may be required to improve hemodynamics until definitive therapy with coronary revascularization can be achieved.

Agents with inotropic properties are often used to optimize cardiac function in patients with low cardiac output states and adequate filling pressures. The beta-1 effects of dobutamine augment

cardiac contractility while the beta-2 effects reduce afterload. Dobutamine may be less effective in patients taking beta blockers; milrinone can be used as an alternative.[78] Milrinone also has vasodilating properties and must be used with caution, owing to its relatively long duration of action. If hypotension occurs with dobutamine or milrinone, an agent with vasoconstricting properties may be needed.[79]

The 2004 American Heart Association/American College of Cardiology guidelines for ST-segment elevation myocardial infarction (STEMI) recommend the use of dopamine as a first-line agent in the case of cardiogenic shock and hypotension, and they recommend norepinephrine for marked hypotension (SBP < 70 mm Hg).[80] However, in a subgroup analysis of a recent multicenter randomized trial comparing dopamine to norepinephrine, dopamine was associated with an increased rate of death ($P = .03$) and a higher rate of arrhythmias (24% vs 12%, $P < .001$) in patients with cardiogenic shock.[24] The 2013 American Heart Association/American College of Cardiology guidelines no longer provide clear recommendations for vasopressor support, but they suggest that dopamine may be "associated with excess hazard."[76] In a small randomized trial of patients with cardiogenic shock, combination norepinephrine and dobutamine therapy produced similar improvements in MAP, oxygen delivery, and renal perfusion when compared to epinephrine. However, epinephrine was associated with a higher rate of lactic acidosis, tachycardia, and arrhythmia, as well as decreased gastric mucosal perfusion.[29] Therefore, norepinephrine-dobutamine therapy may be safer for the treatment of cardiogenic shock associated with hypotension. Phenylephrine is generally avoided in cardiogenic shock, as it increases afterload without augmenting cardiac contractility.[78]

Obstructive Shock

Cardiac Tamponade

In patients with cardiac tamponade, vasoactive agents are often used in an attempt to maintain MAP until definitive therapy with pericardial drainage can be performed. Clinical trials examining the role of vasoactive agents in cardiac tamponade are lacking. In an animal study comparing dopamine and norepinephrine, cardiac output increased by 50% with dopamine but was unchanged with norepinephrine. Norepinephrine more effectively increased MAP, but neither agent improved cerebral or renal blood flow.[81] This study suggests that the hemodynamic benefits of vasoactive agents in cardiac tamponade are limited, and it underscores the importance of pericardial drainage to improve end-organ perfusion.

Massive Pulmonary Embolism

Early mortality with massive pulmonary embolism may be as high as 15%, and the degree of hemodynamic compromise predicts inhospital mortality.[82] There is a lack of clinical trials comparing different vasoactive agents for circulatory shock due to pulmonary embolism. An ideal agent would reduce pulmonary vascular resistance, augment cardiac output, and improve systemic hypotension. In a small observational study, dobutamine increased cardiac output, reduced right-sided filling pressures, reduced pulmonary vascular resistance, and improved oxygen delivery in patients with circulatory shock due to massive pulmonary embolism.[83] In an animal model of acute pulmonary hypertension and right ventricular failure, dobutamine and norepinephrine similarly restored MAP. However, dobutamine increased cardiac output and reduced pulmonary vascular resistance more effectively than norepinephrine.[84] Dobutamine often requires the coadministration of a vasoconstrictor (such as norepinephrine). Milrinone may be a more potent pulmonary vasodilatory agent than dobutamine, but its use in massive pulmonary embolism is limited by an inability to rapidly titrate this agent in unstable patients.[40] Phenylephrine may improve systemic blood pressure in hypotensive patients, but this benefit may be offset by a lack of inotropic effects and a decrease in right ventricular function due to increased pulmonary vascular resistance.

Tools And Techniques

Central Versus Peripheral Administration

Administration of adrenergic agents (such as norepinephrine and dopamine) through peripheral intravenous catheters may cause soft-tissue necrosis if subcutaneous extravasation occurs. This complication may happen with low dose vasopressin as well.[85] Consequently, vasoactive agents should be administered via the central venous system whenever possible. In the case of immediately life-threatening hypotension or impending cardiovascular collapse, vasoactive agents should not be delayed; rather, they should be initiated through peripheral access while attempting central venous catheterization. If subcutaneous extravasation of an alpha-adrenergic agent occurs, the alpha-adrenergic antagonist phentolamine can be used to prevent soft-tissue necrosis.[86] Administration involves subcutaneous infiltration of approximately 1 mL of solution (made by diluting 5-10 mg in 10 mL of normal saline) at the site of extravasation. Usually, doses of < 5 mg are effective, as evidenced by return of normal skin color at the site of blanching.

Bolus-Dose Vasopressors For Postintubation Hypotension

Postintubation hypotension occurs in 23% of ED intubations and independently predicts inhospital mortality.[87] Hypotension often results from vaso-

dilation due to induction agents, and up to 20% of patients require vasopressors.[87] Preparation of vasopressors for continuous infusion can be time-consuming, and life-threatening hypotension may occur abruptly after induction. Bolus-dose vasopressors can be rapidly prepared and administered to maintain blood pressure after induction.[88] Although there are limited data examining this practice, a randomized trial supports the use of bolus phenylephrine to maintain blood pressure following administration of spinal anesthesia.[89] This technique may be useful in treating postintubation hypotension while awaiting the preparation of a vasoactive solution to be used for continuous infusion. **(See Table 5.)** In the authors' clinical experience, bolus-dose norepinephrine and epinephrine are also commonly used to treat postintubation hypotension (albeit with little supporting evidence from the literature).

Clinical Course In The Emergency Department

Determining Stability: Endpoints Of Resuscitation

Blood pressure typically serves as an endpoint of vasopressor titration in patients with shock. In a large retrospective analysis of intensive care unit (ICU) patients, MAP appeared to be a more reliable measure of end-organ perfusion than systolic blood pressure.[90] The optimal MAP in shock remains unknown and probably varies between individual patients. In the Rivers et al early goal-directed therapy study, vasopressors were titrated to maintain a MAP of ≥ 65 mm Hg; the treatment group had a reduced mortality, from 47% to 31% ($P = .009$).[7] However, the MAP goal of ≥ 65 mm Hg in this study was only a single endpoint of resuscitation in a more complicated algorithm for hemodynamic management, and it was the same blood pressure goal used in the control group. Thus, it is not clear whether a MAP goal of ≥ 65 mm Hg contributed to the observed reduction in mortality. In a small study of patients with septic shock who were randomized to a MAP of 65 versus 85 mm Hg using norepinephrine, the lower MAP limit of 65 mm Hg was shown to maintain tissue perfusion. Increasing MAP from 65 to 85 mm Hg did not improve renal function.[91] Although limited evidence supports a MAP of 65 mm Hg as a lower limit, some patients with chronic uncontrolled hypertension may require a higher MAP to maintain tissue perfusion. Clinical findings (including mental status, urine output, and capillary refill) can sometimes be helpful global markers of organ perfusion in these cases; however, it must be emphasized that the practice of relying solely on vital signs and physical examination findings as endpoints of resuscitation will fail to identify a significant number of patients with ongoing tissue hypoxia. Indeed, tissue hypoxia may still occur despite a normal blood pressure; this has been termed "occult hypoperfusion."[92] If tissue hypoxia is not corrected, multisystem organ failure ensues. Therefore, an accurate assessment of the adequacy of oxygen delivery to tissues by measuring serum lactate and venous oxygen saturation is critical to titrating vasoactive agents and resuscitating patients in shock.

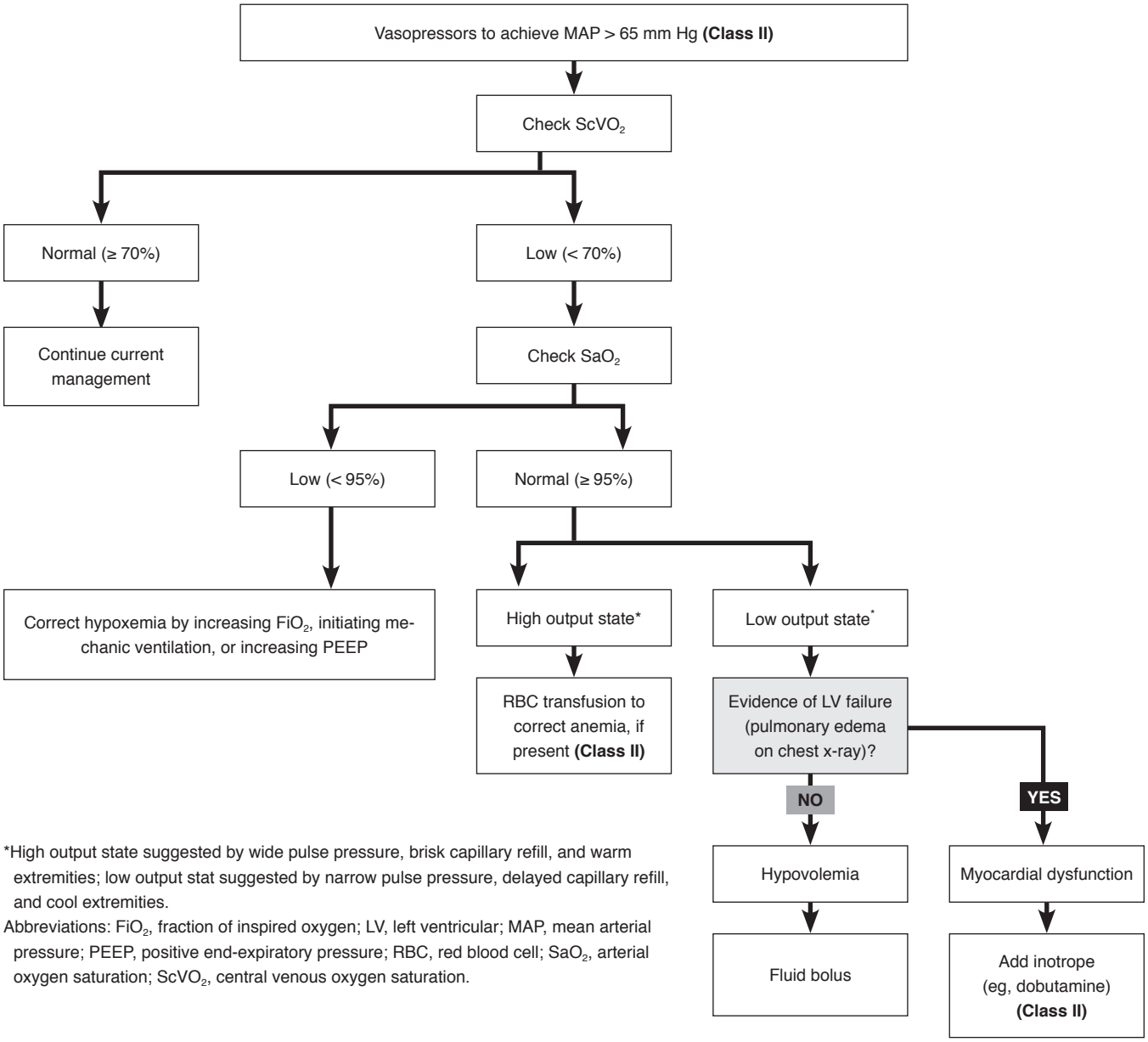
In states of persistent tissue hypoxia, anaerobic metabolism occurs and lactate is produced. An elevated serum lactate level has been consistently shown to correlate with both organ failure and mortality in the critically ill.[93] Furthermore, evidence suggests that a serial decrease in serum lactate provides an objective evaluation of response to therapy in patients with shock.[16,94] If abnormal, lactate should be measured every 2 hours during resuscitation until the level normalizes.[95] Venous oxygen saturation can also serve as an indirect marker of tissue oxygenation. A low venous oxygen saturation in critical illness results from reduced oxygen delivery (due to anemia, hypoxia, or inadequate cardiac output), increased oxygen consumption in the tissues, or any combination thereof. Venous oxygen saturation can be measured from the pulmonary artery using a pulmonary artery catheter (mixed venous oxygen saturation, SVO_2) or the superior vena cava using a central venous catheter (central venous oxygen saturation, $ScVO_2$). However, several randomized trials have not shown benefit from invasive hemodynamic monitoring with a pulmonary catheter and its routine use is not recommended.[96]

Table 5. Preparation And Administration Of Bolus-Dose Vasoactive Agents In The Management Postintubation Hypotension

Vasoactive Agent	Preparation	Prepared Concentration	Administration
Phenylephrine	Inject 2 mL of 10 mg/mL phenylephrine solution into a 250-cc bag of sterile D5W	80 mcg/mL of phenylephrine	1-2 mL (80-160 mcg) IV every 2-5 min, as needed
Epinephrine	Draw up 1 mL of 1:10,000 epinephrine solution into 9 mL of sterile saline	10 mcg/mL of epinephrine	0.5-1 mL (5-10 mcg) IV every 2-5 min, as needed
Norepinephrine	Inject 1 mL of 4 mg/4 mL solution of norepinephrine into a 100-mL bag of sterile saline	10 mcg/mL of norepinephrine	0.5-1 mL (5-10 mcg) IV every 2-5 minutes, as needed

Abbreviations: D5W, 5% dextrose in water; IV, intravenous.

Clinical Pathway For Treatment Of Vasopressor-Dependent Shock Using Venous Oxygen Saturation[104]



*High output state suggested by wide pulse pressure, brisk capillary refill, and warm extremities; low output stat suggested by narrow pulse pressure, delayed capillary refill, and cool extremities.

Abbreviations: FiO_2, fraction of inspired oxygen; LV, left ventricular; MAP, mean arterial pressure; PEEP, positive end-expiratory pressure; RBC, red blood cell; SaO_2, arterial oxygen saturation; $ScVO_2$, central venous oxygen saturation.

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Central venous catheters with continuous $ScVO_2$ monitoring are commercially available, but the value can also be measured intermittently from a standard central line placed in the superior vena cava. Normal venous oxygen saturation is approximately 65% to 75%, and the $ScVO_2$ is generally about 5% higher than the SVO_2.

An example of an algorithmic approach to resuscitation using $ScVO_2$ is provided in the **Clinical Pathway (page 10)**. Several studies have shown improvements in patient outcomes using venous oxygen saturation as an endpoint of resuscitation. In a study of ED patients with decompensated heart failure, $ScVO_2$ was used as evidence of undetected cardiogenic shock. Treatment with inotropes and vasodilators tended to improve $ScVO_2$ and lactate levels.[97] In ED patients with severe sepsis and septic shock, randomization to therapy that included maintaining $ScVO_2 > 70\%$ using dobutamine to augment cardiac output within the first 6 hours of resuscitation improved mortality.[7] Targeting therapy to achieve supranormal cardiac output and oxygen delivery using inotropes may be harmful, and this practice is not recommended.[98]

Two other points with regard to the use of $ScVO_2$ bear mentioning. First, evidence suggests that hemodynamic optimization in the critically ill using $ScVO_2$ reduces mortality when initiated early (during the first 6 hours in the ED) but not late (after admission to the ICU).[99] This observation highlights the importance of early and aggressive resuscitation from shock in the ED using objective end points of resuscitation. Second, a normal $ScVO_2$ value does not guarantee adequate tissue oxygenation. In fact, many patients with shock will have evidence of tissue hypoxia (eg, an elevated lactate) and develop multiorgan failure despite an $ScVO_2 > 70\%$. This clinical scenario likely results from impaired oxygen extraction and utilization in the tissue, resulting in a high venous oxygen content despite ongoing cellular hypoxia. Studies evaluating novel techniques to assess the microcirculation are ongoing and may ultimately allow for more effective titration of vasoactive agents during resuscitation from circulatory shock.[100,101]

Identifying And Managing Deterioration

Patients with profoundly decreased vasomotor tone may undergo clinical deterioration despite escalating doses of vasopressors. Vasopressor-refractory shock occurs when MAP cannot be maintained despite adequate fluid resuscitation and high-dose vasopressors, and it portends a poor prognosis.[102] Multiple vasopressors are often required in patients with refractory shock. Norepinephrine and epinephrine are the most potent vasopressors and should be used preferentially in patients requiring high-dose vasopressors. In a large randomized trial comparing dopamine to norepinephrine for shock, death from refractory shock occurred more frequently in the dopamine group ($P = .05$).[24] In patients with septic shock refractory to vasopressor treatment and adequate fluid resuscitation, corticosteroids resulted in faster reversal of shock, and they may be considered.[18,103] Intravenous hydrocortisone, the most commonly used agent in large trials, is typically administered at a dose of 200 to 300 mg per day in divided doses (50 mg every 6 h or 100 mg every 8 h). Cardiogenic shock represents a special circumstance where deterioration may require the use of mechanical devices (ventricular assist devices or intra-aortic balloon pump) to achieve hemodynamic stability.

Special Circumstances

Pediatrics

An evidence-based review of the use of vasoactive agents in pediatrics is beyond the scope of this article; however, a few considerations are worth highlighting. Because placing a central line in a child can be difficult and the initiation of vasoactive agents should not be delayed, they should be initiated through peripheral or intraosseous access while attempting central venous catheterization.[18] In pediatric patients, physical examination findings may be used as endpoints to titrate vasoactive medications. For example, a capillary refill time of < 2 seconds correlates with an $ScVO_2 > 70\%$ in children.[105] In patients with a low output state despite adequate fluid resuscitation, dopamine, dobutamine, or epinephrine are reasonable first-line agents with inotropic properties. In patients with distributive shock, dopamine has traditionally been the first-line vasopressor. Given increasing evidence that dopamine may be associated with worse outcomes in adults with septic shock, norepinephrine may be a reasonable alternative in children as well.[106] In cases of dopamine-resistant shock, epinephrine can be used in addition to (or in place of) dopamine.

Pregnancy

The need for critical care in the pregnant patient population occurs infrequently, affecting < 1% of pregnancies.[107] Most commonly, shock results from postpartum hemorrhage, obviating the need for vasopressors, in many cases. Septic shock, although rare, remains an important contributor to maternal death.[108] A limited number of studies on the use of vasoactive agents in pregnancy exist, owing to the exclusion of this population from large trials involving the critically ill. Not surprisingly, the choice of vasoactive agents depends primarily on physiologic considerations, animal studies, and experience with hypotension induced by spinal anesthesia.

Uterine arteries are maximally dilated during pregnancy and vascular autoregulation cannot be relied upon to improve fetal oxygen delivery.[109] As

a result, uterine perfusion may be impaired in the setting of maternal hypotension or the use of vasoactive agents. Multiple randomized controlled trials have compared ephedrine, a less-potent synthetic derivative of epinephrine, to phenylephrine for the treatment of hypotension during spinal anesthesia.[110,111] In a systematic review of randomized controlled trials, phenylephrine and ephedrine were equally effective in treating maternal hypotension.[110] Phenylephrine was associated with higher rates of maternal bradycardia but possibly better ureteroplacental perfusion.[110,111]

It is difficult to extrapolate the treatment of hypotension induced by spinal anesthesia to the treatment of other causes of shock in pregnancy. In the absence of evidence from clinical trials involving obstetric patients, we generally extrapolate from the treatment of shock in nonpregnant patients. For example, when treating a pregnant patient with septic shock, we would suggest using norepinephrine as a first-line vasopressor based on the recommendations from the Surviving Sepsis® Campaign Guidelines rather than using phenylephrine as a first-line agent based on extrapolation of data from spinal anesthesia studies. This practice is based on the assumption that improving maternal outcomes using evidence-based treatment of the underlying disease process should, in turn, translate to improved fetal outcomes.

Must-Do Markers Of Quality ED Critical Care

1. The diagnosis of shock does not require the presence of hypotension. Shock is a state of inadequate oxygen delivery to tissues, and it may occur in the setting of a normal blood pressure. An elevated serum lactate level provides objective evidence of anaerobic metabolism in such cases. $ScVO_2$ can also be used as an objective measure of oxygen delivery to tissues, and it can be measured serially to guide resuscitation efforts.
2. Norepinephrine—rather than dopamine—should be used as a first-line agent to maintain adequate blood pressure in patients with septic shock. When compared to norepinephrine, dopamine has been associated with an increased risk of death and tachyarrhythmias. Dopamine is also less effective at restoring blood pressure than norepinephrine.
3. Vasopressors should be administered through a central venous catheter whenever possible, as peripheral administration has been associated with soft-tissue necrosis when subcutaneous infiltration occurs. Central venous access also provides endpoints for resuscitation (central venous pressure, $ScVO_2$) in patients with shock.
4. Lack of physician knowledge regarding appropriate epinephrine administration has been associated with life-threatening complications in patients with anaphylaxis. In adults, 0.3-0.5 mg of 1:1000 (1 mg/mL) solution should be administered intramuscularly in the lateral thigh. The 1:10,000 (0.1 mg/mL) solution can be given intravenously for more-severe cases.
5. The use of "renal-dose" dopamine does not prevent or treat acute kidney injury, and dopamine should not be used for this purpose.

Controversies And Cutting Edge

Renal-Dose Dopamine

Historically, dopamine has been used at doses < 5 mcg/kg/min to increase renal blood flow and urine output in an effort to prevent and treat acute kidney injury. A large randomized controlled trial and a subsequent meta-analysis of dopamine versus placebo failed to demonstrate any objective renal benefit, including peak serum creatinine and need for renal replacement therapy.[112,113] As a result, dopamine should not be used for renal protection.[18]

Disposition

The need for vasoactive agents is a universally accepted indication for admission to the ICU. The Society for Critical Care Medicine "Guidelines for ICU Admission, Triage, and Discharge" categorized patients who require continuous vasoactive agents as Priority 1 (ie, those who will benefit most from the ICU admission).[114] Optimal treatment of patients with cardiogenic shock due to acute myocardial infarction involves emergent revascularization with percutaneous coronary intervention or coronary artery bypass grafting; therefore, patients may require transfer to an appropriate center for definitive care.[77] In addition, patients with cardiogenic shock may require transfer to a specialty center where mechanical devices (ventricular assist devices or intra-aortic balloon pump) can be placed, if necessary.

Summary

Emergency physicians commonly encounter patients with circulatory shock of different etiologies. The management of shock may require the use of vasoactive agents to maintain global tissue perfusion and oxygen delivery. A familiarity with the underlying pathophysiology of shock states, the pharmacology of vasoactive agents, and the endpoints of resuscitation will allow for effective management of the hemodynamically unstable patient. In recent years, high-quality clinical trials have provided more-robust evidence for the use of different vasoactive agents for specific causes of shock.

Case Conclusion

Your colleague chose norepinephrine rather than dopamine for septic shock based on evidence that dopamine may be associated with increased mortality compared to norepinephrine. In addition, norepinephrine appears to be a more potent vasopressor and is less likely to precipitate tachyarrhythmias than dopamine. After a brief discussion with the consulting ICU team, you titrated the norepinephrine to 12 mcg/min to maintain a MAP of > 65 mm Hg. You added vasopressin at a fixed low dose, given the evidence that this may reduce norepinephrine requirements and improve mortality in patients with less-severe shock. The patient's MAP improved, the norepinephrine requirement decreased, and the patient was transported to the ICU. As the ICU team was completing early goal-directed therapy, they noted the patient was oliguric and her $ScVO_2$ was only 64%, suggesting inadequate oxygen delivery despite adequate fluid resuscitation. She had a MAP > 65 mm Hg and a HCT > 30. Because they suspected the patient had sepsis-induced cardiac dysfunction, they added dobutamine 5 mcg/kg/min, and the patient's $ScVO_2$ increased to 72% and her urine output also increased. The patient's blood and urine cultures grew Escherichia coli. Her antibiotics were tailored to this pathogen, and she was tapered off vasoactive agents less than 48 hours after presentation. She was discharged home on hospital day 5.

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Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

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CME Questions

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1. A healthy 46-year-old male presents to the ED with a week-long history of diarrhea and poor oral intake. His initial vitals are as follows: temperature, 37.3°C; heart rate, 120 beats/min; blood pressure, 70/55 mm Hg; and respiratory rate, 22 breaths/min. Physical examination shows dry mucous membranes, cold and clammy extremities with delayed capillary refill, and flat neck veins. Based on available data, the most likely etiology of shock is:
a. Cardiogenic
b. Hypovolemic
c. Distributive
d. Obstructive

2. **Which vasoactive agent may cause an increase in lactate production from skeletal muscle, thus limiting the use of serum lactate as an endpoint of resuscitation?**
   a. Dobutamine
   b. Vasopressin
   c. Epinephrine
   d. Norepinephrine

3. **Which of the following vasoactive agents exhibits selective alpha-adrenergic receptor agonism?**
   a. Norepinephrine
   b. Epinephrine
   c. Dopamine
   d. Phenylephrine

4. **Which of the following vasoactive agents is least likely to precipitate tachyarrhythmias?**
   a. Norepinephrine
   b. Phenylephrine
   c. Dopamine
   d. Milrinone

5. **A 55-year-old man with a history of diabetes presents to the ED with septic shock from pneumonia. After receiving 6 L of intravenous fluid, his central venous pressure is 15 cm H_2O and he has pulmonary edema on chest x-ray. His most recent vitals show a blood pressure of 80/30 mm Hg (mean arterial pressure of 47) and a heart rate of 100 beats/min. What is the most appropriate intervention for treating the patient's shock at this point?**
   a. Continue aggressive intravenous fluid boluses.
   b. Start norepinephrine infusion and titrate to MAP > 65 mm Hg.
   c. Start phenylephrine infusion and titrate to MAP > 65 mm Hg.
   d. Start vasopressin infusion and titrate to MAP > 65 mm Hg.

6. **Which of the following might be expected after the addition of vasopressin at a fixed, low dose in a patient requiring moderate doses (5-15 mcg/min) of norepinephrine for septic shock?**
   a. Vasopressin-related tachyarrhythmias
   b. Lower doses of norepinephrine required to maintain the same blood pressure
   c. Increased mortality
   d. Increased serious adverse events

7. **Which of the following is the correct dose and route of administration of epinephrine for a patient with anaphylaxis?**
   a. 0.3-0.5 mg of 1:1000 solution intramuscularly
   b. 0.3-0.5 mg of 1:10,000 solution intramuscularly
   c. 0.3-0.5 mg of 1:10,000 solution subcutaneously
   d. 1-20 mcg/min of 1:1000 solution intravenously

8. **In a subgroup analysis of a large randomized trial comparing norepinephrine to dopamine, the use of dopamine in cardiogenic shock was associated with which of the following?**
   a. Lower rate of dialysis in patients receiving "renal dose" dopamine
   b. Increased risk of death
   c. Increased risk of symptomatic bradycardia
   d. None of the above

9. **Which of the following vasoactive agents can cause soft-tissue necrosis if subcutaneous infiltration occurs during administration through a peripheral intravenous catheter?**
   a. Dopamine
   b. Norepinephrine
   c. Vasopressin
   d. All of the above

10. **Which of the following is true regarding the use of venous oxygen saturation as an endpoint of resuscitation in shock?**
    a. Targeting a supranormal cardiac output and venous oxygen saturation using inotropes improves mortality.
    b. A normal $ScVO_2$ always indicates adequate oxygen delivery to the tissues.
    c. Early hemodynamic optimization using $ScVO_2$ in ED patients with septic shock improves mortality.
    d. There is no correlation between capillary refill time and central venous oxygen saturation in children.

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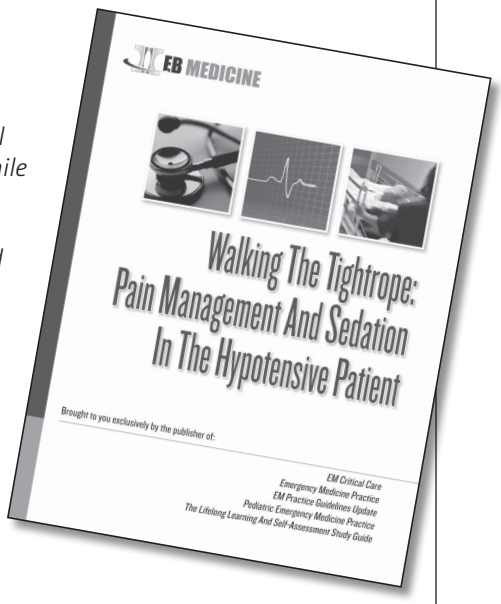

EXCERPT FROM THE ARTICLE:
It's the beginning of your evening shift, and it's a busy one. Upon entering the critical care room, you find your patient to be profusely diaphoretic and writhing in pain while holding his left chest. His vital signs show a blood pressure of 90/50 mm Hg and a pulse of 56 beats per minute. He is afebrile, with a respiratory rate of 20 breaths per minute and an oxygen saturation of 96%. A stat ECG confirms sinus bradycardia and reveals mild diffuse ST depressions. The nurse attempts to establish an IV line as the patient continues to cry out in pain on the stretcher. You quickly weigh your options for analgesia and perhaps sedation given the current differential of (at least) acute myocardial infarction, pulmonary embolus, and thoracic dissection. Meanwhile, several questions come to mind: Should you attend to the blood pressure first with fluids or pressors? Should you try to narrow your potential diagnoses with further testing? Since the patient keeps trying to sit up, should you sedate, paralyze, and intubate him? What rapid sequence induction method is the safest yet most effective? You begin to mull over these questions as you consider your next steps...

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