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The Use of Vasopressors and Inotropes in the Emergency Medical Treatment of Shock

Timothy J. Ellender, MD[a,b,*], Joseph C. Skinner, MD[a,b]

[a]*Department of Emergency Medicine, Indiana University Hospital, Emergency Medical Group Inc., 1701 North Senate Boulevard EMTC-AG001, Indianapolis, IN 46202, USA*
[b]*Multidisciplinary Critical Care Fellowship, Methodist Hospital/Clarian Health, 1701 North Senate Boulevard, Indianapolis, IN 46202, USA*

Shock is a final common pathway associated with regularly encountered emergencies including myocardial infarction, microbial sepsis, pulmonary embolism, significant trauma, and anaphylaxis. Shock results in impaired tissue perfusion, cellular hypoxia, and metabolic derangements that cause cellular injury. Although this early injury is often reversible, persistent hypoperfusion leads to irreversible tissue damage, progressive organ dysfunction, and can progress to death [1].

Cardiovascular collapse (shock) is a common life-threatening condition that requires prompt stabilization and correction. Lambe and coworkers [2] reported a 59% increase in critically ill patients between 1990 and 1999. National estimates report an increase in potential shock with an estimated 1.1 Americans presenting to emergency departments nationally with potential shock (requiring emergent resuscitation within 15 minutes). This marks an estimated increase in emergent resuscitation requirements from 17% (1998) to 22% (2002) [3]. Depending on the etiology, mortality figures vary from 23% to 75% for some causes [3–11]. The clinical manifestations and prognosis of shock are largely dependent on the etiology and duration of insult. It is important that emergency physicians, familiar with the broad differential diagnosis of shock, be prepared to rapidly recognize, resuscitate, and target appropriate therapies aimed at correcting the underlying process. This article focuses on the basic pathophysiology of shock states and reviews

* Corresponding author. Department of Emergency Medicine, Indiana University, Emergency Medical Group Inc., 1701 North Senate Boulevard EMTC-AG001, Indianapolis, IN 46202.
E-mail address: tellende@iupui.edu (T.J. Ellender).

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the rationale regarding vasoactive drug therapy for cardiovascular support of shock within an emergency environment.

Vasoactive drugs have been used to treat the hemodynamic changes associated with shock for over 40 years [12]. In the emergency medical management of patients, vasoactive drug therapy is used to manipulate the relative distribution of blood flow and restore tissue perfusion. These agents are classically subdivided, based on their predominant pathway of activity, into two separate class types: vasopressors and inotropes. Vasopressors modulate vasoconstriction and thereby increase blood pressure, whereas inotropes increase cardiac performance and thereby improve cardiac output (CO). Vasopressor and inotropic agents function primarily through stimulation of adrenergic receptors or through the induction of intracellular processes that mimic sympathetic end points (increased cAMP). Many of the drugs in use have varied effects because of their mixed receptor activity. Most of these act directly or indirectly on the sympathetic nervous system with effects that vary according to the strength of sympathetic receptor stimulus and affinity. Direct-acting drugs operate by stimulating the sympathetic nervous system receptor, whereas indirect-acting drugs cause the release of norepinephrine, which produces the effect.

The composite treatment of shock largely depends on correctly identifying the aberrant mechanisms, eliminating the causative agents, and supporting recovery. Vasoactive drugs are used largely to right cardiovascular imbalances, and the proper selection of one or more agents greatly depends on a basic understanding of the physiologic mechanisms driving a particular shock state [12,13].

Shock is a physiologic state characterized by a systemic reduction in tissue perfusion necessary to meet the metabolic needs of the tissues. Hypoperfusion results in oxygen debt, occurring as oxygen delivery becomes unable to meet metabolic requirements [14–16]. This state of oxygen debt is derived from disruption within the oxygen delivery pathway.

Hypoperfusion and resulting oxygen debt leads to tissue ischemia, general cellular hypoxia, and derangements of critical biochemical processes [4,17] further propagating autonomic dysregulation and organ failure. These effects may be reversible if the shock state is promptly recognized and corrected. Recognized hypoperfusion is a time-dependent emergency. This concept is already established in hemorrhagic-traumatic [18–21], cardiovascular [22–25], septic [26–29], and general critical shock presenting to the emergency department [30–32]. Efforts to correct shock are largely aimed at restoring balance to one or all of three main systems: (1) the pump (CO); (2) the transport system (peripheral circulation); and (3) the transport medium (blood volume) (Table 1) [4].

Shock may be caused by a primary decrease in CO (cardiogenic-obstructive shock); vasodilatation (distributive shock); or low circulating blood volume (hypovolemic shock) (Table 2) [1]. Cardiogenic shock can be further defined by intrinsic dysfunction caused by myopathies, infarction, acute

Table 1
Categories of shock and primary treatment strategies

1° Therapy	Causes of inadequate blood or plasma volume	
Volume infusion	Hemorrhagic shock	Traumatic Gastrointestinal Cavitary hemorrhage
	Hypovolemic shock	Dehydration Gastrointestinal loss (vomitus, diarrhea) Third-spacing caused by inflammation (burns, pancreatitis)
1° Therapy	Causes of cardiogenic (pump) dysfunction and decreased cardiac output	
Chemical support with inotropic agents	Myocardial ischemia	Coronary thrombosis Hypotension with global hypoxia/ischemia
	Cardiomyopathy	Myocarditis Chronic myopathies (ischemic, diabetic, infiltrative, congenital)
	Late hypodynamic septic shock[a]	
	Structural cardiac damage	Ventricular rupture Acute valvular or papillary muscle dysfunction
	Toxic drug overdose[a]	Calcium channel blocker overdose β-blocker overdose
Require correction of underlying process or relief of obstructive processes	Pulmonary embolism[a] Cardiac tamponade Tension pneumothorax	
	Cardiac arrhythmia	Atrial fibrillation with rapid ventricular response Supraventicular tachycardia Ventricular tachycardia
1° Therapy	Causes of abnormal vasomotor tone and vasodilation	
Early volume infusion and chemical support with vasopressor agents	Early hyperdynamic septic shock[a] Anaphylactic shock Central neurogenic shock	
	Toxic drug overdose	Tricyclic antidepressants Opiates Alpha antagonists

[a] Denotes mixed physiologic processes that often necessitate mixed chemical support (inotropes/vasopressors).

Data from Jones AE, Kline JA. Shock. In: Marx, editor. Rosen's emergency medicine: concepts and clinical practice. 6th edition, vol 1. Philadelphia: Mosby; 2006. p. 42.

Table 2
Classification of shock and hemodynamic variables

Shock type	Heart rate	Stroke volume	Cardiac output	Systemic vascular resistance
Cardiogenic	Increased	Decreased	Decreased	Increased
Hypovolemic	Increased	No change or decreased	No change or decreased	Increased
Distributive (spinal[a])	Increased (normal or decreased[a])	Increased (no change[a])	Increased	Decreased

[a] Denotes physiologic variation in spinal shock caused by a predominant decrease in sympathetic input.

valvular dysfunction, and arrhythmias or by extrinsic dysfunction caused by obstructive disorders, such as pulmonary embolism, constrictive pericarditis, pericardial tamponade, or tension pneumothorax [33,34]. Hypovolemic shock, caused by a relative or absolute decreased circulating blood volume, results in a decreased preload that alters stroke volume and leads to a decreased CO. Hypovolemic shock can be caused by hemorrhage from trauma, aneurysm rupture, or gastrointestinal bleeding, or from basic fluid loss caused by diarrhea, burns, or "third spacing." Distributive or vasodilatory shock results from vascular changes that lead to a decrease in vasomotor tone and a loss of peripheral vascular resistance. There are multiple subcauses of distributive shock including sepsis, anaphylaxis, toxic shock syndrome, and central neurologic injury. It is also important to note that vasodilatory shock is the final common pathway of prolonged and severe shock of any cause [35].

Pathologic maldistribution of blood flow is hard to measure [7,36] and shock is hard to define using hemodynamic criteria alone [4,7,14,27,37–39]. Any set mean arterial pressure (MAP) or cardiac index might define dysfunction in one individual, yet it might also represent normal physiology in another [33,36,40]. The identification and treatment of shock is grossly dependent on surrogate markers and estimations of tissue blood flow [32,40–42]. Assessment of the major features of shock (eg, hypotension, decreased capillary blood flow, oliguria, mental status changes, and acidosis) should be done in any patient with a critical illness, or who is at risk of developing shock. Markers of regional perfusion, urine output, and mentation have not been shown to be superior to markers of global perfusion, such as blood lactate levels and measures of arterial base excess [4,7,13]. A current approach to the diagnosis of shock and monitoring of the response to therapy must integrate physical examination findings (eg, confusion, delayed capillary refill, oliguria); hemodynamic variables (eg, MAP, shock index, pulse pressure); and global metabolic parameters (eg, lactate, arterial base excess, mixed venous oxygen saturations) [4,13,32,37–50]. A composite picture of patient parameters is best used to correct or assess the adequacy of perfusion.

Global tissue perfusion and oxygen delivery is determined by blood oxygenation and MAP. Oxygen delivery (DO_2) is a function of arterial oxygen content (Cao_2) and CO [$DO_2 = Cao_2 \times CO \times 10$]. Arterial oxygen content is the sum of bound arterial oxygen ($Hb \times Sao_2 \times 1.38$) and dissolved arterial oxygen ($0.0031 \times Pao2$). Pao_2 is usually disregarded because the number is diminutive. How much oxygen is delivered to the tissues through the microvasculature depends on how many oxygen-carrying units are present, how many of those hemoglobin units are effectively carrying oxygen, and how effectively the heart is working to transport the oxygenated units [15,16]. CO is the product of heart rate and stroke volume; in turn, stroke volume depends on preload, myocardial contractility, and afterload (Table 3).

MAP is derived from the product of systemic vascular resistance (SVR) and CO. SVR is governed by blood viscosity, vessel length, and the inverse of vessel diameter. SVR and CO are important clinical concepts that distinguish the different forms of shock. Consequently, any basic approach to hypotension should begin with an assessment of the patient's volume status and CO. Low CO states are clinically linked to a narrowed pulse pressure, a rising shock index, and a delayed capillary refill with cool peripheral extremities [33,34]. Widened pulse pressures with low diastolic pressures, bounding pulses, warm extremities, and normal capillary refill can be seen with increased CO states [4,32,42].

In patients with evidence of hypoperfusion and increased CO, a decreased SVR or a decreased relative volume should be suspected. Conditions that cause high output and low resistance are classically linked to inflammatory states. The prototypical high output–low resistance condition is septic shock, although severe pancreatitis, anaphylaxis, burns, and liver failure share similar physiologic alterations. Perfusion deficits observed in hyperdynamic shock are derived from a complex interaction of humoral and microcirculatory processes that result in uneven local regional blood flow and a derangement of cellular metabolic processes [49]. In patients with suspected hypoperfusion and clinical evidence of low CO, an assessment of cardiac volumes and global intravascular volume must be reassessed. Historical and physical features often easily differentiate the hypovolemic state whether caused by hemorrhage (trauma) or volume loss (diarrhea, vomiting). Clinical features, such as elevated jugular venous pulses, peripheral edema, a cardiac gallop, or pulmonary rales, help to distinguish the hypotensive patient with low CO and high intravascular volumes [7,33,34]. These patients tend to be cold and clammy because of their increased SVR and usually have historical features and clinical signs (EKG changes) that help further differentiate the cardiac origins of shock.

Principles of management

The management of shock first focuses on identifying the underlying cause and applying some combination of fluid resuscitation, vasoconstrictors,

Table 3
Hemodynamic measurements and physiologic variables

Measurement	Determining parameters	Formulas/ measurements	Normal values
MAP	SVR CO SBP DBP	MAP = SVR × CO MAP = (SBP + DBP)/2	Normal MAP should be 65 mmHg or greater
SVR	Blood vessel diameter Blood vessel length Blood viscosity		In a 70-kg person, the resting SVR is 900–1200 dyn·s/cm^5 (90–120 MPa·s/m^3)
CO	HR SV	CO = HR × SV	In a 70-kg person, a normal resting CO is approximately 4900 mL/min
SV	Preload/EDV Afterload ESV Contractility EF	SV = EDV − ESV	In a 70-kg person, the given SV is approximately 70 mL at rest
EF	SV EDV	EF = (SV/EDV) × 100%	In a healthy 70-kg person, the SV is approximately 70 mL and the left ventricular EDV is 120 mL, giving an ejection fraction of 70/120, or 58%
Preload	Left ventricular stretch Relates to EDV LVEDP LVEDR	(LVEDP × LVEDR)/2 × ventricular thickness	
Afterload	LVESP MAP SVR		
PP	SBP DBP	PP = SBP − DBP	In a 70-kg person, the resting PP is 40 mm Hg
SI	HR DBP	SI = HR/SBP	In a 70-kg person, a normal SI is <0.5

Abbreviations: CO, cardiac output; DBP, diastolic blood pressure; EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; HR, heart rate; LVEDP, left ventricular end diastolic pressure; LVEDR, left ventricular end diastolic radius; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; SI, shock index; SV, stroke volume; SVR, systemic vascular resistance.

inotropic agents, and potentially vasodilators in a coordinated attempt to right physiologic irregularity, correct perfusion deficits, and maintain oxygen delivery (Table 4). Clinically, this is achieved by improving blood pressure and CO through the optimization of preload, augmentation of SVR, and the increase of cardiac contractility. To achieve these goals,

Table 4
Pharmacologic agents used to support cardiac output and blood pressure

Receptor activity							
Vasoactive agent	α1	α2	β1	β2	Dopamine	Other	Clinical effect
Epinephrine	++++	+++(+)	+++	0(+)	0		▲ in SVR predominates, vasodilator in low dose ▲CO by ▲inotrope and ▲HR
Ephedrine	++	0	++(+)	++	0		▲ in SVR predominates Mild ▲CO by ▲inotrope
Norepinephrine	++++	+++	+++	0(+)	0		▲▲ in SVR predominates because of alpha effects ▼CO s/t ▲ in SVR offset by inotrope *▲HR at higher doses may limit clinical effectiveness*
Phenylepherine	+++	0	0	0	0		▲▲ in SVR predominates CO neutral at low doses s/t ▲venous return offsets the ▲SVR effect on CO *At high doses, ▲ in SVR predominates with ▼CO*
Dopamine							
0.5–2 μg/kg/min	0	(+)	+	+	++	Dopamine	Dose 1-▲CO by ▲inotrope
3.0–10 μg/kg/min	+	(+)	++	+	++		Dose 2-▲SVR and ▲CO by ▲inotrope and ▲HR
10–20 μg/kg/min	+(++)	(+)	++(++)	+(+)	++		Dose 3-▲ in SVR predominates *▲HR at higher doses may limit clinical effectiveness*
Dobutamine	0(+)	0(+)	++++	+++	0		▼▲SVR ▲CO by ▲inotrope *Minimal stimulation to HR*
Isoproterenol	0	0	++++	++++	0		▼SVR ▲CO by ▲inotrope and ▲HR *▼SVR often limits utility in shock*
Vasopressin	0	0	0	0	0	V1 receptor	▲▲ in SVR predominates
Amrinone/milrinone	0	0	0	0	0	PDE inhibition	▼SVR ▲CO by phosphodiesterase inhibition

0, no effect; +, minimal receptor stimulation; ++, mild; +++, moderate; ++++, strong receptor stimulation; -, debated activity; (), variable effects; ▲, increase; ▼, decrease.
Abbreviations: CO, cardiac output; HR, heart rate; PDE, phosphodiesterase; SVR, systemic vascular resistance.

the physician can use a number of vasoactive agents. Vasopressor agents largely improve perfusion pressure and preserve regional distribution of CO through an increase in MAP above autoregulatory thresholds [12,51]. Vasopressor agents may also improve cardiac preload and increase CO by decreasing venous compliance and augmenting venous return [7,12]. Inotropes improve oxygen delivery and CO through an increase in rate and contractility [13,29,40,52,53].

Receptor physiology

Vasopressors and inotropes are broadly divided into adrenergic agonists and nonadrenergic agonists. The main categories of adrenergic receptors relevant to vasoactive therapy are the α_1-, α_2-, β_1-, and β_2-adrenergic receptors, and the dopamine receptors. Discussion of nonadrenergic mechanisms typically revolves around activation of vasopressin-specific receptors, in particular V_1, and the modulation of internal cellular phosphodiesterase activity.

Alpha-adrenergic receptors

Alpha receptors share a number of general functions including some vasoconstriction of the veins and coronary arteries [12,51]. α_1 Receptor stimulation exerts a primary effect on smooth muscle with resultant constriction. In the smooth muscle of blood vessels, the principal effect is vasoconstriction. α_1 activity has been linked to metabolic alterations and potentially to increased cardiac contractility, although the exact mechanisms of these activities are unclear [54–56]. Stimulation of postsynaptic α_2 receptors causes vasodilatation by endothelial nitric oxide production [51,57]. It is thought that this mixed constrictive-dilatory alpha activity helps maintain perfusion balance, particularly within the coronary arteries [58].

Beta-adrenergic receptors

β_1 Receptor stimulation primarily affects the heart. β_1 Agonism produces increases in heart rate and contractility, leading to improved cardiac performance and output. Heart rate increases are enacted by increased sinoatrial nodal conduction (chronotropic effect); increased automaticity and conduction of the ventricular cardiac muscle; and increased atrioventricular nodal conduction (dromotrophic effect) [59]. Stroke volumes increase as a result of cardiac muscle contractility (inotropic effect). β_2 Receptor stimulation causes relaxation of smooth muscle. In smooth muscle beds of small coronary arteries, arteries of visceral organs, and arteries of skeletal muscle β_2 activation results in vasodilation. Additionally, β_2 stimulation results in mild chronotropic and inotropic improvement, although these effects are minimal [59].

Dopaminergic receptors

There are over seven subtypes of dopamine receptor [60,61]. D_4 receptors have been identified in human hearts. Through dopamine receptors, dopamine increases CO by improving myocardial contractility, and at certain doses increasing heart rate [60]. In the kidney, dopamine acts by D_1 and D_2 receptors to stimulate diuresis and naturesis [61]. In the human pulmonary artery D_1, D_2, D_4, and D_5 receptor subtypes may account for vasorelaxive effects of dopamine [62].

Vasopressin receptors

Vasopressin is a peptide hormone whose primary role is to regulate the body's retention of water. Vasopressin, or antidiuretic hormone, is released when the body is dehydrated, causing the kidneys to conserve water (but not salt), concentrating the urine and reducing urine volume. It also raises blood pressure by inducing moderate vasoconstriction through its stimulation of V_1 receptors present throughout the vasculature, but most predominantly within the smooth muscle of peripheral arterioles [63–65]. High-level activation greatly increases vascular resistance and is a dominant compensatory mechanism for restoring blood pressure in hypovolemic shock [65]. Under normal physiologic conditions, V_1 stimulated vasoconstriction results in no net change in blood pressure because of baroreflex activation [64,65]. Vasopressin has also been linked to paradoxical vasodilation that is largely dependent on the vascular bed type and on the degree of receptor activation [64–66].

Therapeutic considerations

There are several important concepts to consider when selecting individual agent-receptor pathways. Many of the agents used to treat shock act on multiple different receptors and can cause mixed effects, some of which can be undesirable. Secondly, many of these agents have specific dose-response curves for which different receptor subtypes are activated at varying dose-dependent levels. This is particularly challenging when titrating or mixing these agents. Lastly, the human body uses many autoregulatory functions. Many of the desired responses (eg, vasoconstriction) can stimulate feedback responses that might counter the intended effect (increased perfusion). In this example, stimulated vasoconstriction leads to an increase in SVR and a resultant increase in MAP. Elevated MAPs can trigger reflexive bradycardia causing a decrease in CO (decreased perfusion). Additionally, increases in SVR (afterload) can also negatively impact CO, particularly in patients with weakened or ischemic myocardium. Common complications associated with vasopressors and inotropic agents include dysrhythmias, myocardial ischemia, hyperglycemia, and hypoperfusion. With all of these factors in

mind, the choice of agent should be selective and titrated to the minimal effective dose to achieve target end points (MAP, urine output, and mentation).

Specific agents

Epinephrine is a circulating catecholamine hormone that is synthesized from norepinephrine primarily in the adrenal medulla. It has a full range of alpha and beta agonistic properties with a host of effects that ultimately limit the ease of clinical use [67]. Epinephrine's main limitations are its potential provocation of dysrhythmias [67,68], potential for myocardial ischemia, and more profound splanchnic vasoconstriction than other agents that may cause abdominal organ ischemia [69–72].

In the emergency department, epinephrine is most useful as a primary agent for the treatment of anaphylaxis and as a secondary agent for the treatment of sepsis and severe bronchospasm. At doses of 2 to 10 μg/min, epinephrine's beta receptor stimulation predominates [67,73]. Epinephrine's β_1 stimulation causes an increase in heart rate (chronotropy) and an increase in stroke volume (inotrope) with a resultant increase in CO and cardiac oxygen consumption. At this dose, epinephrine also induces some β_2 stimulation that results in vasodilation in skeletal muscle arterioles offsetting some of its alpha-induced vasoconstriction. The end product of this predominant beta activity results in an increased CO, a decreased SVR, and variable effects on MAP [67,73]. At doses above 10 μg/min, alpha receptor stimulation results in generalized vasoconstriction and an increased MAP mediated through an increased SVR [67]. At variable doses, epinephrine also stimulates a number of important metabolic responses and directly stimulates the kidney, which produces renin. Through activation of the renin-angiotensin system, epinephrine indirectly causes additional vasoconstriction.

Ephedrine is a sympathomimetic agent with a structure similar to the other synthetic derivatives of epinephrine. Ephedrine acts on alpha and beta receptors with less potency than epinephrine and also stimulates the release of norepinephrine accounting for additional indirect alpha and beta effects [73]. Ephedrine's combined receptor activity causes an increase in systolic blood pressure and a modest inotropic effect. It has been shown to improve coronary and cerebral blood flow, but also has been linked to decreased renal and splanchnic blood flow [73]. Ephedrine is rarely used in a continuous infusion and its clinical use is mainly limited to treatment of hypotension associated with spinal anesthesia. Consequently, it is not likely to be useful in an emergency department setting.

Phenylephrine has pure alpha activity and results in veno and arteriolar vasoconstriction with minimal direct effects on inotrope or chronotropy [73,74]. It causes an increase in systolic, diastolic, and MAP and can lead to reflex bradycardia [73,75]. Phenylephrine has little effect on heart rate or contractility, so arrhythmia potentiation is minimal. CO may be

decreased because of a marked increase in SVR (afterload), but most studies document normal CO maintenance [75,76]. The associated increased oxygen demand may induce coronary ischemia in vulnerable patients, although this is largely theoretic. Phenylephrine's vasoconstrictive effects have been associated with decreased renal and splanchnic perfusion [75,76].

The standard starting dose of phenylephrine is 10 to 20 μg/kg/min. In the emergency department, this agent may be clinically useful as a second-tier agent for the support of hyperdynamic vasodilatory shock (sepsis) [66]; in shock caused by central neurologic causes (neurogenic); and in other states where a low SVR is suspected and CO is not impaired [75]. It also may prove useful in hypotension caused by tachydysrhythmias because of its ability to stimulate reflex bradycardia.

Norepinephrine is the primary neurotransmitter of the postganglionic sympathetic nerves. It acts on both α- and β-adrenergic receptors producing potent vasoconstriction and a less pronounced increase in CO [66,73]. The potent vasoconstrictor effects act to increase venous return and improve cardiac preload. Norepinephrine's vasoconstriction is primarily seen as a disproportionate increase in systolic blood pressure over diastolic pressure that can lead to a reflex bradycardia. This bradycardic response is often countered by norepinephrine's mild chronotropic effects, leaving the heart rate unchanged [73,77]. In low doses (2 μg/min), norepinephrine stimulates β-adrenergic receptors. In usual clinical doses (>3 μg/min), norepinephrine stimulates alpha receptors promoting vasoconstriction.

In early theoretic work, norepinephrine was thought to negatively impact the pulmonary vascular beds causing vasoconstriction and potentiation of pulmonary hypertension [73], although this has been largely dismissed by later studies in animal models [78–80]. Like other agents that increase inotrope and afterload, norepinephrine increases myocardial oxygen demand [81]. This is generally offset by a relative perfusion balance created by the mixed alpha and beta activity, but should be considered in patients with coronary compromise [73]. Norepinephrine, like other vasoconstrictors, can induce ischemia. This is of particular concern within the renal [82–84] and splanchnic vascular beds [12,13,85], where profound vasoconstriction may cause unintended organ injury. Norepinephrine's negative effects on hepatosplanchnic perfusion has drawn great controversy [13,77] and in recent studies these negative effects have been questioned [70,72,85].

It is important to consider the results of studies in context to the treatment population. In the case with norepinephrine, most of the data available have been studied in a septic model that because of humoral and microcirculation abnormalities is unlike other shock states [12,49]. Several trends have been uncovered in the use of norepinephrine in septic shock. Norepinephrine has been shown to be more effective at improving blood pressure [86], has demonstrated mortality benefits over other agents [87], and has largely been adopted as the first-line agent of choice for the hemodynamic support of septic shock [12,13,29,66,88–90]. In an emergency department

setting, norepinephrine should be the agent of choice for treating hypotension associated with sepsis. It can also serve as an adjunct to other vasodilatory conditions, such as anaphylaxis and neurogenic shock, and might prove useful in states with ventricular dysfunction [4,59].

Dopamine is the immediate precursor of norepinephrine in the catecholamine cascade. When administered intravenously, dopamine has a variety of dose-dependent effects mediated by direct and indirect adrenergic activity. Directly, dopamine stimulates α- and β-adrenergic receptors and may be converted to norepinephrine. Indirectly, dopamine stimulates the release of norepinephrine from sympathetic nerves [59,73,91]. These indirect mechanisms and dose-dependent variability make predicting the hemodynamic effects of dopamine difficult.

At low infusion rates (0.5–2 μg/kg/min), dopamine stimulates D_1 receptors resulting in selective vasodilatation of the renal, splanchnic, cerebral, and coronary vasculature [73,91]. Even at low doses, some beta stimulation occurs, which may increase MAP and CO. At rates from 2 to 5 μg/kg/min, dopamine stimulates norepinephrine release and has mixed receptor activity. Infusions of 5 to 10 μg/kg/min stimulate β_1 receptors increasing stroke volume, heart rate, and CO [73,91]. At doses greater than 10 μg/kg/min, dopamine activates both β_1 and α-adrenergic receptors [12]. With escalating doses (>10 μg/kg/min), alpha effects predominate causing vasoconstriction in most vascular beds [73]. There is extensive overlap, however, especially in critically ill patients. Dopamine has been shown to produce a median increase MAP of 24% in volume-optimized patients who remain hypotensive. Stroke volume was the major contributor to increased MAP, with heart rate contributing to a lesser extent and minimal contribution from SVR [66,85].

Dopamine's broad range of receptor activity offers primary benefits and clinical disadvantages. Like other adrenergic agents, concerns over dopamine's effect on hepatosplanchnic perfusion have been raised [69,85] and studies have shown that dopamine's effects may be more profound than those of other agents [92,93]. Additionally, the renal protective mechanisms of dopamine have been questioned [93] and "reno-protection" has largely been rejected [94]. Tachydysrhythmias often limit the clinical predictability of dopamine [95].

Dopamine is stable in premixed form and in emergency medical applications; it often is the most readily available vasoactive agent. Either norepinephrine or dopamine is recommended as a first-line agent for the treatment of septic shock by the Surviving Sepsis Campaign [90]. It also has clinical use in treating neurogenic and other states where the stimulation of heart rate, contractility, and the ability to modulate vascular resistance is of benefit.

Dobutamine is a synthetic catecholamine that is viewed primarily as an inotropic agent. It is predominantly a β_1 agonist with only weak alpha and β_2 effects. The selective β_1 activity of dobutamine primarily increases the inotropic effect because of increased stroke volume and heart rate with a variable effect on blood pressure [66]. The end effect of dobutamine's

stimulus response is an increased CO and a decreased SVR that result in a global reduction in ventricular wall tension, sympathetic cardiac stress, and myocardial oxygen consumption [96]. Dobutamine's typical therapeutic doses range from 2.5 to 10 μg/kg/min.

Dobutamine might be used by the emergency practitioner to augment inotropic activity and improve perfusion in septic shock patients with global myocardial dysfunction [90]. It is also a commonly used agent to support contractility and cardiac decompensation, although its long-term effect on morbidity has been questioned in congestive heart failure [59].

Isoproterenol, a catecholamine structurally similar to epinephrine, is primarily an inotropic agent that produces β_1 and β_2 stimulation. Isoproterenol stimulates inotropic and prominent chronotropic activity that increases contractility, heart rate, and oxygen consumption [73]. Isoproterenol's prominent β_2 activity causes vasodilatation and creates the potential to produce arrhythmias. Both can be limiting factors of its use in shock. Isoproterenol is generally used for its chronotropic effects and may be useful in the treatment of hypotension associated with bradycardia or heart block.

Vasopressin is an endogenous hormone with vasoconstrictive effects whose relative deficiency has been tied to refractory hypotension in vasodilatory shock [97]. There is support for using a low-dose continuous infusion (0.01–0.03 U/min) in conjunction with other agents to treat refractory vasodilatory shock [12]. Vasopressin's use in other vasodilatory states like those seen with profound cardiogenic shock has not been solidified [98]. Its use has been linked to the reduction of mesenteric and renal blood flow, although results regarding the effects are conflicting [98]. Many questions remain unanswered regarding vasopressin's clinical effect and the Surviving Sepsis Campaign recommends it not be used as a first-line agent [90].

Amrinone and milrinone are phosphodiesterase-3 inhibitors that lead to the accumulation of intracellular cAMP, affecting a similar chain of events in vascular and cardiac tissues seen with β-adrenergic stimulation [99,100]. The end result of this activity produces vasodilation and a positive inotropic response. These drugs lead to a short-term improvement in hemodynamic performance and an improvement in hemodynamic variables. Like dobutamine, they are used to improve cardiac function and treat refractory heart failure. These agents are largely limited in shock states because of their vasodilatory properties [99]. Although these drugs have been shown to provide short-term clinical hemodynamic improvements, studies have largely failed to translate these into long-term mortality benefits [100–104].

Alternative agents

Glucagon, a polypeptide hormone, in large dose infusion is beneficial in the treatment of β-blocker overdose, tricyclic overdose, and calcium channel blocker overdose [105–114]. Glucagon is thought to have its own receptor that is separate from adrenergic receptors. Stimulation of this receptor

stimulates increased intracellular cAMP, which promotes inotrope and chronotropy [108,110]. It is generally given as a 5-mg bolus followed by a 1 to 5 mg/h infusion, which can be titrated up to 10 mg/h to achieve the desired patient response. High-dose insulin is the most recently proposed remedy for cardiovascular support in drug toxicity [115–121]. Insulin has an intrinsic positive inotropic effect and seems to promote calcium entry into the cells by means of an unknown mechanism. Although the therapeutic efficiency of high-dose insulin has been effective in animal models, no randomized human trials have been performed [106]. Anecdotally, insulin given as a 0.5 units/kg intravenous bolus, then as 0.5 to 1 U/kg/h intravenous infusion with dextrose 10% solution, has been shown to be effective in calcium channel and β-blocker toxicity [106]. Calcium salts have been shown to increase blood pressure and CO without effecting heart rate by increasing the intracellular pool of calcium available for release during depolarization [122–124]. One gram of a 10% solution (10 mL) of calcium chloride administered as a slow intravenous push has shown some efficacy in treating β-blocker [122–124] and calcium channel antagonist toxicity [125,126].

Clinical applications

Authors have penned opinions on vasoactive therapy selection for years. Many of these opinions are based on pharmacology modeling, animal studies, or limited design studies. One Cochran review [127] and a recent series review [128] evaluated the data supporting the selection of one vasoactive drug over another and both produced limited answers. They were able to find only eight studies that provided randomized, controlled data and based on the limitations of these data were unable "to determine whether a particular vasopressor is superior to other agents in the treatment of shock states" [127,128]. It is important to note that most of the evidence available on vasoactive drugs has been gathered through clinical treatment of hypotension in very specific shock states. It is beneficial to consider and choose agents based on specific evidence available for the individual shock state being treated. Several specific shock states are reviewed (Table 5).

Anaphylactic shock

Anaphylaxis, initiated by an unregulated IgE-mediated hypersensitivity response [129], is associated with bronchospasm, systemic vasodilation, increased vascular permeability, and a loss of venous tone [130]. Anaphylactoid reactions are clinically indistinguishable responses that are not IgE-mediated [131]. In this disease, mast cells release histamine, triggering bronchial smooth muscle contraction, vascular smooth muscle relaxation, and an increase in the vascular bed capacitance, which is not adequately filled by the normal circulating blood volume [132]. Platelets are activated

Table 5
Vasoactive drugs for shock states

Shock state	First-tier agents	Second-tier agents
Anaphylactic shock	Epinephrine, 1 mL of 1:10,000 solution (100 μg), can be given as a slow IV push, then as a 0.02 μg/kg/min infusion (5–15 μg/min)	Norepinephrine infused at 0.1–1 μg/kg/min (0.5–30 μg/min)
Cardiogenic shock, left ventricular	SBP <70, norepinephrine infused at 0.1–1 μg/kg/min (0.5–30 μg/min) SBP 70–90, dopamine infused at 15 μg/kg/min SBP >90, dobutamine infused at 2–20 μg/kg/min	Amrinone, 0.75 mg/kg loading dose, then 5–10 μg/kg/min (not recommended post-MI) Milrinone, 50 μg/kg loading dose, then 5–10 μg/kg/min (not recommended post-MI)
Cardiogenic shock, pulmonary embolism	Dobutamine infused at 5 μg/kg/min Norepinephrine infused at 0.1–1 μg/kg/min	Phenylephrine infused at 10–20 μg/kg/min
Hemorrhagic shock	Volume resuscitation	Dopamine infused at 5–15 μg/kg/min as a temporizing adjunct
Neurogenic shock	Dopamine infused at 5–15 μg/kg/min	Norpinephrine infused at 0.1–1 μg/kg/min Phenylephrine infused at 10–20 μg/kg/min
Septic shock	Norepinephrine infused at 0.1–1 μg/kg/min Dobutamine infused at 5 μg/kg/min	Dopamine infused at 5–15 μg/kg/min Epinephrine infused at 0.02 μg/kg/min
Toxic drug overdose with shock	Norepinephrine infused at 0.1–1 μg/kg/min	Phenylephrine infused at 10–20 μg/kg/min Glucagon given as a 5-mg IV bolus, then as a 1–5 mg/h infusion Calcium salts: calcium gluconate, 0.6 mL/kg bolus, then a 0.6–1.5 mL/kg/h infusion Insulin started at 0.1 units/kg/h IV and titrated to a goal of 1 unit/kg/h

Abbreviations: IV, intravenous; MI, myocardial infarction; SBP, systolic blood pressure.

in this cascade and release platelet-activating factor, which amplifies peripheral vasodilation and has a role in coronary and pulmonary artery vasoconstriction. The combined effects result in a reduction in volume and cardiac preload, a reduction in inotrope, and the consequent decrease in effective output. Consequently, hypotension and tissue hypoperfusion ensue.

Death from anaphylactic reactions is most commonly linked to unresolved bronchospasm, upper airway collapse from edema, or cardiovascular collapse [133]. Shock occurs in 30% to 50% percent of cases [132,133]. Shock in anaphylaxis shares variable components with hypovolemic shock caused by capillary fluid leak, distributive shock caused by the loss of vasomotor tone, and cardiogenic shock caused by inotropic reductions [131–134]. Knowledge of this physiologic distribution is important to the emergency management of anaphylaxis and specifically to the selection of therapies.

Treatment

Rapid assessment of the patient's airway and cardiopulmonary condition should be performed. Pharmacologic therapy for anaphylactic shock is generally guided by data from observational or animal studies. The balance of evidence is aimed at reversing the effects of anaphylactic mediators. Dependent on the severity of presenting symptoms, this generally involves treatment with intravenous fluids, early antihistamines, bronchodilators, steroids, and epinephrine [135–137]. Early fluid resuscitation is required to correct relative volume deficits and restore cardiac preload.

Epinephrine is the vasoactive drug of choice in anaphylactic shock [136,138,139]. Epinephrine's catecholamine effects counteract the vasodepression, bronchoconstriction, fluid transudation, and cardiac depression seen in anaphylaxis [138]. It is generally given to patients with early signs of angioedema, bronchospasm, or hypotension. Early administration is typically given subcutaneously or intramuscularly. Clinical guidelines [136] recommend giving 0.3 to 0.5 mL of a 1:1000 (1 mg/mL) solution of epinephrine intramuscularly into the anterior or lateral thigh because of evidence of more rapid absorption by intramuscular routes [140]. Repeated doses may be administered in conjunction with aggressive fluid resuscitation every 3 to 5 minutes based on the clinical severity or symptom response.

For refractory or profound hypotension, epinephrine may be administered by continuous infusion at 5 to 15 μg/min and titrated to effect. In the case of difficult intravenous access, epinephrine (3–5 mL of 1:10:000 dilution) can be delivered by an endotracheal tube with desired effects [141]. Supplementary vasoactive agents (dopamine, norepinephrine, or phenylephrine) can be used to alter venous capacitance in persistent hypotension [138,139]. Additionally, an intravenous bolus of 1 mg of glucagon repeated at 5-minute intervals, particularly in patients on β-blockers, has been shown to provide inotropic and chronotropic support in patients with refractory hypotension and bradycardia [142,143]. Vasopressin has also gained

attention as a secondary agent for the treatment of severe anaphylaxis that is unresponsive to epinephrine [144].

Neurogenic shock

Neurogenic shock is caused by the sudden loss of the autonomic nervous system signal to the smooth muscle in vessel walls and to the nodal centers of the heart as a result of severe central nervous system (brain or spinal cord) damage. With the sudden loss of background sympathetic stimulation, the vessels vasodilate causing a sudden decrease in peripheral vascular resistance (decreased MAP) and the heart experiences a predominant parasympathetic stimulus promoting bradycardia (decreased CO) [145].

Treatment

Treatment of neurogenic shock with aggressive volume resuscitation and prompt hemodynamic augmentation results in improved outcomes [146–150]. The weight of evidence defending medical support strategies is limited and is largely based on case series. The collective experience suggests that maintenance of MAP at 85 to 90 mm Hg improves spinal cord perfusion and impacts neurologic outcome [150]. Vasoactive agents are typically started after or concomitantly with volume resuscitation. Typically, agents with mixed receptor activity and stronger beta agonism (dopamine, norepinephrine) are initiated before the addition of a pure alpha agonist (phenylephrine) to elevate the MAP and stimulate chronotropy [149,150].

Cardiogenic shock with acute left ventricular dysfunction

Cardiogenic shock is a state of inadequate tissue perfusion caused by cardiac dysfunction and is most commonly associated with acute myocardial infarction with left ventricular failure [34]. Cardiogenic shock, defined by sustained hypotension with tissue hypoperfusion (oliguria, cool extremities) despite adequate left ventricular filling pressure, complicates approximately 6% to 7% of acute myocardial infarctions and has an associated mortality of 60% to 90% [151,152]. Support for aggressive therapy has been championed by several large trials (GUSTO-1 and SHOCK) [6,153]. The largest mortality benefits in these trials were seen with early support, timely revascularization, and intra-aortic balloon pump augmentation [6,153,154].

Treatment

Prompt treatment of hypotension and hypoperfusion is essential to the management of cardiogenic shock. American College of Cardiology–American Heart Association guidelines for the management of patients with ST-elevation myocardial infarction recommend an empiric intravenous volume

challenge of 250 mL of isotonic saline be given in patients with suspected cardiogenic shock when there is no evidence of volume overload (pulmonary congestion, venous distention, respiratory distress) [155]. The guidelines for early emergency department management of complicated ST-elevation myocardial infarction caution against vigorous fluid challenges in patients with extensive left ventricular infarction, particularly the elderly [155]. Aggressive fluid therapy might be indicated in right ventricular (RV) dysfunction caused by a RV infarction and is commonly required to compensate for the venodilation and hypotension associated with inferior myocardial infarction [33,155].

Sympathomimetic drugs remain first-line agents in the treatment of cardiogenic shock associated with acute ischemic left ventricular dysfunction [33,34]. The guidelines generally use systolic blood pressure to guide vasoactive management. In patients with a systolic blood pressure ranging from 70 to 100 mm Hg who are less sick and show no signs of shock, the guidelines generally recommend an intravenous dobutamine infusion (2–20 μg/kg/min) be initiated to help support stroke volume and reduce afterload. In shock states with signs of hypoperfusion, initial therapy should begin with a dopamine infusion (5–15 μg/kg/min) to provide inotropic and vasoconstrictive support. In profoundly hypotensive patients (systolic blood pressure $<$70 mm Hg) norepinephrine is recommended as a 0.5 to 30 μg/min infusion [155].

Cardiogenic shock with right ventricular dysfunction

RV dysfunction can be classified into impaired RV contractility, RV pressure overload, and RV volume overload. Patients with acutely decompensated RV function, however, often suffer from a combination of all three entities [156].

RV function is better suited to volume overload than pressure overload compared with the left ventricle (LV) [157]. The thin-walled RV is compliant, but does not have the myocardial bulk and contractility to overcome elevated afterload, unless it is conditioned over time to gradual increases in pulmonary vascular resistance [158]. Depressed RV contractility, secondary to RV infarction, cardiomyopathy, and sepsis, leads to dilation of the normal chamber, impaired relaxation, and subsequent increased end-diastolic pressures. This causes a shift in the normal contour of the interventricular septum toward the LV and an increase in intrapericardial pressures that limit both RV and LV filling [159].

RV pressure overload, secondary to pulmonary artery obstruction (pulmonary, fat, and amniotic fluid embolism), pulmonic stenosis, or pulmonary hypertension (associated with lung disease hypercarbia and hypoxemia, left heart disease, chronic thromboembolic disease and acute respiratory distress syndrome), leads to increased RV wall tension, RV chamber dilatation, and impaired diastolic and systolic function [160]. With overload, the

interventricular septum shifts inward on the LV chamber. The increased wall tension of pressure overload results in increased myocardial oxygen consumption, which when coupled with decreased coronary perfusion and decreased oxygen supply can lead to myocardial ischemia or infarction [161]. Even in compensated states, failure can result from abrupt changes in pulmonary resistance or increased volumes. All of these pathways for impaired RV dysfunction result in a similar cascade of depressed RV CO. This depressed RV CO leads to decreased LV preload, then depressed LV CO, and subsequent systemic hypotension. This cascade is further exacerbated by the dyskinesis of the interventicular septum. Systemic hypotension in turn lowers coronary perfusion pressure and the vicious cycle termed "autoaggravation" continues to worsen RV dysfunction [162–164].

Treatment

The treatment of RV failure is aimed at disrupting the autoaggravation cycle. The specific clinical therapies, thrombolysis, percutaneous intervention, and possible surgical interventions are determined by the etiology of the acutely decompensated RV. Emergency management should primarily focus on supportive therapy as a bridge to final correction. Determining if volume is needed in the setting of RV failure can be difficult, because in all of the settings of RV failure, there is some degree of RV dilatation. Ultimately, fluid challenges and monitoring heart rate, blood pressure, cardiac performance, and urine outputs direct the further management of RV failure. As with LV failure secondary to myocardial infarction, an initial fluid challenge may be advocated if frank signs of volume overload are clinically absent [161,165].

There are no absolute guidelines to direct appropriate use of vasopressors or inotropes in the setting of acute RV failure. Hemodynamic support often requires the use of vasopressors and inotropes in addition to volume resuscitation, or if the RV is deemed volume overloaded vasodilators are indicated [43,161,166]. Norepinephrine, epinephrine, phenylephrine, dopamine, and vasopressin are vasoactive agents that could be used to offset systemic hypotension that often occurs with RV failure. Increasing MAP and afterload may seem counterintuitive; however, the RV is perfused by the coronary arteries in both diastole and systole [167]. Maintaining a pressure head that increases RV myocardial perfusion can be advantageous in the setting of increased RV myocardial oxygen demand. The ideal agent increases systemic vasoconstriction without increasing pulmonary vascular resistance; however, there are no human data to advocate for one agent over another. Norepinephrine has been supported in animal models of pulmonary embolism, which have shown improved survival, CO, and coronary blood flow with minimal changes in pulmonary vasculature with its use [80]. Epinephrine has been advocated in case-based literature for therapy in shock complicating pulmonary embolism [168]. Vasopressin has been used

in low doses to treat milrinone-induced hypotension without detriment to CO or pulmonary artery pressures [169]. Theoretically, norepinephrine, epinephrine, and dopamine have β_2 activity that can lead to decreased pulmonary vascular resistance to differing degrees. This benefit is lost, however, when alpha and β_1 activity targeted to increase CO overpowers the early β_2 effects and increases pulmonary vascular resistance and myocardial oxygen demand [164]. There are no outcome data to support one agent over another for hypotension in the setting of RV failure.

There is no selective inotropic agent for the RV. Inotropic support can augment cardiac contractility by β_1 activity (dobutamine-isoproterenol); phosphodiesterase inhibition (milrinone-amrinone); or calcium sensitization (levosimendan). There have been recent studies comparing inotropes in LV failure; however, there are no trials specifically isolating RV failure. The Levosimendan Infusion versus Dobutamine trial and Calcium Sensitizer or Inotrope or None in Low-Output Heart Failure trial both demonstrated increased survival with levosimendan over dobutamine or placebo [147,170,171]. Levosimendan is a calcium sensitizer. It increases contraction by increasing sensitivity of troponin C to calcium. The Survival of Patients with Acute Heart Failure in Need of intravenous Inotropic Support trial, however, failed to demonstrate a difference in survival between dobutamine and levosimendan [172]. Additionally, levosimendan, although available in other countries, is only available as an investigational drug in the United States.

Although dopamine, dobutamine, and milrinone-amrinone have historically been used in cardiogenic shock patients (LV dysfunction), there have not been studies specifically evaluating their use in isolated RV failure. The use of these agents can neither be supported nor refuted with the current available evidence for RV dysfunction. Contrastingly, isoproterenol, amrinone, and milrinone have been investigated in animal models of acute pulmonary embolism and have not been shown to be favorable [173,174]. Many questions remain unanswered regarding RV support and there is no clear front-runner for ''agent of choice'' in this clinical scenario.

Summary

There are few studies that provide evidence for a particular vasopressor or inotropic strategy in the early emergency department management of shock. Most recommendations for vasoactive strategies are largely based on pharmacodynamic modeling, animal research, empiric experience, and limited human trials performed in a critical care environment. Despite these limitations, a basic knowledge of available evidence can help guide a best practice approach until large, prospective, randomized, and well-conducted studies are completed. Understanding the background physiology of shock states and the actions and limitations of individual vasoactive agents can

help the emergency medicine physician to tailor therapy to specific patient presentations.

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