

Review Article

Pharmacologic agents for acute hemodynamic instability: Recent advances in the management of perioperative shock- A systematic review

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ABSTRACT

Despite the growing body of evidence evaluating the efficacy of vasoactive agents in the management of hemodynamic instability and circulatory shock, it appears no agent is superior. This is becoming increasingly accepted as current guidelines are moving away from detailed algorithms for the management of shock, and instead succinctly state that vasoactive agents should be individualized and guided by invasive hemodynamic monitoring. This extends to the perioperative period, where vasoactive agent selection and use may still be left to the discretion of the treating physician with a goal-directed approach, consisting of close hemodynamic monitoring and administration of the lowest effective dose to achieve the hemodynamic goals. Successful therapy depends on the ability to rapidly diagnose the etiology of circulatory shock and thoroughly understand its pathophysiology as well as the pharmacology of vasoactive agents. This review focuses on the physiology and resuscitation goals in perioperative shock, as well as the pharmacology and recent advances in vasoactive agent use in its management.

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INTRODUCTION

Circulatory shock is defined as inadequate oxygen delivery to the tissues, typically in the setting of hypotension.^[1] The current definition of hypotension varies, but a systolic arterial blood pressure <90 mmHg and/or a mean arterial blood pressure (MAP) <60–70 mmHg is generally accepted.^[1–3] If circulatory shock is not corrected rapidly, tissue hypoxia and cellular death ensue. The mortality associated with circulatory shock in the intensive care unit ranges from 16% in those with trauma/hypovolemic shock,^[4] 48% in those with cardiogenic shock,^[5] and up to 60% in those with septic shock.^[6] Inevitably, these patients will present perioperatively and will require ongoing management with vasoactive agents, a term collectively referring to vasopressor and inotrope medications.

Conventionally, these agents are used in a supportive context with the assumption that clinical recovery will be facilitated by their temporary use.^[7,8] Despite using these drugs since the 1940s, their use today

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remains guided largely by opinion.^[8,9] In the general population of critically ill patients with circulatory shock, surveys have shown that agent selection is based on clinical experience and preference^[10] and, interestingly, despite the growing body of evidence, this practice has recently been validated.^[11] Similarly, perioperative studies have demonstrated significant variability in agent selection in cardiac surgery.^[12-14] In a recently published meta-analysis of 23 randomized controlled trials comparing commonly used vasoactive agents (dopamine, norepinephrine, epinephrine, phenylephrine, vasopressin, and terlipressin), either alone or in combination with dobutamine or dexmedetomidine for the management of hypotensive shock showed no difference in mortality based on agent use and concluded that currently, there is no sufficient evidence that any of the agents are clearly superior.^[11] However, the presumption is that current vasoactive agent selection for the management of circulatory shock is based on correctly identifying the underlying physiologic deficit and choosing a drug with the optimal pharmacologic properties to manage it, thus a thorough understanding of these concepts is required.

PHYSIOLOGY

Most causes of circulatory shock are characterized by low cardiac output (CO). CO is the product of stroke volume (SV) and heart rate (HR) and is a major determinant of MAP and the delivery of oxygen (DO₂):

$$CO = SV \times HR.$$

$$MAP = CO \times SVR.$$

$$DO_2 = CaO_2 \times CO \text{ (in dL/min)}.$$

Thus, optimizing SV and HR will improve CO, MAP, and DO₂, keeping in mind that SV and overall myocardial performance is determined by five other factors in addition to inotropy (contractility) that requires consideration: (1) HR and rhythm (atrioventricular synchrony), (2) myocardial blood flow, (3) preload, (4) afterload, and (5) diastolic function. However, depending on the underlying cause of shock, the sympathetic nervous system compensation intended to restore normal organ perfusion pressure is manifested in different ways [Table 1].^[15,16] In the example of distributive shock, the underlying pathophysiology prevents the compensatory increase in SVR seen in most types of circulatory shock, resulting in

refractory hypotension despite a normal or elevated CO and DO₂. Although the CO and DO₂ are normal, hypotension below the normal organ autoregulatory range (e.g. MAP <60–65 mmHg) still results in impaired organ blood flow.^[17-19] This occurs because the absolute organ perfusion pressure (or driving pressure) is too low, and the normal autoregulatory decrease in organ vascular resistance is insufficient to restore normal organ blood flow.^[18] This relationship is expressed by relating Ohm's law to fluid flow:^[20]

$$\text{Organ blood flow} = (\text{Organ perfusion pressure}) / (\text{organ vascular resistance})$$

Organ perfusion pressure is the difference between organ arterial and venous pressure. Because normal organ venous pressure is typically negligible, the organ perfusion pressure is usually equal to the organ arterial pressure, which is the MAP, thus demonstrating the direct relationship between organ blood flow and MAP:

$$\text{Organ blood flow} = MAP / (\text{organ vascular resistance})$$

The resuscitation goals intended to preserve organ oxygen delivery in all types of circulatory shock are:

- **Primary resuscitation:** Rapidly reestablish normal organ perfusion pressure with an MAP >60–65 mmHg^[2,17,19]
- **Secondary resuscitation:** Rapidly reestablish adequate DO₂.^[22]

An MAP >60–65 mmHg must be achieved in primary resuscitation to maintain vital cerebral and coronary perfusion.^[17,19] Because CO is a determinant of both MAP and DO₂, further resuscitation focused on augmenting CO is preferred.^[23,24] However, MAP is the product of CO and SVR, therefore transiently increasing the SVR with vasopressors to achieve an MAP >60–65 mmHg is acceptable while secondary resuscitation is ongoing.^[25,26] Achieving the MAP goal of 60–65 mmHg quickly has recently been underscored by a retrospective study of critically ill patients where an MAP <50 mmHg in a subset of comorbid patients was found to result rapidly in cardiac arrest, likely as a consequence of coronary hypoperfusion.^[27] Following successful primary resuscitation, secondary resuscitation involves first ensuring adequate volume status (correcting hypovolemia) then, subsequently administering other vasoactive agents if necessary while monitoring the resuscitation endpoints proved in goal-directed therapy (GDT).^[22,28,29]

Table 1: Types of circulatory shock and their clinical picture

Type of shock	MAP	CO	DO ₂	CVP	MPAP	PCWP	SVR	Common clinical examples	Treatment ^b
Hypovolemic	↓→	↓	↓	↓	↓	↓	↑	Hemorrhage Capillary leak	Volume resuscitation
Obstructive	↓	↓	↓	↑	↑	↑→	↑→	Pulmonary embolus Tension pneumothorax	Inotropes
Cardiogenic	↓→	↓	↓	↑	↑	↑	↑	Myocardial infarction Arrhythmia	Inotropes
Distributive	↓	↑	↑	↓	↓	↓	↓	Systemic inflammatory response syndrome ^a Anaphylaxis	Vasopressors

^aSepsis and trauma, ^bTreatment of the underlying cause of circulatory shock is the primary objective and pharmacologic therapy with vasopressors and/or inotropes is used as a temporizing measure to maintain organ perfusion pressure (MAP >65 mmHg) and CO while the underlying process is corrected. MAP: Mean arterial pressure, CO: Cardiac output, CVP: Central venous pressure, MPAP: Mean pulmonary artery pressure, PCWP: Pulmonary capillary wedge pressure, SVR: Systemic vascular resistance, DO₂: Delivery of oxygen, ↑: Increased, ↓: Decreased, →: No change. Hadian M, Pinsky MR. Functional hemodynamic monitoring. *Curr Opin Crit Care* 2007;13:318-23

PERIOPERATIVE GOAL-DIRECTED THERAPY

GDT, initially brought to the forefront in the management of sepsis,^[22] has continued to evolve^[2,30] and is now being expanded to the perioperative period. Although the concept in septic shock has recently been called into question^[31,32] and may not be superior to clinical judgment (“usual care”) and/or the utilization of other less invasive resuscitation endpoints (such as lactate),^[33] it seems plausible that after years of integrating GDT protocols into physician education and practice that these methods now reflect “usual care,” thereby potentially biasing their results. The evolving concept of perioperative GDT currently includes the use of fluids and/or vasoactive agents to achieve hemodynamic endpoints and minimize postoperative complications and has recently been reviewed.^[34] With emerging evidence demonstrating the adverse effects of aggressive fluid resuscitation perioperatively^[35-41] and meta-analysis favoring goal-directed versus liberal fluid therapy,^[42] initiating perioperative GDT to optimize fluid status and hemodynamics, with the appropriate use of fluids as well as the use of earlier/preemptive inotropes and vasopressors, is likely the paradigm of the future. This is supported by recent meta-analysis suggesting that although GDT does not improve mortality, it may reduce complications and hospital length of stay^[43] and subsequent meta-analysis found a reduction in cardiovascular complications with this practice.^[44] However, a follow-up large, randomized trial of perioperative GDT in high-risk patients undergoing noncardiac surgery did not definitely support the practice but did demonstrate a nonsignificant trend supporting GDT.^[45] Therefore, at this point, no consensus on the true benefit of perioperative GDT exists, but further prospective study is underway.

Regarding the end points of resuscitation used in GDT, right-sided filling pressures poorly predict preload^[46,47] and although minimally invasive hemodynamic monitors are becoming widely available, most of these indirectly monitor endpoints and require further study. In contrast, intraoperative transesophageal echocardiography (IOTEE) in high-risk patients can quickly and accurately diagnose the etiology of intraoperative hypotension and allows the clinician to rapidly assess the results of intervention by monitoring cardiac volume/preload and function as well as utilizing Doppler to quantitate SV and CO. Although conclusive study demonstrating the efficacy of IOTEE in perioperative GDT is currently lacking, the early use of IOTEE in septic shock has been shown to change management by limiting fluid administration and initiating early inotropic support in patients with left ventricular (LV) systolic dysfunction, who otherwise would not have met Surviving Sepsis Campaign criteria for inotropic therapy.^[48] Furthermore, IOTEE is considered by many as the gold standard to assess intraoperative hemodynamic instability and monitor preload,^[47,49] therefore its use in perioperative GDT is plausible.

OVERVIEW OF VASOACTIVE AGENTS

Vasopressors

Vasopressors are primarily used in cardiopulmonary resuscitation (CPR) and in the treatment of circulatory shock, where the main clinical benefit of raising the MAP is to restore rapidly organ perfusion pressure. However, some vasopressors have inotropic properties as well, and the predominant effect is usually dose-dependent. In CPR, vasopressors cause profound systemic vasoconstriction that preferentially increases coronary perfusion pressure in an attempt to restore myocardial blood flow, oxygen delivery, and the return

of spontaneous circulation.^[50,51] In circulatory shock characterized by refractory hypotension, vasopressors are used in a supportive context until definitive therapy can be initiated, with the assumption that clinical recovery will be facilitated by temporarily restoring and maintaining normal organ perfusion pressure.^[7,8]

In the example of distributive shock, vasopressors correct the underlying deficit in SVR, thus restoring organ perfusion pressure.^[52,53] The importance of organ perfusion pressure has recently been emphasized as vasopressors are now being recommended as secondary agents where the indication is less obvious – Circulatory shock characterized by low CO and persistent hypotension that is refractory to conventional treatment. Historically, vasopressors have been used with extreme caution in this setting to avoid the complications associated with excessive vasoconstriction (increasing systemic and organ vascular resistance beyond normal physiologic values) such as further impairment of CO, DO₂, and organ blood flow, together possibly increasing mortality.^[23,24] However, **excessive vasoconstriction primarily occurs when these agents are given in the setting of inadequate volume resuscitation** with or without preexisting low CO.^[54] Considering this, patients receiving vasoactive agents require careful monitoring and frequent reevaluation, so these agents can be titrated to the minimal effective dose.

Vasopressor agents are broadly classified below by their clinical effect as: (1) Pure vasoconstrictors or (2) **inoconstrictors (vasoconstrictors with inotropic**

properties). Further classification of these agents is illustrated in Figure 1 and their standard dosing, receptor binding, and adverse effects are listed in Table 2.^[8] Although some adrenergic agents stimulate many receptors producing various cardiovascular effects, their vasopressor actions are mediated via alpha-1 receptors resulting in arterial and venous vascular smooth muscle contraction and an increase in systemic and pulmonary vascular resistance and venous return.^[8,55,56] The nonadrenergic agents such as vasopressin, exerts its vasopressor effects through **V1 receptor stimulation** resulting in vascular smooth muscle contraction,^[8] and **methylene blue scavenges nitric oxide and inhibits nitric oxide synthesis**, thus reversing the vasodilatory effects of nitric oxide on the endothelium and vascular smooth muscle.

Inotropes

Inotropy (contractility) refers to the force and velocity of cardiac muscle contraction, and the term inotrope generally refers to a drug that produces positive inotropy (increased contractility). Inotropes differ from vasopressors, which primarily produce vasoconstriction and a subsequent rise in MAP. As with vasopressors, some inotropes have vasopressor properties as well, and the predominant effect is usually dose-dependent. In circulatory shock characterized by low CO (e.g., cardiogenic and obstructive shock), the main clinical benefit of increasing contractility with inotropes is to increase SV and CO to restore adequate DO₂ to vital organs until definitive therapy can be initiated.^[7,8]

All inotropes increase CO by increasing the force of contraction of cardiac muscle, but the other determinants of myocardial performance are variably affected. For example, some inotropes directly increase HR, some indirectly decrease HR (reflex), while others have no effect, some inotropes increase venous tone (venoconstriction) and arterial tone (afterload) while others decrease these through vasodilation, and some improve diastolic function. Therefore, any given agent may have multiple and dose-dependent effects to be considered. In cardiogenic shock, the failing ventricle is very sensitive to afterload, so inotropes that produce systemic vasodilation (inodilators) should be first-line agents as long as systemic hypotension does not occur. Although supraphysiologic goals for CO have not shown benefit and may cause harm,^[23,57,58] maximal doses of a first agent are inadequate to meet goals, then a second drug should be added, with consideration given to agents with different mechanisms of action to maximize effects.

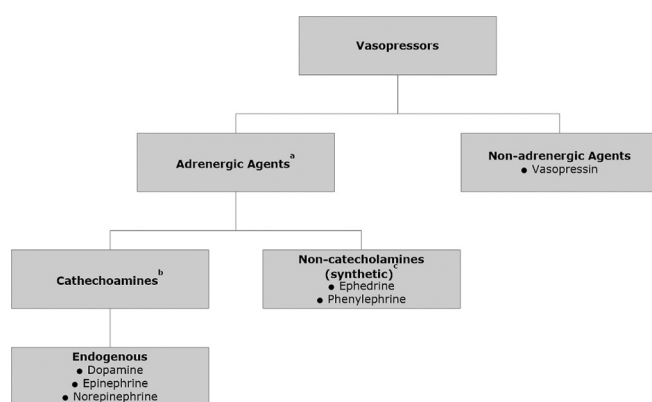


Figure 1: Vasopressor classification^[8,91] a: Adrenergic agents mimic sympathetic nervous system stimulation and are also termed “sympathomimetics;” b: Catecholamines structurally contain a catechol group and are rapidly metabolized by catechol-O-methyltransferase and monoamine oxidase corresponding to their short duration of action (1–2 min), making them ideal agents for titration; c: Noncatecholamines have longer durations of action (approximately 5–15 min) since they are not metabolized by catechol-O-methyltransferase

Table 2: Standard dosing of vasoactive agents, their receptor binding (or mechanism of action), and major adverse effects

Drug	IV infusion dose*	Receptor activity or mechanism of action				Adverse effects
		Alpha-1	Beta-1	Beta-2	Dopamine	
Isoproterenol	>0.15 mcg/kg/min	0	++	++	0	Arrhythmias, myocardial ischemia, hypotension
Milrinone	Load 20-50 mcg/kg then 0.25-0.75 mcg/kg/min	Phosphodiesterase inhibitor				Hypotension
Levosimendan	12-24 mcg/kg then 0.05-0.2 mcg/kg/min	Calcium-sensitizer				Hypotension
Dobutamine	2-20 mcg/kg/min	-	++	+	0	Arrhythmias, tachycardia, myocardial ischemia, hypotension
Dopamine	1-5 mcg/kg/min	-	-	-	++	Arrhythmias, myocardial ischemia, hypertension, tissue ischemia
	5-10 mcg/kg/min	+	++	+	++	
	10-20 mcg/kg/min	++	++	+	++	
Epinephrine	0.01-0.03 mcg/kg/min	-	++	+	0	Arrhythmias, myocardial ischemia, hypertension, hyperglycemia, hypermetabolism/lactic acidosis
	0.03-0.1 mcg/kg/min	+	++	+	0	
	>0.1 mcg/kg/min	++	++	+	0	
Norepinephrine	Start 0.01 mcg/kg/min and titrate to effect (max 30 mcg/min)	++	++	-	0	Arrhythmias, hypertension, tissue ischemia
Phenylephrine	0.15-0.75 mcg/kg/min	++	0	0	0	Bradycardia, hypertension, excessive vasoconstriction
Vasopressin	0.01–0.04 units/min	V1 receptor agonist				Hypertension, excessive vasoconstriction

*Doses are guidelines and the actual administered dose should be determined by patient response; ++: Potent, +: Moderate, -: Minimal, 0: None, IV: Intravenous. Schlichtig R, Kramer DJ, Pinsky MR. Flow redistribution during progressive hemorrhage is a determinant of critical O₂ delivery. J Appl Physiol 1991;70:169-78

Inotropes are broadly classified below by their clinical effects as: (1) **Inodilators** agents that produce inotropy and vasodilation or^[2] **inoconstrictors** agents that produce inotropy and vasoconstriction. Further classification of these agents is illustrated in Figure 2.^[8] The commonly used adrenergic agents stimulate the adrenergic receptors as listed in Table 3 to produce their cardiovascular effects.^[8] The standard dosing of inotropes, their receptor binding (or mechanism of action), and adverse effects are listed in Table 2.^[8,21]

COMMON VASOACTIVE AGENTS AND LITERATURE REVIEW

Pure vasoconstrictors

- Phenylephrine stimulates only alpha receptors resulting in arterial and **venous vasoconstriction**, clinically producing an increase in SVR, MAP, venous return, and baroreceptor-mediated reflex bradycardia. The **increase in SVR** (afterload) and **reflex bradycardia may decrease CO**, so phenylephrine should only be used transiently in general and with caution in patients with preexisting cardiac dysfunction (low CO).^[59,60] Perioperatively, phenylephrine is used to correct hypotension, improve venous return, and decrease the HR in patients with various cardiac conditions (e.g. aortic stenosis and hypertrophic cardiomyopathy).^[8] In

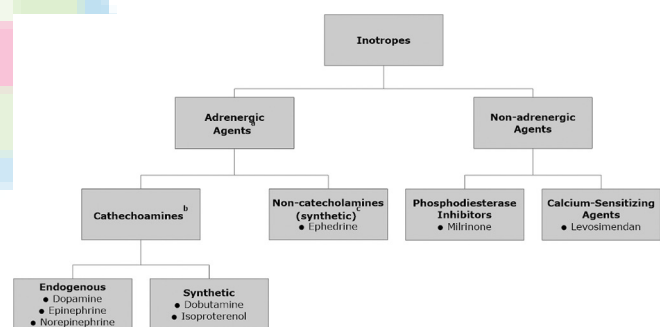


Figure 2: Inotrope classification.^[8,91] a: Adrenergic agents mimic **sympathetic nervous system stimulation** and are also termed "sympathomimetics;" b: Catecholamines structurally contain a catechol group and are rapidly metabolized by catechol-O-methyltransferase and monoamine oxidase corresponding to their short duration of action (1–2 min), making them ideal agents for titration; c: Noncatecholamines have longer durations of action (approximately 5–15 min) since they are not metabolized by catechol-O-methyltransferase

addition, the use of phenylephrine to maintain hemodynamic stability during liver transplantation has demonstrated less blood loss and lower lactate levels compared to inotropes, an effect attributable to its ability to increase vascular resistance and thus reduce portal blood flow.^[61] Phenylephrine is considered a first-line agent in hyperdynamic (normal CO) septic shock as it restores SVR and organ perfusion pressure.^[2,52] Also, phenylephrine's reflex bradycardia may prove

Table 3: Adrenergic receptors with cardiovascular effects

Adrenergic receptor	Location	Cardiovascular effects
Beta-1	Myocardium	Inotropy (increased contractility) Chronotropy (increased heart rate) Dromotropy (increased conduction)
Beta-2	Systemic arterioles Pulmonary arterioles Veins	Vasodilation
Alpha-1	Systemic arterioles (receptor density)* Skin (high) Skeletal muscle (high) Abdominal viscera/splanchnic (moderate) Kidney (moderate) Myocardium (minimal) Brain (minimal) Pulmonary arterioles Veins	Vasoconstriction

*Vasoconstriction of vascular beds with moderate and high alpha-1 receptor density allows the redistribution of blood flow to vital organs with minimal receptor density (brain and myocardium), and is the basis for adrenergic vasopressor use in cardiopulmonary resuscitation. During progressive hemorrhage, the fraction of CO distributed to the dermal/skin, splanchnic, and renal vascular beds declines while the fraction of CO distributed to the brain and myocardium increases.^{a,b} CO: Cardiac output. Kaihara S, Rutherford RB, Schwentker EP, Wagner HN, Jr. Distribution of cardiac output in experimental hemorrhagic shock in dogs. *J Appl Physiol* 1969;27:218-22. ^bSchlichtig R, Kramer DJ, Pinsky MR. Flow redistribution during progressive hemorrhage is a determinant of critical O₂ delivery. *J Appl Physiol* 1991;70:169-78

useful in the treatment of hypotension caused by tachyarrhythmias or when tachyarrhythmias occur in response to other vasoactive agents used in the treatment of circulatory shock^[2]

- **Vasopressin** (antidiuretic hormone) levels are increased in response to early shock to maintain organ perfusion,^[62] but **levels fall dramatically as shock progresses.**^[63,64] Unlike the adrenergic agents, vasopressin does **not stimulate adrenergic receptors** and is not associated with their adverse effects,^[65] and its **vasopressor effects are relatively preserved during hypoxemic and acidemic conditions**, making it **useful in refractory** circulatory shock and CPR,^[65-72] specifically asystole.^[73] Vasopressin, due to its alternate mechanism of action, not only improves hemodynamics but also **improves the vascular response to adrenergic agents**, allowing a reduction in their dosing^[67,70,74] which may reduce the adverse effects seen with adrenergic agents, this is commonly referred to as an **adrenergic sparing effect**.

Vasopressin is primarily indicated in distributive shock, usually as a secondary agent,^[2] but its ability to increase MAP and not adversely impact CO has recently been demonstrated in **refractory cardiogenic shock**,^[75] underscoring the physiologic importance of maintaining organ (myocardial) perfusion pressure.^[8] Considering this, the use of vasopressin has shown utility perioperatively, where its preemptive use in high-risk patients undergoing cardiac surgery has demonstrated hemodynamic stability after cardiopulmonary bypass and an adrenergic agent sparing effect.^[76] Moreover, recent *in vitro* study^[55] supports the emerging clinical observations^[77] that compared to adrenergic agents such as norepinephrine, **vasopressin produces selective systemic vasoconstriction, with minimal effect on the pulmonary vasculature.** This has significant application, particularly in cardiac surgery, where vasopressin would **improve right ventricular (RV) function by increasing coronary perfusion without altering RV afterload**, suggesting it **may be the drug of choice** to improve MAP in the setting of **RV failure.** Its **30–60 min duration** of action is much longer than adrenergic agents, making titration more challenging

- **Methylene blue** inhibits the vasodilatory effects of nitric oxide on the endothelium and vascular smooth muscle. Historically, methylene blue has not been considered a vasoactive agent, but its expanding use in vasoplegic syndrome prompted its inclusion here. Vasoplegic syndrome is generally defined as an MAP <50 mmHg with a low SVR (<600–800 dynes/s/cm²) despite vasoactive agent administration.^[78,79] The syndrome is also typically accompanied by low filling pressures (central venous pressure <5–10 mmHg, pulmonary capillary wedge pressure <10 mmHg).^[78,79] The incidence of **vasoplegic syndrome in cardiac surgery varies but has been reported as high as 42%** in comorbid patients undergoing **ventricular assist device placement**^[80] and the mortality may be as high as 25%.^[81] Methylene blue has been used as a rescue agent for perioperative vasoplegic syndrome in multiple clinical scenarios including cardiac surgery, protamine reaction, **sepsis, and anaphylaxis.**^[81-84] It has even been used prophylactically in high-risk patients undergoing cardiac surgery.^[79] Suggested risk factors for perioperative vasoplegic syndrome in cardiac surgery have been reviewed, and include preoperative LV ejection fraction <35%, ventricular assist device implantation, prolonged CPB, and

the preoperative use of intravenous heparin, angiotensin-converting enzyme inhibitors, calcium channel blockers, and beta-blockers.^[81] The dose of methylene blue varies in the literature but in cardiac surgery, a dose of 1.5–2.0 mg/kg IV infused over 1 h is generally acceptable.^[85,86] In some cases, this initial bolus is followed by a continuous infusion. Methylene blue has a rapid onset, but unlike most vasoactive agents, it has a long half-life of approximately 5.25 h.^[87] It is eliminated by the kidney and is contraindicated in renal failure and should be avoided in patients with known glucose-6-phosphate dehydrogenase deficiency.^[81] Adverse effects have been reviewed and include transient color change of the skin and urine to greenish-blue, cardiac arrhythmias (transient nodal rhythm and ventricular ectopy), coronary vasoconstriction, decreased CO, increased PVR, and decreased renal and mesenteric blood flow; however, these effects were transient and dose dependent (usually at doses >2 mg/kg).^[81] Although the use of perioperative methylene blue is currently controversial,^[88] a recent meta-analysis of randomized controlled trials in hypotensive patients demonstrated no harm.^[89] Therefore, due to the high mortality associated with perioperative vasoplegic syndrome, the use of methylene blue as a rescue agent should be considered in the setting of refractory hypotension.

Inoconstrictors

- **Epinephrine**, in low doses, increases CO because beta-1 inotropic and chronotropic effects predominate, while the minimal alpha-1 vasoconstriction is offset by beta-2 vasodilation, resulting in increased CO with decreased SVR and variable effects on the MAP.^[90] At higher doses, alpha-1 vasoconstrictive effects predominate, producing increased SVR, MAP, and CO.^[8] Thus, in the acutely failing ventricle (e.g., low CO syndrome after cardiac surgery), epinephrine maintains coronary perfusion pressure and CO. Epinephrine is used in CPR to restore coronary perfusion pressure and in the management of symptomatic bradycardia unresponsive to atropine or a temporizing measure while awaiting the availability of a pacemaker.^[92] It is a second-line agent in septic^[2] or refractory circulatory shock and is the drug of choice in anaphylaxis because of its efficacy to maintain MAP, partly due to its superior recruitment of splanchnic reserve (about 800 mL), compared to other vasoactive agents, which helps to restore

venous return and CO.^[93] Consequently, the degree of splanchnic vasoconstriction appears to be greater than with equipotent doses of norepinephrine or dopamine in patients with severe shock,^[94] thus limiting its liberal use among clinicians. However, recent prospective study in critically ill patients demonstrated no difference in 28 and 90 days mortality compared to norepinephrine when using MAP as the sole endpoint, thus tempering the theoretical safety concerns held by many.^[95]

- **Norepinephrine** has potent alpha-1, modest beta-1, and minimal beta-2 activity.^[8] Thus, norepinephrine produces powerful vasoconstriction and a reliable increase in SVR and MAP, but a less pronounced increase in HR and CO, compared to epinephrine.^[96] Therefore, caution must be used in the setting of the failing ventricle. Reflex bradycardia usually occurs in response to the increased MAP, such that its modest beta-1 chronotropic effect is mitigated, and the HR remains relatively unchanged. Because norepinephrine is the predominant endogenous adrenergic agent and sepsis can lead to its depletion, its use as the first-line agent in septic shock has been argued as intuitive.^[97,98] Current Surviving Sepsis Campaign guidelines support its use as the first-line agent,^[2] especially in hyperdynamic (normal CO) septic shock because of its ability to increase SVR and MAP, thus correcting the physiologic deficit in organ perfusion pressure, compared to other agents that instead increase MAP by increasing CO (e.g., dopamine).^[23,58,99] Although its recommendation in cardiogenic shock no longer formally exists, it may still be useful in the presence of severe hypotension (systolic blood pressure <70 mmHg) in the setting of LV systolic dysfunction due to its ability to improve MAP, thereby restoring coronary and organ perfusion pressure.^[100]
- **Dopamine** is the immediate precursor to norepinephrine and is characterized by dose-dependent effects that are due to both direct receptor stimulation and indirect effects^[8] due to norepinephrine conversion and release.^[101] Doses <5 mcg/kg/min stimulate dopamine receptors and have minimal cardiovascular effects. At moderate doses between 5 and 10 mcg/kg/min, dopamine weakly binds to beta-1 receptors, promotes norepinephrine release, and inhibits norepinephrine reuptake in presynaptic sympathetic nerve terminals, resulting in increased inotropy and chronotropy, and a mild increase in SVR via alpha-1 adrenergic receptor stimulation.^[8] At higher doses

of 10–20 mcg/kg/min, alpha-1 receptor-mediated vasoconstriction dominates.^[8] Dopamine remains the treatment for symptomatic bradycardia unresponsive to atropine or as a temporizing measure while awaiting the availability of a pacemaker.^[92] Otherwise, the clinical use of dopamine continues to decline due to its indirect effects, significant variations in plasma concentrations in patients receiving the same dose, and recent study demonstrating a higher incidence of arrhythmia and higher mortality in cardiogenic^[102] and septic shock.^[103] Consequently, previous recommendations for its use in cardiogenic shock with SBP 70–100 mmHg with signs or symptoms of end-organ compromise,^[100] based on its alpha-1 activity to correct the deficit in organ perfusion pressure, have been removed.^[104] Also citing this evidence, dopamine is no longer a first-line treatment for septic shock, but may be reserved for select patients with a low risk of arrhythmia who present with hypodynamic (low CO) septic shock and/or bradycardia,^[2] as dopamine increases inotropy and chronotropy (thereby increasing CO and MAP) with a minimal increase in SVR.

- **Ephedrine** acts primarily on alpha and beta receptors,^[105] similar to epinephrine but with less potency. Ephedrine also releases endogenous norepinephrine from sympathetic neurons and inhibits norepinephrine reuptake, accounting for additional indirect alpha and beta receptor effects. Ephedrine's combined effects result in an increased HR, CO, and MAP. Ephedrine is a noncatecholamine and because of its longer duration of action, its dependence on endogenous norepinephrine for its indirect effects and its potential to therefore deplete norepinephrine, it is not ideal for infusion and is therefore rarely used except in the setting of transient anesthesia-related hypotension.

Inodilators

- **Isoproterenol** has potent beta-1 and beta-2 activity with virtually no alpha activity. Its principal actions are inotropy, chronotropy, and systemic and pulmonary vasodilation.^[8] Despite its inotropy, the systemic vasodilation decreases venous return, resulting in a minimal increase in CO and a drop in MAP.^[8] Because of this, isoproterenol is limited to situations where hypotension and shock result from bradycardia or heart block.^[92]
- **Dobutamine** primarily stimulates beta-1 and beta-2 receptors resulting in increased chronotropy, inotropy, and systemic and pulmonary vasodilation.

The net result is increased HR, CO, and decreased SVR with or without a small reduction in MAP. Dobutamine is frequently used to treat low CO following cardiac surgery primarily due to its inotropic and pulmonary vasodilatory effects.^[106] Although its recommendation in cardiogenic shock no longer formally exists, it may still be useful in early cardiogenic shock without evidence of organ hypoperfusion.^[100] However, if organ hypoperfusion is present, an inoconstrictor should be chosen to restore organ perfusion pressure.^[100] Dobutamine remains recommended therapy in septic shock with low CO.^[2]

- **Milrinone**, a nonadrenergic phosphodiesterase inhibitor, increases intracellular levels of myocardial and vascular smooth muscle cAMP by inhibiting its breakdown, leading to increased myocardial contractility and smooth muscle relaxation resulting in pulmonary and systemic vasodilation. Thus, milrinone improves RV function in the setting of pulmonary hypertension,^[106] more so than the adrenergic inodilators. In addition, milrinone uniquely improves diastolic relaxation (lusitropy). Being a nonadrenergic agent, it has the advantage of not being affected by beta-blocker use or the characteristic diminished beta receptor responses seen in chronic heart failure and does not produce the adverse effects associated with beta-receptor stimulation.^[8,106] Milrinone's vasodilatory properties limit its use in hypotensive patients,^[107] and its 30–60 min half-life is significantly longer than the adrenergic inodilators.^[106]
- **Levosimendan** is a nonadrenergic calcium-sensitizing agent that produces inotropy by calcium sensitization of myocardial contractile proteins, without increasing intracellular calcium, and vasodilatation within the systemic and pulmonary circulation, by activation of adenosine triphosphate-sensitive potassium channels.^[108] Levosimendan produces similar clinical effects to milrinone,^[109,110] but is also limited by hypotension and a long duration of action (80 h due to active metabolites). Levosimendan is a relatively new agent and is not currently approved for use in the United States.

CONCLUSION

Despite the growing body of evidence evaluating the efficacy of vasoactive agents in the management of circulatory shock, it appears no agent is superior, and the recent meta-analysis of 23 randomized controlled

trials comparing commonly used agents supports this.^[11] This is becoming increasingly accepted as current guidelines from the American College of Cardiology and the American Heart Association no longer publish detailed algorithms for the management of cardiogenic shock,^[100] and have instead replaced them with a single statement: **Vasoactive agents should be individualized** and guided by invasive hemodynamic monitoring.^[104] Based on this, vasoactive agent selection may currently be individualized and **left to the discretion** of the **treating physician** with a goal-directed approach. However, circulatory shock in the comorbid patient is a complex process; therefore, the ability to rapidly diagnose the etiology and firmly understand its pathophysiology as well as the pharmacology of vasoactive agents is ultimately paramount importance to guide successful therapy.

In summary, the following recommendations can be made regarding the current management of perioperative circulatory shock: (1) Vasoactive agent selection should be based on correcting the underlying physiologic deficits and the agent ultimately chosen probably does not matter as long as the hemodynamic goals are achieved;^[22,26] (2) achieving supraphysiologic goals for CO has not been shown benefit patients and may cause harm,^[23,57,58] but if maximal doses of a first agent are inadequate to meet goals, then a second drug should be added, with consideration given to agents with different mechanisms of action to maximize effects; and (3) patients receiving vasoactive agents require careful monitoring and frequent reevaluation so these agents can be titrated to the minimal effective dose to avoid potential adverse effects.

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Conflicts of interest

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