

CLINICAL PRIMER

Vasoactive Agent Selection Strategies in the Management of Cardiogenic Shock

Erin A. Bohula¹ MD, DPhil; David A. Morrow² MD, MPH

ABSTRACT: Cardiogenic shock is defined by inadequate blood flow to vital organs because of cardiac insufficiency and is often, but not always, manifest by hypotension. In an effort to mitigate end-organ hypoperfusion and modulate blood pressure, medical management with vasoactive agents is the initial strategy in virtually all patients with cardiogenic shock. This clinical primer describes the pharmacologic profiles of the currently used vasoactive agents and available comparative effectiveness data, reviews the pathophysiology of the most common phenotypic forms of cardiogenic shock, and provides a strategic framework for vasoactive agent selection and titration that integrates the pharmacology, pathophysiology, and hemodynamic derangements that define each shock phenotype. The practice-based approach to vasopressor selection strategy for the management of cardiogenic shock outlines the following steps: first, emergently protect the mean arterial pressure; then, define the hemodynamic phenotype of cardiogenic shock and identify (and address, in parallel) potential etiologies and contributors; next, set additional hemodynamic goals beyond mean arterial pressure; last, tailor pharmacotherapy through iterative assessments of perfusion and ongoing hemodynamic derangements.

Key Words: cardiogenic shock ■ inopressor ■ inotrope ■ SCAI stage ■ SHARC ■ vasoactive ■ vasopressor

Cardiogenic shock (CS) is defined by inadequate blood flow to vital organs (end-organ hypoperfusion) because of cardiac insufficiency and is often, but not always, manifest by persistently low blood pressure (hypotension).^{1–3} CS is highly prevalent in intensive care units, affecting >1 in 5 admissions to cardiac intensive care units.⁴ In-hospital mortality varies depending on CS etiology, hemodynamic profile, and severity of initial presentation, but is typically 30% to 50%.^{1,3,5} It is important to note that few invasive or mechanical therapies have been shown to be beneficial for preventing the sequelae of shock (multiorgan system failure and death) and these therapies are only relevant for small subsets with CS. Early culprit-vessel revascularization for acute myocardial infarction (MI)-related shock is beneficial but relevant to only ~25% of patients with CS, and early mechanical circulatory support (MCS) has proven benefit in a highly selected subset of patients with MI that accounts for only 5% of all CS.^{6–9} In an effort to mitigate end-organ hypoperfusion and modulate blood pressure, medical man-

agement with vasoactive agents is the initial strategy in virtually all patients with CS and the primary treatment in the majority of patients with CS, particularly those with ongoing hypotension.^{8,10,11} In clinical trials of patients with acute MI CS (AMI-CS) and hypotension, ~90% of patients were treated with at least 1 vasopressor.^{6,8,10} In clinical registries of patients with a broader range of etiologies of CS, >90% were treated with vasoactives and 50% required 2 or more agents.^{11,12}

In the face of near universal use of vasoactive agents in the management of CS, this clinical primer (1) reviews the pathophysiology of the most common phenotypic forms of CS, (2) describes the pharmacologic profiles of vasoactive agents and comparative effectiveness data, where available, and (3) provides a strategic framework for medical management of CS. The maturation of classification systems for shock phenotype and severity have provided a new foundation that informs this framework for medical management of CS.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Correspondence to: Erin A. Bohula, MD, DPhil, 350 Longwood Avenue, First Office Floor, Boston, MA 02115. Email ebohula@bwh.harvard.edu

© 2026 American Heart Association, Inc.

Circulation is available at www.ahajournals.org/journal/circ

Nonstandard Abbreviations and Acronyms

AMI-CS	acute myocardial infarction cardiogenic shock
CS	cardiogenic shock
LV	left ventricular
MAP	mean arterial pressure
MCS	mechanical circulatory support
MI	myocardial infarction
PVR	pulmonary vascular resistance
RAP	right atrial pressure
RV	right ventricular
SHARC	Shock Academic Research Consortium
SVR	systemic vascular resistance

CS DEFINITIONS AND CLASSIFICATIONS

Historical definitions of CS have variably included the following elements: (1) hypotension; (2) evidence of end-organ hypoperfusion; (3) inadequate cardiac index, defined as less than 2.2 L/min per m²; and (4) elevated end-diastolic pressures on the right (>10–15 mmHg) or left (>18 mmHg).¹ More recently, the Shock Academic Research Consortium (SHARC) expert panel defined CS as any cardiac disorder that results in both clinical and biochemical evidence of sustained tissue hypoperfusion.³ End-organ hypoperfusion is defined as at least 1 of the following: elevated arterial lactate (>2 mmol/L), acute kidney injury (creatinine ≥2 times the upper limit of normal) or oliguria (urine output <0.5 ml/kg/h), acute hepatic injury (alanine transaminase >3 times the upper limit of normal), cool or mottled extremities, or altered mental status not explained by an alternative cause.³ Within the SHARC framework, CS is further stratified into normotensive CS (defined by a systolic blood pressure ≥90 mmHg in the absence of vasoactive agents or MCS) or hypotensive CS (defined by a systolic blood pressure <90 mmHg for ≥30 minutes or the requirement for vasoactive agents or MCS to maintain a systolic blood pressure ≥90 mmHg). This distinction is critically important to (1) highlight that hypotension does not define shock (rather shock is defined by hypoperfusion) and to (2) inform strategies for medical management of normotensive versus hypotensive CS. Last, the SHARC statement also subclassified CS according to etiology, including acute myocardial infarction (AMI-CS), heart failure caused by primary ventricular dysfunction absent an acute MI (heart failure CS), postcardiotomy, and secondary causes (eg, valvular disease, incessant arrhythmia, or tamponade), highlighting important distinctions with respect to prognosis as well as options for targeted, pathogenesis-directed treatments (eg, revascularization in AMI-CS).

SELECTED SHOCK PHENOTYPES

Comparative effectiveness data about choice of specific vasoactive agents are extremely limited (discussed below). Therefore, vasoactive agent selection for medical management of CS is generally dictated by pathophysiologic principles, meaning that the choice of vasoactive agent aligns with the pharmacologic profile of each agent along with the shock phenotype and its underlying pattern of hemodynamic derangements with the aim to normalize those derangements. It is helpful to consider a subset of shock phenotypes to facilitate pattern recognition and to outline a framework for vasoactive agent selection for each phenotype.

For the purposes of this clinical primer, we will focus on the following phenotypes: “classic” left ventricular (LV)–predominant CS with hypotension, vasodilatory CS (or mixed shock) with hypotension, normotensive CS, right ventricular (RV)–predominant CS, and shock caused by dynamic LV outflow obstruction (Table 1). The approach to secondary CS, such as tamponade, severe valvular disease, or massive pulmonary embolism, is not included in this primer as rapid definitive management to reverse the mechanical process is the focus of care in affected patients. In addition, the approach to patients without hypoperfusion (ie, not meeting the SHARC definition of shock), such as SCAI stage B, is not included in this primer.

“Classic” LV–predominant CS is the most common phenotype of shock encountered in cardiac intensive care units (~65%).^{11,13} It is characterized by hypoperfusion with a low cardiac index (<2.2 L/min/m²) and an elevated systemic vascular resistance (SVR) (often >2200 dyn/s/cm⁵, where normal is ~800–1200 dyn/s/cm⁵) as a compensatory mechanism to preserve mean arterial pressure (MAP; where MAP – right atrial pressure [RAP] = cardiac output × SVR and cardiac output = heart rate × stroke volume), and frequently with increased LV end-diastolic pressure. Most patients with classic CS are hypotensive (henceforth termed “classic CS with hypotension”); however, ≥15% of patients with CS are able to maintain an adequate MAP because of robust vasoconstriction (“normotensive CS”).¹ In such cases, it is important to recognize the pattern of global end-organ hypoperfusion that reflects a shock state, as abnormalities are often misinterpreted as individual organ dysfunction in the absence of hypotension (eg, concern for acute infectious hepatitis as the pathogenesis of acute liver injury).

Vasodilatory CS (also called mixed shock) is the second most frequent phenotype of CS encountered in cardiac intensive care units (15%–20%).^{11,13} Vasodilatory CS is distinguished from classic CS by an inappropriately low SVR. Mixed shock can be categorized as either primary CS with superimposed vasoplegia or as primary vasodilatory shock with underlying myocardial dysfunction leading to inadequate compensation.¹⁴ Among those with primary CS, vasoplegia may result from either a

Table 1. Shock Phenotypes With Typical Hemodynamic Profiles

Shock subtypes	Summative definition	RAP	PAWP	CI	SVR	MAP	PAPI
Cardiogenic shock subtypes							
Classic cardiogenic	Hypoperfusion caused by ↓ CI and ↑ SVR, with or without hypotension			↓	↑	↓ (Hypotensive CS) normal or ↑ (normo- tensive CS)	
Left-sided		Normal or ↑	↑				Normal
Right-sided		↑	Normal or ↓				↓
Biventricular		↑	↑	↓			
Vasodilatory cardiogenic (mixed)	Hypoperfusion caused by inadequate CI and inappropriately ↓ SVR	Normal or ↑	↑	Normal or ↓*	↓	↓	Normal or ↓
Obstructive/mechanical							
Venous return (eg, tension PTX)	Hypoperfusion with a ↓ CI caused by mechanical or obstructive process	↓	↓	↓	↑	Usually ↓	↓
RV outflow (eg, PE, pHTN)		↑	↓				↓
Tamponade		↑	↑				Normal or ↓
Severe left-sided valvular		Normal or ↑	↑	Normal			
Noncardiogenic shock							
Hypovolemic	Hypoperfusion with a ↓ CI caused by inadequate volume	↓	↓	↓	↑	↓	Normal
Distributive	Hypoperfusion caused by ↓ SVR	Normal or ↓	Normal or ↓	↑	↓	↓	Normal

Pulmonary artery pulsatility index (PAPI) is [pulmonary artery systolic pressure minus pulmonary artery diastolic pressure]/right atrial pressure (RAP), where threshold for abnormal is <1. Surrogates may be used to approximate invasive hemodynamic measures. Jugular venous pressure or inferior vena cava dimensions can be used to estimate RAP. Pulmonary edema on imaging or examination implies ↑ pulmonary artery wedge pressure (PCWP). Perfusion markers (urine output barring oliguric acute kidney injury; lactate, mental status) approximate cardiac index (CI). Delayed capillary refill (ie, >2–3 s) or cool, mottled extremities imply increased systemic vascular resistance (SVR). MAP indicates mean arterial pressure; PE, pulmonary embolism; pHTN, pulmonary hypertension; PTX, pneumothorax; and RV, right ventricular.

*Inadequate increase to compensate for vasoplegia.

distinct, superimposed vasoplegic process/insult (eg, postarrest or sepsis) or evolution of protracted or profound classic CS culminating in a systemic inflammatory response syndrome that drives vasodilation.¹⁴

Dynamic LV outflow obstruction is an uncommon phenotype but is worth discussing as its management with vasoactive agents is quite distinct from other shock phenotypes. In this condition, dynamic, physical obstruction to LV emptying impairs cardiac output (Table 1). Pathogenesises include hypertrophic obstructive cardiomyopathy, “nutcracker” or “suicide LV” (acute hyperdynamic LV function with cavitory obstruction after correction of aortic stenosis), and stress cardiomyopathy with functional obstruction caused by basilar LV hyperkinesis.

RV-predominant CS is generally invoked when hemodynamic indices are dominantly abnormal for the right heart, with absolute and relative elevations in right-sided pressures (RAP >10 mmHg; RAP/pulmonary artery wedge pressure >0.86), or a reduction in RV functional indices (pulmonary artery pulsatility index <1.0) (Table 1).¹⁵ Management will depend on the underlying pathogenesis, which includes RV myocardial dysfunction (eg, ischemia), RV outflow obstruction (eg, severe pulmonary hypertension, particularly pulmonary arterial hypertension, massive pulmonary embolism), or insufficient venous return (eg, tension pneumothorax).

Management of biventricular shock (Table 1) should combine and balance the principles for management of

isolated RV- and LV-predominant shock, including treating systemic hypotension while avoiding worsening systemic and RV afterload, supporting biventricular inotropy, and careful volume management to maximize biventricular stroke volume while minimizing potential RV impingement on LV filling.

VASOACTIVE THERAPIES: CLASSES, INDIVIDUAL AGENTS AND COMPARATIVE EFFECTIVENESS

A useful descriptive framework for vasoactives categorizes agents according to the functional impact on myocardial contractility and arterial vascular smooth muscle. Inopressors have an inotropic and chronotropic effect, thereby increasing cardiac output and heart rate, as well as a vasopressor effect, through vasoconstriction (Table 2). Inodilators have an inotropic and chronotropic effect, but in contrast, promote vasodilation. Pure vasopressors promote vasoconstriction, without a direct effect on myocardial contractility.

INOPRESSORS

The inopressors—epinephrine, norepinephrine, and dopamine—are all in the catecholamine family and activate α- and β-adrenergic receptors, resulting in increased heart

Table 2. Vasoactive Agents: Indications in Cardiogenic Shock, Receptor Binding, Hemodynamic Effect, and Major Clinical Side Effects

Drug	Class	Clinical indication	Receptor binding*					Hemodynamic effect	Major side effects
			α_1	β_1	β_2	DA	Other receptor or MOA		
Inopressors (↑ CO, ↑ HR, and ↑ SVR)									
Dopamine	Catecholamine	Shock (classic or vasodilatory CS with hypotension) Symptomatic bradycardia unresponsive to atropine	+++	++++	++	+++++	N/A	↑ CO (all doses), ↑ ↑HR (all doses) and ↑ SVR (mod-high doses), likely ↑ PVR	Atrial or ventricular arrhythmias Peripheral or visceral ischemia caused by vasoconstriction
Norepinephrine	Catecholamine	Shock (classic or vasodilatory CS with hypotension)	+++++	+++	+	N/A	N/A	↑ CO, ↑ HR ↑ ↑SVR, likely ↑ PVR	Atrial or ventricular arrhythmias Peripheral or visceral ischemia caused by vasoconstriction
Epinephrine	Catecholamine	Shock (classic or vasodilatory CS with hypotension) Cardiac arrest Anaphylaxis	+++++	++++	+++	N/A	N/A	↑ ↑CO, ↑ ↑HR, ↑ SVR, likely ↑ PVR	Atrial or ventricular arrhythmias Can drive lactic acidosis Peripheral or visceral ischemia caused by vasoconstriction
Inodilators (↑ CO, ↑ HR, and ↓ SVR)									
Milrinone	Phosphodiesterase inhibitor	Low CI (normotensive CS, other CS with adequate MAP, RV dominant CS)	N/A	N/A	N/A	N/A	PDE inhibitor	↑ CO, ↑ HR, ↓ SVR, ↓ PVR	Ventricular arrhythmias Hypotension
Dobutamine	Catecholamine	Low CI (normotensive CS, other CS with adequate MAP, RV dominant CS)	+	+++++	+++	N/A	N/A	↑ CO, ↑ HR, ↓ SVR, ↓ PVR	Atrial or ventricular arrhythmias Hypotension
Isoproterenol	Catecholamine	Bradycardias (especially torsade des pointes) Brugada syndrome	0	+++++	+++++	N/A	N/A	↑ ↑HR, ↑ CO, ↓ SVR,	Atrial or ventricular arrhythmias Can drive lactic acidosis
Levosimendan	Calcium-sensitizing agent	Decompensated HF	N/A	N/A	N/A	N/A	Myofilament Ca^{2+} sensitizer, PDE-3 inhibitor	↑ CO, ↑ HR, ↓ SVR,	Tachycardia, enhanced AV conduction Hypotension
Vasopressors (↑ SVR)									
Vasopressin	Synthetic antidiuretic hormone (ADH)	Shock (vasodilatory CS or RV dominant CS with hypotension) Cardiac arrest	N/A	N/A	N/A	N/A	V1 receptors (vascular smooth muscle) V2 receptors (renal-collecting duct system)	↑ SVR, ↔ PVR	Hyponatremia Peripheral or visceral ischemia caused by vasoconstriction
Phenylephrine	Catecholamine	Decrease dynamic LV outflow obstruction; rescue option for refractory vasodilation (vasodilatory CS) Increase MAP with aortic stenosis and hypotension	+++++	0	0	N/A	N/A	↑ SVR, ↑ PVR	Reflex bradycardia Peripheral or visceral ischemia caused by vasoconstriction Tissue necrosis with extravasation
Angiotensin II	Peptide hormone	Rescue option for refractory/ catecholamine-resistant vasodilation (vasodilatory CS)	N/A	N/A	N/A	N/A	Binds to AT II receptor type 1 (vascular smooth muscle) and ↑ aldosterone release	↑ SVR	Venous > arterial thrombotic and thromboembolic events Concomitant ACE inhibitor increases effect Concomitant ARB decreases effect

(Continued)

Table 2. Continued

Drug	Class	Clinical indication	Receptor binding*					Hemodynamic effect	Major side effects
			α_1	β_1	β_2	DA	Other receptor or MOA		
Methylene blue	Redox agent	Rescue option for refractory vasodilation (vasodilatory CS)	N/A	N/A	N/A	N/A	Inhibits nitric oxide synthase and guanylate cyclase	↑ SVR	Interferes with pulse oximetry leading to underestimate of true oxygen saturation (direct measurement of SaO ₂ by blood gas accurate) Hemolysis in G6PD deficiency

+ to +++++, minimal to maximal relative receptor affinity. α_1 indicates α_1 -adrenergic receptor; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AS, aortic stenosis; AT, angiotensin; AV, atrioventricular; β_1 , β_1 -adrenergic receptor; β_2 , β_2 -adrenergic receptor; CO, cardiac output; CS, cardiogenic shock; DA, dopamine receptors; G6PD, glucose-6-phosphate dehydrogenase; HCM, hypertrophic cardiomyopathy; HF, heart failure; HR, heart rate; IM, intramuscular; IV, intravenous; LV, left ventricular; LVOT, left ventricular outflow tract; MAP, mean arterial pressure; max, maximum; MOA, mechanism of action; N/A, not applicable; PDE, phosphodiesterase; PVR, pulmonary vascular resistance; RV, right ventricular; and SaO₂, arterial blood oxygen saturation.

*0, Zero significant receptor affinity.
Adapted from Overgaard and Dzavik¹⁶ and van Diepen et al.¹

rate, cardiac output, and vascular tone (Table 2). Although the overarching hemodynamic impact is similar between inopressors, the potency of receptor activation differs between the agents, which can result in somewhat distinct effects. Dopamine has a unique, dose-dependent stimulation of dopamine and β_1 and α_1 receptors. At low doses, dopaminergic receptor stimulation dominates; at moderate doses, β_1 activation results in augmentation of cardiac output and HR; at high doses, α_1 stimulation prevails, manifest as vasoconstriction (Table 2). Epinephrine is generally considered to have greater relative β_1 stimulation compared with norepinephrine, resulting in greater increases in cardiac output and heart rate; norepinephrine is generally considered to have greater relative α_1 stimulation compared with epinephrine, resulting in greater increases in SVR.¹⁷

As these agents improve cardiac output and increase blood pressure, they are usually considered first-line in the treatment of classic or vasodilatory CS with hypotension. It is important to note that despite the pervasive use of these agents and the potential for differential effects, very few studies have evaluated the comparative effectiveness or safety of these agents in shock and even fewer in CS. In the SOAP (Sepsis Occurrence in Acutely Ill Patients) II trial, treatment with dopamine at doses up to 20 $\mu\text{g/kg/min}$ was not associated with a difference in the primary end point of all-cause mortality, but was associated with a higher rate of tachyarrhythmias (24.1% versus 12.4%), a secondary end point, in a heterogeneous population of all-comers with shock ($n=1679$) compared with norepinephrine (Table 3).¹⁸ In a subgroup analysis of patients with CS ($n=280$, 17% of total trial population), dopamine was associated with more arrhythmic events and with a nonsignificant pattern towards increased mortality (approximately 50% versus 40% at 28 days), but with no evidence of true heterogeneity for mortality by shock type (P interaction for mortality by shock type, 0.87).¹⁸ Two other small trials observed higher heart rate and lac-

tate level with epinephrine compared to norepinephrine (Table 3).^{19,20} In the OptimaCC study (Epinephrine Versus Norepinephrine for Cardiogenic Shock After Acute Myocardial Infarction) that enrolled 57 highly selected patients with AMI-CS, there was a suggestion of a greater rate of refractory shock—a post hoc end point that included persistent lactate elevation—with epinephrine compared with norepinephrine.¹⁹ It is important to note that this finding may not reflect actual refractory CS as epinephrine is known to increase lactate through proposed mechanisms *unrelated* to cardiac output or global perfusion (eg, epinephrine is believed to drive skeletal muscle production of lactate in a perfusion independent fashion), and it is unknown whether such hypoperfusion-independent lactate elevations correlate with worse outcomes.²³ On the other hand, such lactate elevation can pose a challenge with respect to (1) acid-base status and (2) serial assessment for improvement in perfusion. For the latter, it is important to consider other markers of perfusion.

Based on the limited data, the American Heart Association's Scientific Statement on Contemporary Management of Cardiogenic Shock concluded that “the optimal first-line vasoactive medication in cardiogenic shock remains unclear.”¹ This uncertainty has led to a high degree of variability in clinical practice patterns, but a general trend towards more use of norepinephrine over epinephrine and dopamine.¹⁸ Data from the American Heart Association Cardiogenic Shock Registry indicates norepinephrine is the most commonly used agent, used in approximately 65% of patients with CS supported by vasoactive medications, with epinephrine being used in 29% and with dopamine used in only 6%.¹² In the DanGer Shock trial, which enrolled European patients with AMI-CS, norepinephrine, epinephrine, and dopamine were used in 81%, 37%, and 23% of participants, respectively.⁶

A theoretical argument can be made that epinephrine may have the potential for more favorable

Table 3. Randomized Controlled Trials of Vasoactive Agents that Included Patients With Cardiogenic Shock

Study	Treatment	Population	Primary end point	Other end points
SOAP II (2010) ¹⁸	Dopamine vs norepinephrine	1679 patients with shock, including sepsis (n=1044), cardiogenic (n=280), hypovolemia (n=263), and other (n=92)	Death at 28 days 52.5% vs 48.5% OR, 1.17 (95% CI, 0.97–1.42); <i>P</i> =0.10 In CS subgroup, HR ~0.75 favoring norepinephrine (interaction <i>P</i> =0.87)	• Arrhythmias: 24.1% vs 12.4%; <i>P</i><0.001 • Mechanical ventilation-free days at 28 days: 8.5±11.2 vs 9.5±11.4 (<i>P</i>=0.13) • Renal replacement-free days at 28 days: 12.8±12.4 vs 14.0±12.3 (<i>P</i>=0.07) • Vasopressor support-free days at 28 days: 11.0±12.1 vs 12.5±12.1 (<i>P</i>=0.01)
OptimaCC (2018) ¹⁹	Epinephrine vs norepinephrine	57 patients with AMI-CS and LV EF<40%	Cardiac index No difference with <i>P</i> =0.43	• Refractory CS (post hoc end point): 37% (10 of 27) vs 7% (2 of 30); <i>P</i>=0.01 • Arrhythmias: 41% vs 33%; <i>P</i>=0.56 • Death at 60 days: 52% vs 37%; <i>P</i>=0.25
CAT Study (2008) ²⁰	Epinephrine vs norepinephrine	280 patients with shock, including severe sepsis (n=158) and AMI-CS (n=27)	Time to attainment of MAP goal for ≥24 hours without vasopressors Median 35.1 hours (IQR, 13.8–70.4) vs 40.0 hours (14.5–120.0) HR, 0.88 (95% CI, 0.69–1.12); <i>P</i> =0.26	• Death at 28 days: 22.5% vs 26.1%; HR, 0.86 (95% CI, 0.57–1.31); <i>P</i>=0.48 • Vasopressor-free days: median, 26.0 (IQR, 19.2–27.3) vs 25.4 (13.8–27.3); <i>P</i>=0.31
DOREMI (2021) ²¹	Milrinone vs dobutamine	192 patients with cardiogenic shock	Composite of in-hospital death, resuscitated cardiac arrest, heart transplant or MCS, MI, TIA or stroke, initiation of renal replacement therapy 49% vs 54% RR, 0.90 (95% CI, 0.69–1.19); <i>P</i> =0.47	• In-hospital death: 37% vs 43%; RR, 0.85 (95% CI, 0.60–1.21) • Resuscitated cardiac arrest: 7% vs 9%; HR, 0.78 (95% CI, 0.29–2.07) • Heart transplant or MCS: 12% vs 15%; HR, 0.78 (95% CI, 0.36–1.71) • Renal replacement: 22% vs 17%; HR, 1.39 (95% CI, 0.73–2.67)
VANCS (2017) ²²	Vasopressin vs norepinephrine	300 patients with vasoplegic shock and cardiac index >2.2 l/min/m ² (not CS) after cardiac surgery	Composite of mortality or severe complications (stroke, mechanical ventilation >48 hours, deep sternal wound infection, reoperation, or acute renal failure) within 30 days 32% vs 49% HR, 0.55 (95% CI, 0.38–0.80); <i>P</i> =0.0014	• Death at 30 days: 15.4% vs 15.9%; HR, 0.99 (95% CI, 0.56–1.76); <i>P</i>=0.98 • Mechanical ventilation >48 hours: 5.4% vs 8.6%; HR, 0.62 (95% CI, 0.26–1.49); <i>P</i>=0.28 • Sternal wound infection: 4.7% vs 9.9%; HR, 0.46 (95% CI, 0.19–1.23); <i>P</i>=0.09 • Reoperation: 6.7% vs 6.6%; HR, 0.8 (95% CI, 0.52–1.23); <i>P</i>=0.31 • Stroke: 2.7% vs 2.6%; HR, 1.03 (95% CI, 0.26–4.11); <i>P</i>=0.97 • Acute renal failure: 10.3% vs 35.8%; HR, 0.26 (95% CI, 0.15–0.46); <i>P</i><0.0001 • Atrial fibrillation: 63.8% vs 82.1%; HR, 0.38 (95% CI, 0.22–0.65); <i>P</i>=0.0004

AMI-CS indicates acute myocardial infarction cardiogenic shock; CS, cardiogenic shock; DOREMI, Dobutamine Compared with Milrinone; EF, ejection fraction; HR, hazard ratio; IQR, interquartile range; LV, left ventricular; MAP, mean arterial pressure; MCS, mechanical circulatory support; MI, myocardial infarction; OR, odds ratio; RR, relative risk; SOAP, Sepsis Occurrence in Acutely Ill Patients; TIA, transient ischemic attack; and VANCS, Vasopressin Versus Norepinephrine in Patients With Vasoplegic Shock After Cardiac Surgery.

physiological effects in CS (with greater cardiac contractile support with less vasoconstriction because of its mixed β_1 - and β_2 -receptor agonism, particularly at low-moderate doses) versus norepinephrine (with more increase in afterload and less contractile support of the heart than the other agents because of its predominant α_1 -adrenergic agonism). As such, we will often consider the use of epinephrine over norepinephrine in CS with hypotension, monitoring for idiosyncratic elevations of lactate. We prefer dopamine when relative bradycardia is thought to be contributor to shock in light of its greater relative chronotropic effects. Conversely, if a patient's course is complicated by tachyarrhythmias, we tend to (1) avoid agents with greater chronotropy, and therefore greater arrhythmogenicity, favoring norepinephrine over dopamine, or (2) consider an adrenergic-sparing strategy for MAP support with the addition of vasopressin.

INODILATORS

Because of the effects of increased inotropy and vasodilation, inodilators are most often used as the initial agent among patients with normotensive CS or as add-on therapy after MAP stabilization with an inopressor in hypotensive (classic or vasodilatory) CS. Dobutamine is a catecholamine with β_1 - and β_2 -receptor agonism, resulting in inotropy, chronotropy, and vasodilation (Table 2). Milrinone is a phosphodiesterase inhibitor (regulating cAMP bioactivity) with inotropic and vasodilating actions.¹ The DOREMI (Dobutamine Compared with Milrinone) trial found no difference in the rate of a broad and heterogeneous primary composite outcome that included in-hospital death, cardiac arrest, MI, need for MCS, stroke, or renal replacement in 192 patients with CS randomized to dobutamine versus milrinone (Table 3).²¹

The choice between agents often depends on clinician comfort/familiarity and consideration of the differences in pharmacokinetics. Milrinone has a longer half-life than dobutamine (approximately 2.5 hours with normal renal function for milrinone versus 2 minutes for dobutamine), can accumulate with renal dysfunction, tends to correlate with greater pulmonary vasodilatation and less exacerbation of tachycardia, and does not lead to tachyphylaxis. As such, we tend to use dobutamine early in a patient's course to allow for more rapid titration and in patients with renal dysfunction. We tend to favor milrinone in patients with difficult to manage tachyarrhythmias, pulmonary hypertension, or an expectation of prolonged use (eg, home inotropic support). If used in patients with renal dysfunction, we tend to uptitrate milrinone cautiously to avoid bioaccumulation and resultant excessive vasodilation.

VASOPRESSORS

The mechanism by which pure vasopressors increase vasoconstriction varies across agents. Vasopressin, or antidiuretic hormone, results in arterial smooth muscle contraction through V1 receptor agonism on the systemic vasculature (Table 2). Vasopressin is typically used for refractory vasodilatory shock, particularly septic shock. However, vasopressin may be used as part of an "adrenergic-sparing" approach, particularly in the setting of vasodilatory CS, based on the hypothesis that endogenous vasopressin may be depleted over time in critically ill patients.²⁴ Clinical trial data of outcomes are limited with vasopressin use in CS, but it has been evaluated in a small study of 300 patients with postcardiotomy shock with vasoplegia, hypotension, and preserved cardiac output, where it decreased the rate of a composite end point of mortality or severe complications compared to norepinephrine (Table 3).²² Vasopressin has been reported to have minimal impact on pulmonary vascular resistance (PVR); as a result, it is often used as a first-line agent in hypotension with RV-predominant shock in an effort to increase SVR without increasing RV afterload.^{25,26} Phenylephrine is a pure α agonist that also increases PVR. Angiotensin II is a peptide hormone that increases blood pressure through binding to the angiotensin II receptor type 1 in vascular smooth muscle resulting in vasoconstriction and an increase in aldosterone release.²⁷ Methylene blue is a redox agent that inhibits nitric oxide synthase, resulting in vasoconstriction.²⁸ These 3 agents are rarely used in patients with CS, but may be considered as a potential rescue therapy for profound vasoplegia that is refractory to other interventions.

STRATEGIC APPROACH TO MEDICAL MANAGEMENT OF CS BY PHENOTYPE

As highlighted above, there are extremely limited comparative effectiveness data to guide vasoactive agent

choice or strategy; as such, the following is based on our practice-based approach, integrating pharmacology, pathophysiology, and the hemodynamic derangements that define each shock phenotype. Our stepwise approach starts with the initial, emergent goal to "protect the MAP," as a first attempt to restore perfusion to the vital organs, as much as possible (Central Illustration). Next, we attempt to define the hemodynamic phenotype and to identify potential etiologies, to provide etiology-targeted interventions, and reverse contributors. With an understanding of the shock phenotype and potential etiology, we then set additional hemodynamic goals beyond the MAP (Central Illustration). We generally aim for normalization of hemodynamic parameters; however, there are clinical scenarios where we alter those targets based on specific disease states (eg, higher RAP goal in the setting of acute RV MI). Last, we tailor our pharmacotherapy to an iterative assessment of the (1) persistence of hypoperfusion and (2) ongoing hemodynamic derangements. Note that although invasive hemodynamics may be helpful, noninvasive assessments through clinical examination, imaging, vital signs, and laboratory values can be used as surrogates (Table 1). Specifically, jugular venous pressure or inferior vena cava dimensions can be used to estimate RAP; pulmonary edema on imaging or examination implies increased pulmonary artery wedge pressure; perfusion markers (urine output barring oliguric acute kidney injury; lactate, mental status) are more important than estimated cardiac index; delayed capillary refill (ie, >2–3 s) or cool, mottled extremities imply increased SVR. Acknowledging the absence of randomized controlled trials testing the utility of invasive hemodynamics in shock states, our practice aligns with guideline recommendations to consider placement of a pulmonary arterial catheter when there is (1) diagnostic uncertainty as to the hemodynamic or shock phenotype, (2) uncertainty about hemodynamic status (ie, whether hemodynamic goals have been achieved), and (3) no improvement despite empiric interventions.²⁹

It is important to note that we follow the same algorithmic approach across the spectrum of Society for Cardiovascular Angiography and Interventions (SCAI) shock stages (eg, C–E) and SHARC etiology. We find that defining the SCAI shock stage is useful to define the prognosis as well as to guide the rapidity of iterative assessments and therapeutic escalation, including for medical management with vasoactives and consideration of temporary mechanical support. Identifying the SHARC etiology can help to direct provision of etiology-targeted therapies (step 2 in algorithm).

In classic CS with hypotension, we aim to protect the MAP initially using an inopressor. In contrast, in patients with an adequate MAP, initial inodilator or vasodilator therapy is preferred as discussed in the next paragraph. Once the MAP is at goal, we assess whether perfusion (ie, cardiac index) is adequate. If not, we will either add an inodilator (which may require increasing the dose of

Step-Wise Strategic Approach to Vasoactive Selection for CS

Step 1: Protect the MAP

Step 2: Define the pathophysiology with respect to:

- Shock phenotype (see A below)
- Etiology and contributors (see B below)

Step 3: Set HD goals (see C below)

Step 4: Tailor pharmacotherapy to address persistent HD derangements and achieve HD goals.

Consider whether chronotropy desirable and risk of tachyarrhythmia

Concurrent Considerations to Guide Selection and Implementation

A

Shock Phenotype

- Classic CS w/ Hypotension
- Vasodilatory CS w/ Hypotension
- RV Dominant CS
- Normotensive CS
- Dynamic LV Outflow Obstruction

B

Etiologies and Contributors

- Pursue etiology-targeted rx and address reversible causes, including:**
- Early revascularization in AMI
 - tMCS from LV dominant CS from STEMI
 - Definitive intervention for mechanical causes of CS†
 - Manage unstable arrhythmias
 - Reverse metabolic derangements
 - Treat toxidromes

C

Approximate HD Goals‡

- Primary Goals:**
- MAP 65-75 mm Hg
 - CI >2.2 liters/min/m²
 - PCWP 14-18 mm Hg
 - RAP 5-10 mm Hg
- Additional considerations:**
- SVR 800-1000 dynes/sec/cm⁵
 - PAPI >1.0
 - PVR <240 dynes/sec/cm⁵

Tailored Approach According to Shock Phenotype

Classic CS with Hypotension*†

- Step 1:** Protect MAP with inopressor(s)
- Step 4:** Once MAP = goal, if CI still ↓
- Add inodilator OR
 - ↑ inopressor (but avoid ↑↑MAP; Consider Epi over other agents)

Vasodilatory CS with Hypotension*†

- Step 1:** Protect MAP with inopressor(s)
- Step 4:** As titrating inopressor, reassess HD
- If CI at goal but MAP still ↓, add vasopressor (Vaso) or ↑ inopressor (avoiding ↑↑ inotropy and HR)
 - If MAP at goal but CI still ↓, add inodilator or ↑ inopressor (but avoid ↑↑MAP; Consider Epi over other agents)

RV Dominant CS*†

- Step 1:** Protect MAP with vasoactive that ↑SVR but not PVR (Vaso > Epi > others)
- Step 4:** If CI still ↓
- ↓PVR to ↑RV CI by:
 - Reversing hypoxia, acidosis, hypothermia, ↓PEEP
 - If PCWP not ↑↑, consider adding pulm vasodilator (inhaled pulm vasodilator or inodilator)
 - ↑RV CI with inodilator (if MAP allows) or inopressor (Epi > others)

Normotensive CS *†

- Step 4:** Two initial strategic options:
- ↓SVR to ↑CI with pure vasodilator
 - Simultaneously ↓SVR and ↑CI with inodilator OR combination of inodilator and vasodilator
 - Reassess and titrate vasodilator and/or inodilator, as needed

Dynamic LV Outflow Obstruction

- Step 1:** Protect MAP by:
- Ensuring adequate volume
 - Adding pure vasopressor
- Step 4:** If CI still ↓, add negative inotrope to ↓obstruction

Central Illustration. Strategic Approach to Early Medical Management of Cardiogenic Shock

†Including pericardial drainage for tamponade, VSD closure, valve intervention for severe aortic stenosis or acute severe mitral or aortic regurgitation, and pharmacologic or mechanical treatment of massive pulmonary embolism. *Assuming normal or elevated filling pressures. If hypovolemia contributory pathogenesis to low output state, resuscitate. †If congested, volume removal (eg, diuresis or renal replacement therapy) in parallel. CI indicates cardiac index; CS, cardiogenic shock; Epi, epinephrine; MAP, mean arterial pressure; PAPI, pulmonary artery pulsatility index ([pulmonary artery systolic pressure minus pulmonary artery diastolic pressure]/RAP); PAWP, pulmonary artery wedge pressure; PEEP, positive end-expiratory pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SVR, systemic vascular resistance; tMCS, temporary mechanical circulatory support; and Vaso, vasopressin.

inopressor) or consider cross-titration to epinephrine from norepinephrine, if applicable. Our strategy for vasodilatory CS with hypotension is similar; we start with an inopressor. However, with iterative assessments, we may appreciate that perfusion is adequate but hypotension persists. In this case, we often add vasopressin as an “adrenergic-sparing” agent as described above. If the MAP is at goal, but perfusion is still lacking, we generally add an inodilator, if the MAP tolerates.

In normotensive CS, there are 2 strategies to consider: (1) targeted reduction of the SVR with vasodilators, which would be expected to result in an increase in cardiac output, or (2) simultaneous improvement of contractility and reduction of the SVR with an inodilator or combination of inodilator and vasodilator. Continuous parenteral vasodilator therapy includes nitroprusside, a potent arterial vasodilator that can lead to cyanide/thiocyanate toxicity with prolonged use, or nitroglycerin, a venodilator that *may* act as an arterial vasodilator at higher doses.

In the case of dynamic LV outflow obstruction, the aim is to minimize obstruction through ensuring adequate volume status, increasing afterload and avoiding increased contractility. A common approach would include a combination of IV fluids, vasopressor therapy (eg, phenylephrine or vasopressin), and β blockade (eg, IV esmolol infusion). The management of RV-predominant CS will depend on the underlying pathogenesis. As guiding principles, we aim to treat systemic hypotension through an increase in SVR while minimizing the impact on RV afterload. We often start with vasopressin because of its PVR-neutral impact on MAP. If additional support is required, we tend to use epinephrine, which will also offer RV inotropy, and avoid phenylephrine. We avoid or mitigate factors known to increase PVR, such as hypoxia, hypercarbia, acidosis, hypothermia, and positive pressure ventilation/excessive positive end-expiratory pressure. In the absence of left-sided congestion, we consider the addition of pulmonary vasodilators, such as inhaled nitric oxide or inhaled prostacyclin, to lower the PVR with an aim to increase RV output. Last, we also consider supporting RV contractility with an inodilator or inopressor; the choice will depend on an assessment of the relative benefit versus risk of decreasing RV afterload with possible systemic hypotension (inodilator) or increasing RV afterload while protecting the MAP (inopressor).

FUTURE DIRECTIONS

As highlighted, the data to guide medical management of CS, including for vasoactive choice and strategy, are quite limited. Ongoing studies include CAPITAL DOREMI 2 (Inotrope Versus Placebo Therapy for Cardiogenic Shock; NCT05267886), which is assessing the benefit of an inotrope versus placebo for SCAI stage C or D patients for the composite end point of mortality, sustained hypotension, persistent lactate elevation, need for MCS, sustained arrhythmia, or resuscitated cardiac arrest, and the PACCS

trial (Pulmonary Artery Catheter in Cardiogenic Shock Trial; NCT05485376), which is evaluating the benefit of early pulmonary arterial catheter use within 6 hours in heart failure CS for mortality. Other areas of interest for future research in CS include additional studies comparing the efficacy and safety of the various vasoactive agents, trials to define optimal hemodynamic targets, and additional studies evaluating the utility of invasive hemodynamics in populations outside of heart failure CS. Relevant to this primer, we are eager to see a well-powered randomized trial to assess the comparative efficacy and safety of the inopressors in hypotensive classic and vasodilatory CS, with respect to hemodynamic support, requirement for other supportive therapies (eg, renal replacement or mechanical circulatory support), safety end points (eg, limb ischemia, arrhythmic events), and mortality as well as a study of vasopressin in hypotensive CS to test the adrenergic-sparing strategy.

CONCLUSIONS

Medical management with vasoactive agents is the initial strategy in virtually all patients with CS. Comparative data for the efficacy and safety of the various agents are lacking. As a result, we rely on a framework that integrates pharmacological and pathophysiologic principles, tailored to the shock phenotype.

ARTICLE INFORMATION

Affiliation

Division of Cardiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Disclosures

E.A.B. and D.A.M. are members of the TIMI Study Group. The TIMI Study Group receives grants (to institution) from 4TEEN4 Pharmaceuticals, Abbott, Abiomed, Amgen, Anthos Therapeutics, ARCA Biopharma, AstraZeneca, Beijing Inno Medicine Co, Boehringer Ingelheim, Clearly, Daiichi-Sankyo, 4TEEN4, Ionis Pharmaceuticals, Janssen Research and Development, Marea Therapeutics, MedImmune, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Saghamos Therapeutics, Softcell Medical Limited, Verve Therapeutics, and Zora Biosciences. E.A.B. reports receiving consulting fees from Merck, Amgen, Novo Nordisk, Kowa, Medscape, and Esperion. D.A.M. reports consulting fees from Abbott Laboratories, Merck, Novartis, Regeneron, and Roche Diagnostics.

REFERENCES

1. van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, Kilic A, Menon V, Ohman EM, Sweitzer NK, et al; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Mission: Lifeline, Council on C, Stroke N, Council on Quality of C, Outcomes R and Mission L. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation*. 2017;136:e232–e268. doi: 10.1161/CIR.0000000000000525
2. Berg DD, Bohula EA, Morrow DA. Epidemiology and causes of cardiogenic shock. *Curr Opin Crit Care*. 2021;27:401–408. doi: 10.1097/MCC.0000000000000845
3. Waksman R, Pahuja M, van Diepen S, Proudfoot AG, Morrow D, Spitzer E, Nichol G, Weisfeldt ML, Moscucci M, Lawler PR, et al. Standardized definitions for cardiogenic shock research and mechanical circulatory support devices: scientific expert panel from the Shock Academic Research Consortium (SHARC). *Circulation*. 2023;148:1113–1126. doi: 10.1161/CIRCULATIONAHA.123.064527

4. Bohula EA, Katz JN, van Diepen S, Alviar CL, Baird-Zars VM, Park JG, Barnett CF, Bhattal G, Barsness GW, Burke JA, et al; Critical Care Cardiology Trials Network. Demographics, care patterns, and outcomes of patients admitted to cardiac intensive care units: the Critical Care Cardiology Trials Network prospective North American multicenter registry of cardiac critical illness. *JAMA Cardiol*. 2019;4:928–935. doi: 10.1001/jamcardio.2019.2467
5. Naidu SS, Baran DA, Jentzer JC, Hollenberg SM, van Diepen S, Basir MB, Grines CL, Diercks DB, Hall S, Kapur NK, et al. SCAI SHOCK stage classification expert consensus update: a review and incorporation of validation studies: this statement was endorsed by the American College of Cardiology (ACC), American College of Emergency Physicians (ACEP), American Heart Association (AHA), European Society of Cardiology (ESC) Association for Acute Cardiovascular Care (ACVC), International Society for Heart and Lung Transplantation (ISHLT), Society of Critical Care Medicine (SCCM), and Society of Thoracic Surgeons (STS) in December 2021. *J Am Coll Cardiol*. 2022;79:933–946. doi: 10.1016/j.jacc.2022.01.018
6. Moller JE, Engstrom T, Jensen LO, Eiskjaer H, Mangner N, Polzin A, Schulze PC, Skurk C, Nordbeck P, Clemmensen P, et al; DanGer Shock I. Microaxial flow pump or standard care in infarct-related cardiogenic shock. *N Engl J Med*. 2024;390:1382–1393. doi: 10.1056/NEJMoa2312572
7. Hochman JS, Sleeper LA, White HD, Dzavik V, Wong SC, Menon V, Webb JG, Steingart R, Picard MH, Menegus MA, et al; SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. One-year survival following early revascularization for cardiogenic shock. *JAMA*. 2001;285:190–192. doi: 10.1001/jama.285.2.190
8. Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, Nordbeck P, Geisler T, Landmesser U, Skurk C, et al; CULPRIT-SHOCK Investigators. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med*. 2017;377:2419–2432. doi: 10.1056/NEJMoa1710261
9. O'Brien CG, Brusca SB, Barnett CF, Berg DD, Baird-Zars VM, Park JG, Richardt G, Hennesdorf M, Empen K, Fuernau G, et al; IABP-SHOCK II Trial Investigators. Intra-aortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med*. 2012;367:1287–1296. doi: 10.1056/NEJMoa1208410
10. Berg DD, Bohula EA, van Diepen S, Katz JN, Alviar CL, Baird-Zars VM, Barnett CF, Barsness GW, Burke JA, Cremer PC, et al. Epidemiology of shock in contemporary cardiac intensive care units. *Circ Cardiovasc Qual Outcomes*. 2019;12:e005618. doi: 10.1161/CIRCOUTCOMES.119.005618
11. Patel SM, Berg DD, Bohula EA, Palazzolo MG, Batchelor WB, Drakos SG, Kilic A, Kormos RL, Samsky MD, Jessup M, et al. Contemporary practice patterns of vasoactive use in cardiogenic shock in the American Heart Association Cardiogenic Shock Registry. *J Am Heart Assoc*. 2025;14:e044373. doi: 10.1161/JAHA.125.044373
12. Berg DD, Bohula EA, Patel SM, Alfonso CE, Alviar CL, Baird-Zars VM, Barnett CF, Barsness GW, Bennett CE, Chaudhry SP, et al. Epidemiology of cardiogenic shock using the Shock Academic Research Consortium (SHARC) consensus definitions. *Eur Heart J Acute Cardiovasc Care*. 2024;13:709–714. doi: 10.1093/ehjacc/zuac098
13. van Diepen S, Poss J, Senaratne JM, Gage A, Morrow DA. Mixed cardiogenic shock: a proposal for standardized classification, a hemodynamic definition, and framework for management. *Circulation*. 2024;150:1459–1468. doi: 10.1161/CIRCULATIONAHA.124.069508
14. Kanwar MK, Everett KD, Gulati G, Brenner MI, Kapur NK. Epidemiology and management of right ventricular-predominant heart failure and shock in the cardiac intensive care unit. *Eur Heart J Acute Cardiovasc Care*. 2022;11:584–594. doi: 10.1093/ehjacc/zuac063
15. Overgaard CB, Dzavik V. Inotropes and vasopressors: review of physiology and clinical use in cardiovascular disease. *Circulation*. 2008;118:1047–1056. doi: 10.1161/CIRCULATIONAHA.107.728840
16. Allwood MJ, Cobbald AF, Ginsburg J. Peripheral vascular effects of noradrenaline, isopropylnoradrenaline and dopamine. *Br Med Bull*. 1963;19:132–136. doi: 10.1093/oxfordjournals.bmb.a070031
17. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL; SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362:779–789. doi: 10.1056/NEJMoa0907118
18. Levy B, Clere-Jehl R, Legras A, Morichau-Beauchant T, Leone M, Frederique G, Quenot JP, Kimmoun A, Cariou A, Lassus J, et al; Collaborators. Epinephrine versus norepinephrine for cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol*. 2018;72:173–182. doi: 10.1016/j.jacc.2018.04.051
19. Myburgh JA, Higgins A, Jovanovska A, Lipman J, Ramakrishnan N, Santamaria J; CAT Study Investigators. A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med*. 2008;34:2226–2234. doi: 10.1007/s00134-008-1219-0
20. Mathew R, Di Santo P, Hibbert B. Milrinone as compared with dobutamine in the treatment of cardiogenic shock. Reply. *N Engl J Med*. 2021;385:2108–2109. doi: 10.1056/NEJMc2114890
21. Hajjar LA, Vincent JL, Barbosa Gomes Galas FR, Rhodes A, Landoni G, Osawa EA, Melo RR, Sundin MR, Grande SM, Gaiotto FA, et al. Vasopressin versus norepinephrine in patients with vasoplegic shock after cardiac surgery: the VANCs randomized controlled trial. *Anesthesiology*. 2017;126:85–93. doi: 10.1097/ALN.0000000000001434
22. James JH, Luchette FA, McCarter FD, Fischer JE. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. *Lancet*. 1999;354:505–508. doi: 10.1016/S0140-6736(98)91132-1
23. Filomia S, Del Buono MG, Saponara G, d'Aiello A, Pedicino D, Moroni F, Abbate A, Sanna T. Vasopressin in cardiogenic shock: pathophysiology, clinical evidence, and therapeutic perspectives [published online February 3, 2026]. *ESC Heart Fail*. 2026;13. doi: 10.1093/ehj/ehf/vxag053
24. Rajagopal S, Ruetzler K, Ghadimi K, Horn EM, Kelava M, Kudelko KT, Moreno-Duarte I, Preston I, Bovino LL, R, Smilowitz NR, et al; American Heart Association Council on Cardiopulmonary CCP, Resuscitation, the Council on C and Stroke N. Evaluation and management of pulmonary hypertension in noncardiac surgery: a scientific statement from the American Heart Association. *Circulation*. 2023;147:1317–1343. doi: 10.1161/CIR.0000000000001136
25. Currihan DA, Hughes RJ, Wright CE, Angus JA, Soeding PF. Vasoconstrictor responses to vasopressor agents in human pulmonary and radial arteries: an in vitro study. *Anesthesiology*. 2014;121:930–936. doi: 10.1097/ALN.0000000000000430
26. Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, Busse LW, Altaweel L, Albertson TE, Mackey C, et al; ATHOS-3 Investigators. Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med*. 2017;377:419–430. doi: 10.1056/NEJMoa1704154
27. Smith BA, Robinson R, Most AK. From theory to therapy: methylene blue's emerging role in the management of septic shock. *J Pharm Pract*. 2026;39:57–66. doi: 10.1177/08971900251350554
28. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e876–e894. doi: 10.1161/CIR.0000000000001062