

Inotropic and vasopressor therapy in the intensive care unit

Physiopathology and evidence-based insights

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Abstract: Vasoactive and inotropic agents play a pivotal role in the management of critically ill patients with shock. A comprehensive understanding of their underlying physiological mechanisms, combined with evidence from clinical research, is crucial for guiding their appropriate use. This review explores the effects of the most commonly used agents and evaluates the clinical evidence supporting their application in critical care, highlighting their impact on hemodynamic stabilization and patient outcomes.

Keywords: Acute circulatory failure; Critical care; Hemodynamic support; Inotrope; Intensive care unit; Shock; Vasopressors

Physiology and mechanism of action

Adrenergic receptors

Catecholamines, a class of sympathomimetic amines, are fundamental in the treatment of shock. Their chemical structure consists of a catechol nucleus, which is an aromatic benzene ring bearing two hydroxyl groups, coupled with an ethylamine side chain.¹

Their effects are exerted by stimulating three primary classes of receptors: α -adrenergic, β -adrenergic, and dopaminergic receptors, all of which belong to the family of seven-transmembrane-domain receptors. These receptors are linked to G proteins, which mediate intracellular signaling and modulate cellular activities through protein phosphorylation pathways (Figure 1).

α -Adrenergic receptors are categorized into two main types, α_1 and α_2 , each comprising three subtypes. α_1 receptors are primarily postsynaptic and are mainly found in the smooth muscle of blood vessels, the genitourinary tract, the intestine, and in hepatocytes and cardiac tissue. They are linked to phospholipase C via a Gq protein. Upon activation, phospholipase C converts membrane phosphatidylinositol into inositol triphosphate and diacylglycerol, which subsequently triggers intracellular calcium release, resulting in enhanced inotropy and vasoconstriction (Figure 1).

α_2 receptors are primarily presynaptic and are minimally expressed in the heart. Their activation inhibits the release of norepinephrine from sympathetic nerve endings.²

In the vasculature, α_2 receptors are linked to an inhibitory G protein that decreases adenylate cyclase activity, leading to reduced cyclic adenosine monophosphate (cAMP) production. This mechanism induces vasoconstriction, predominantly affecting veins.

Additionally, α_2 receptors are present on β -cells within the islets of Langerhans, where they suppress insulin secretion, and on platelets, where they facilitate aggregation.

β -Adrenergic receptors are divided into three subtypes: β_1 (primarily in the heart), β_2 (located in the heart, vascular smooth muscle, bronchial and intestinal smooth muscle, genitourinary smooth muscle, striated muscle, hepatocytes, and leukocytes), and β_3 (found in cardiac and adipose tissue). Activation of β -adrenergic receptors enhances myocardial contractility (positive inotropic effect), increases heart rate (positive chronotropic effect), boosts excitability (positive bathmotropic effect), improves conduction velocity (positive dromotropic effect), and accelerates myocardial relaxation (positive lusitropic effect).

At the vascular and peripheral levels, β_2 receptor activation promotes vasodilation and relaxation of smooth muscle cells. The impact of β -receptor stimulation extends beyond the cardiovascular system, as it also induces insulin resistance, enhances proteolysis and glycogenolysis, and activates Na/K-ATPase pumps, all of which contribute to the development of hyperlactatemia (Figure 1).

From an immunological perspective, β_1 receptor activation may favor proinflammatory responses associated with innate immunity, whereas β_2 receptor stimulation consistently exerts anti-inflammatory effects. β_2 activation increases intracellular cAMP and activates protein kinase A, which inhibits nuclear factor- κ B (NF- κ B) nuclear translocation, thereby reducing the transcription of proinflammatory cytokines (e.g., TNF- α , IL-1 β) and enhancing IL-10 release.^{3,4}

Experimental data in vitro and in vivo suggest that β_2 stimulation attenuates the production of TNF- α and IL-6 while promoting IL-10 release, skews the immune response toward a Th2 phenotype, reduces NK cell cytotoxicity, and promotes the emergence of immunosuppressive neutrophils.^{3,4} Conversely, a β_1 -agonist (i.e., dobutamine) does not influence cytokine production in experimental endotoxemia⁵

β_3 receptors exhibit a lower affinity for catecholamines and are less susceptible to desensitization mechanisms. They are

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Hemodynamics (2026) 2:e0027

Received: 16 June 2025; Accepted 4 May 2026

Published online 5 June 2026

DOI: 10.1097/ha9.0000000000000027

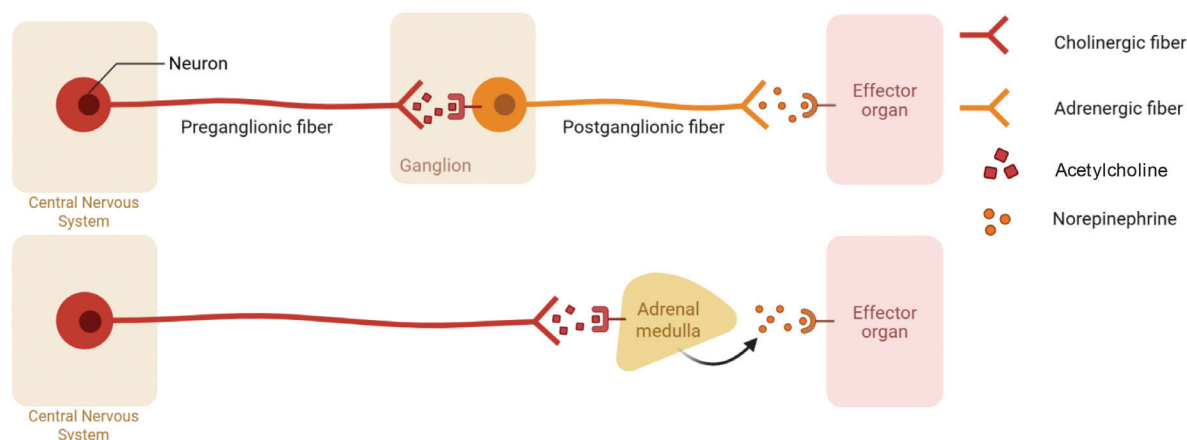
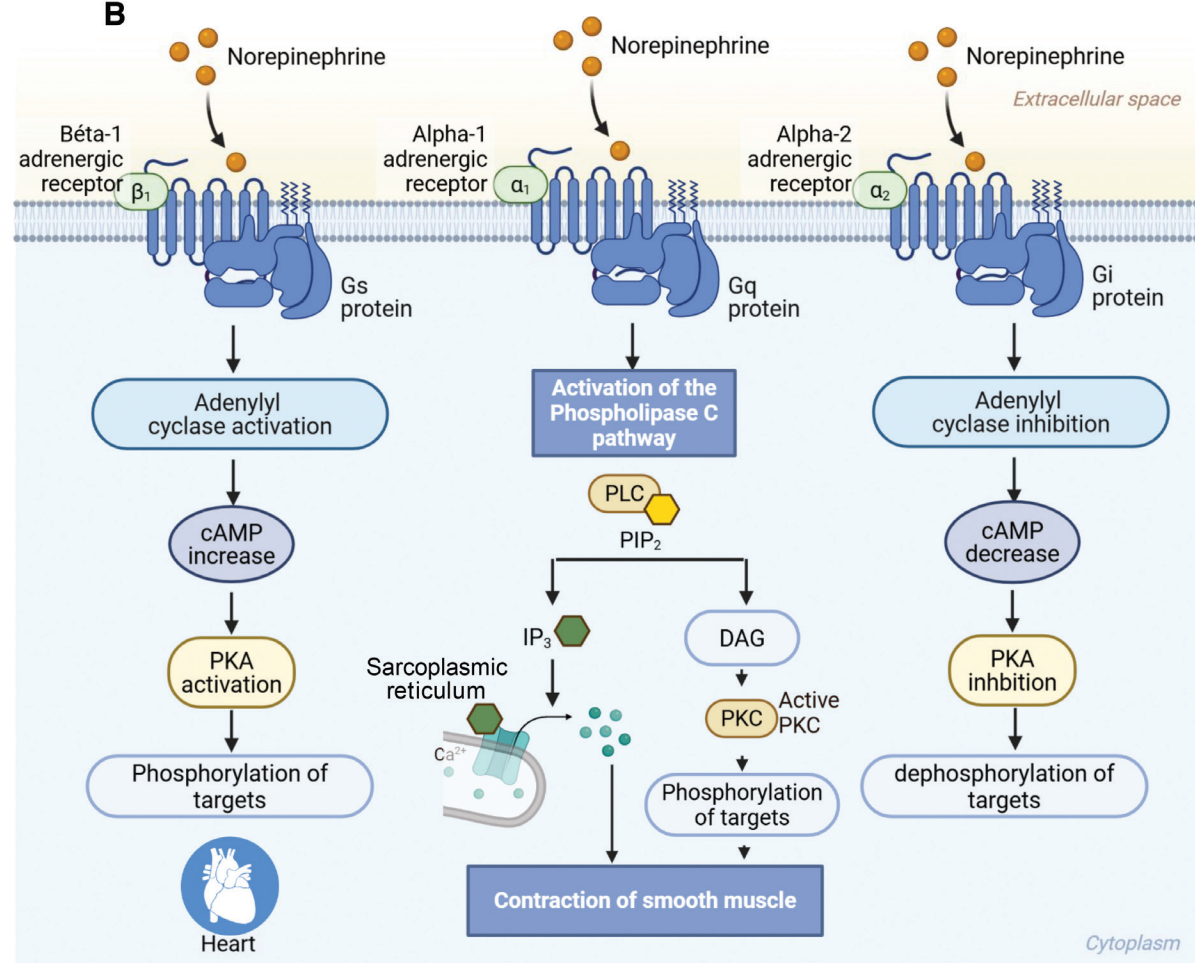
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Figure 1. Mechanisms of action of vasoactive agents at adrenergic receptors and associated intracellular signaling pathways. (A) Organization of the sympathetic nervous system, including preganglionic and postganglionic fibers, as well as the adrenal medulla, leading to the release of norepinephrine and epinephrine at the effector organ level. (B) Main adrenergic receptors and their associated G-protein–coupled signaling pathways. β_1 -adrenergic receptor activation is coupled to Gs proteins, leading to adenylyl cyclase activation, increased cAMP levels, PKA activation, and enhanced cardiac contractility and heart rate. α_1 -adrenergic receptor activation is coupled to Gq proteins, resulting in phospholipase C activation, IP₃ and DAG production, increased intracellular calcium, and vascular smooth muscle contraction. α_2 -adrenergic receptor activation is coupled to Gi proteins, leading to inhibition of adenylyl cyclase and decreased cAMP levels. Figure created with BioRender.com. DAG indicates diacylglycerol; Gi, inhibitory G protein; Gs, stimulatory G protein; Gq, Gq protein; IP₃, inositol trisphosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C.

believed to reduce contractility, especially when β_1 and β_2 pathways are intensely stimulated.⁶

Vasopressin receptors

Vasopressin and its analogues exert their effects through several G-protein-coupled receptors, mainly V1a, V1b, and V2 receptors. Their distribution and physiological effects are summarized in Table 1.

Renin-angiotensin system receptors

Angiotensin II is the main effector peptide of the renin-angiotensin-aldosterone system and exerts its physiological effects primarily through two G-protein-coupled receptors: angiotensin type 1 (AT1) and type 2 (AT2) receptors. Activation of AT1 receptors mediates most of the classical cardiovascular and renal effects of the system, including arterial and venous vasoconstriction, stimulation of aldosterone and vasopressin secretion, increased sympathetic activity, and enhanced renal sodium and water reabsorption. In contrast, AT2 receptor activation generally counterbalances AT1-mediated effects by promoting vasodilation, nitric oxide release, and anti-inflammatory and antiproliferative pathways.⁷

Phosphodiesterase-3 pathway

Phosphodiesterase type 3 (PDE3) is an intracellular enzyme that regulates cAMP signaling in cardiomyocytes and vascular smooth muscle cells. By hydrolyzing cAMP, PDE3 limits protein kinase A activation and thereby modulates myocardial contractility and vascular tone. Increased intracellular cAMP

enhances calcium handling in cardiomyocytes, resulting in increased myocardial contractility, while in vascular smooth muscle cells, it reduces intracellular calcium availability and promotes vasodilation. Through these mechanisms, PDE3 contributes to the regulation of cardiac performance and systemic vascular resistance.⁸

Vasopressor treatments

Epinephrine

Pharmacology and mechanism of action

Epinephrine is an endogenous hormone synthesized from norepinephrine. It is mainly produced, stored, and released by chromaffin cells in the adrenal medulla in response to stress. Its effects are direct and do not depend on norepinephrine release. Epinephrine has shown a rapid distribution (plasma peak concentrations within 15 seconds) and a short plasma half-life (≈ 2 –3 minutes) following intravenous administration.⁹ During continuous intravenous infusion, steady-state plasma concentrations are achieved within 10–15 minutes, and levels decrease rapidly after discontinuation, reflecting its rapid clearance through extensive metabolism in the liver and extrahepatic tissues by catechol-O-methyltransferase and monoamine oxidase.⁹ Intramuscular administration resulted in a delayed and lower peak concentrations, with greater interindividual variability compared with intravenous administration.¹⁰ Due to its intra- and extrahepatic metabolism, epinephrine clearance is not affected by renal or hepatic insufficiency.

In healthy individuals, when administered as a continuous infusion at low doses (0.02–0.1 $\mu\text{g/kg/minute}$), epinephrine primarily activates β -receptors. This leads to an increase in heart

Table 1

Main vasoactive and inotropic receptors and their effects.

Receptors	Localization	Effects
Adrenergic receptors		
α_1	Vascular smooth muscle cells (arterial and venous), liver	Vasoconstriction
α_2	Presynaptic nerve terminals, central nervous system, platelets	Inhibition of norepinephrine release (negative feedback), mild vasoconstriction
β_1	Heart	↗ Heart rate, contractility
	Kidney (juxtaglomerular cells)	↗ Renin release
β_2	Vascular smooth cells, bronchi	Vasodilatation, bronchodilatation, immunosuppressive effects
β_3	Adipose tissue, myocardium	Lipolysis, possible negative inotropic effect
Vasopressin and analogues receptors		
V1a receptor	Vascular smooth muscle cells, renal medulla, bladder, testis, adipocytes, spleen, brain, platelets	Vasoconstriction, cytokine modulation, endothelial effects
V1b receptor	Anterior pituitary, adrenal medulla, pancreas	Release of endogenous catecholamines, vasopressin regulation ("negative feedback"), secretion of cortisol and insulin
V2 receptor	Renal collecting tubule	Free water reabsorption
	Endothelium	Vasodilation (via NO stimulation) and release of factor VIII and platelet aggregation
V3 receptor	Pituitary gland	Release of ACTH
P2 receptor	Heart	Coronary vasoconstriction and negative inotropism (controversial)
Oxytocin receptor	Uterus, mammary glands, brain	Uterine and mammary gland contraction
	Endothelium → NO	Vasodilation
Angiotensin receptors		
AT1	Vascular smooth muscle, adrenal cortex, kidney, heart	Potent vasoconstriction, aldosterone release, sodium retention, proinflammatory effects
AT2	Fetal tissues, endothelium	Vasodilatation, antiproliferative effects (debated)
Phosphodiesterase		
PDE3	Cardiomyocytes, vascular smooth muscle	Contractility, vasodilatation

ACTH indicates adrenocorticotrophic hormone.

Hemodynamic effects of vasopressors					
	Catecholamines		Vasopressin analogues		Angiotensin
	Epinephrine	Norepinephrine	Vasopressin	Terlipressin	Angiotensin II
Heart Rate	↑	↑	↓	↓	↑
Inotropism	↑	↑	→	→	unknown
Cardiac Output	↑	↑	→ or ↓ ²	→ or ↓	→
Right ventricular systolic function	↑	↑	→	→	unknown
Mean Arterial Pressure	↑	↑	↑	↑	↑
Mean Systemic Filling Pressure	→	↑	→	→	unknown
Coronary Blood Flow	↑	↑	↑ or → ³	unknown	unknown
Splanchnic Blood Flow	↑	→	↑ or ↓	unknown	unknown
Renal Blood Flow	↓	→ or ↑	→ or ↓ ⁴	unknown	↓
Cutaneous Blood Flow	↓	↑ or ↓ ¹	↓	↓	unknown

Figure 2. Hemodynamic effects of vasopressors. ¹Interindividual variability. ²Reduced with doses of vasopressin higher than 0.03 IU/minute and preserved with doses lower than 0.03 IU/minute. ³Improvement of coronary perfusion only in experimental models. ⁴In experimental models: reduced in endotoxemic models with vasopressin doses >0.05 IU/minute, but preserved in bacterial models with doses of 0.03 IU/minute.

rate, stroke volume, cardiac output, and left ventricular stroke work, along with an overall decrease in systemic vascular resistance due to enhanced cardiac output.¹¹

Epinephrine injection increases pulse pressure (as a surrogate of the stroke volume), whereas mean arterial pressure (MAP) and diastolic blood pressure slightly decrease, and, simultaneously, pulmonary vascular resistance is reduced. Through α -receptor activation, epinephrine decreases renal and cutaneous blood flow and can elevate pulmonary arterial pressure. Conversely, it enhances splanchnic, muscular, and coronary blood flow (Figure 2).

At higher doses (>0.1 $\mu\text{g/kg/minute}$), α -receptor stimulation becomes more pronounced, resulting in increased systemic vascular resistance and elevated arterial pressure. The effect on cardiac output varies depending on the extent of afterload elevation.

The extracirculatory effects of epinephrine are primarily mediated by β_2 -receptor activation, leading to metabolic stress,^{12,13} bronchodilation, and the inhibition of mast cell degranulation.³ Additionally, epinephrine raises blood glucose levels by stimulating glycogenolysis and gluconeogenesis¹⁴ and lowers serum potassium¹⁵ by promoting intracellular potassium transfer. A transient metabolic lactic acidosis, attributed to increased muscle activity and unrelated to hypoxia, has been observed in healthy volunteers¹⁶ and in patients with shock.¹⁷

Epinephrine in anaphylactic shock

Epinephrine is the first-line treatment for patients with anaphylactic shock due to its potent vasoconstrictive properties, which counteract histamine-induced vasodilation, and its β_2 -mediated action, which inhibits mast cell degranulation, thereby reducing bronchospasm and capillary hyperpermeability.

In patients with anaphylactic shock, epinephrine is administered through direct intravenous titration using iterative boluses of 0.1–0.2 mg every 1–2 minutes, followed by continuous

intravenous infusion if needed. In extreme emergencies, intramuscular administration (0.5 mg) is an alternative that can be administered by any healthcare provider. Nebulization (1–2 mg in 5 ml) is also an option in cases of laryngeal edema. However, the use of nebulized epinephrine in laryngeal edema is not supported by robust evidence from clinical trials.

Epinephrine in septic shock

In patients with septic shock, epinephrine administration raises arterial pressure by increasing cardiac output.^{18,19} Systemic vascular resistance typically exhibits an increase, although individual patient responses can vary, particularly depending on epinephrine dose.^{19,20} Epinephrine enhances right ventricular contractility but has minimal impact on pulmonary circulation.²¹

In patients with septic shock, epinephrine moderately increases heart rate but does not appear to elevate the risk of ventricular or supraventricular arrhythmias or severe ischemic events compared with the combination of norepinephrine and dobutamine.²² Epinephrine administration results in elevated lactate concentrations.^{22–24} This hyperlactatemia, although not inherently harmful, is primarily of metabolic and muscular origin and results from β -receptor stimulation rather than tissue hypoxia.²⁵

In addition, epinephrine exhibits immunosuppressive properties, as it inhibits TNF- α production and enhances IL-10 release during experimental endotoxemia in humans.²⁶

The Surviving Sepsis Campaign suggests epinephrine as a third-line agent after norepinephrine and vasopressin (Table 2).²⁷

Epinephrine in cardiac arrest

Epinephrine is the first-line medication for cardiac arrest in non-shockable rhythms. The recommended dose is 1 mg for adults and 10 $\mu\text{g/kg}$ for children, administered intravenously every two cycles of cardiopulmonary resuscitation (CPR), or roughly every

Table 2 Hemodynamic effects of vasoactive and inotropic agents and their positioning within the recommendations in patients with septic shock.					
Agent	Main mechanism	Arterial effect	Venous effect	Cardiac effect	Recommendation for septic shock ²⁷
Vasopressor Norepinephrine	$\alpha 1 > \beta 1$ agonist	Vasoconstriction	↑ Venous tone ↑ Mean systemic filling pressure	Mild ↑ contractility	First-line vasopressor
Vasopressin	V1a receptor agonist		Likely splanchnic venoconstriction Limited data	↓ Heart rate No effect of inotropic or ↓ cardiac output	In addition of norepinephrine in septic shock
Angiotensin	AT1 receptor		Possible venoconstriction Limited data	No direct effect	Not recommended in patients with septic shock
Epinephrine	$\alpha 1$ and $\beta 1$ agonist		Possible venoconstriction Limited data	↑ Contractility	Suggest in third line (weak recommendation, low quality of evidence)
Inodilator Dobutamine	$\beta 1 > \beta 2$ agonist	Vasodilatation	Minimal effect	↑ Contractility ↑ Heart rate	For adults with septic shock with persistent hypoperfusion and cardiac dysfunction despite adequate fluid resuscitation and arterial blood pressure, the recommendation suggests adding dobutamine to norepinephrine or using epinephrine alone
Levosimendan	Calcium sensitizer and K-ATP channel opener		Possible ↓ venous tone Limited data	↑ Contractility	For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, the recommendations suggest against using levosimendan
Mirinone	PDE3 inhibitor		Possible ↓ venous tone Limited data	↑ Contractility	For adults with septic shock and ongoing requirement for vasopressors, there is "insufficient evidence" to make a recommendation on use of oral midodrine

4–5 minutes. If intravenous access is unavailable, intraosseous administration is an alternative.

During cardiopulmonary arrest, the use of epinephrine enhances survival rates but is associated with an increased risk of severe neurological sequelae in survivors.²⁸

Epinephrine in cardiogenic shock

A small randomized trial involving 57 patients compared norepinephrine and epinephrine in the management of cardiogenic shock. Epinephrine transiently increased heart rate without producing significant differences in cardiac index. Importantly, the study was prematurely terminated for safety concerns due to a higher incidence of adverse events in the epinephrine group, including metabolic disturbances (metabolic acidosis and increased level of lactate) and an increased risk of refractory shock, defined as cardiogenic shock with severe cardiac dysfunction, elevated lactate levels, and acute organ failure (e.g., oliguria or liver failure) despite high doses of vasoactive agents.²⁹ A meta-analysis of individual patient data from cohorts totaling 2583 patients with cardiogenic shock demonstrated a significant increase in mortality among those receiving epinephrine.³⁰ Based on these findings, the use of epinephrine is not recommended for the management of cardiogenic shock (Table 2).^{31,32}

Norepinephrine

Pharmacology and mechanism of action

Norepinephrine is the chemical mediator released by postganglionic sympathetic neurons and the adrenal glands. It is metabolized by monoamine oxidase and catechol-O-methyltransferase enzymes, as well as through reuptake at nerve endings. Additionally, norepinephrine acts as the precursor for epinephrine synthesis, differing structurally by a single methyl group on the terminal amine.

Like all catecholamines, norepinephrine has a very short half-life (<3 minutes), requiring continuous infusion in clinical practice. Its pharmacokinetic is not significantly affected by renal or hepatic insufficiency. During renal replacement therapy, norepinephrine clearance remains minimal (<0.2% of the administered dose), reflecting a predominant nonrenal metabolism.³³ Consequently, renal replacement therapy does not significantly impact norepinephrine pharmacokinetic or dosing. However, norepinephrine clearance is reduced in septic shock, and the degree of impairment correlates with the severity of the shock.

Norepinephrine is available in different salt formulations (e.g., tartrate, bitartrate, or hydrochloride). The pure molecular “base” form of norepinephrine is not suitable for intravenous administration and is therefore not used clinically; only salt formulations are administered in practice. However, doses are often expressed in terms of norepinephrine base equivalents. This distinction may lead to discrepancies when comparing doses across studies or in clinical practice if not clearly specified. Importantly, norepinephrine tartrate contains approximately half the active base, such that 1 µg of norepinephrine base corresponds to about 2 µg of norepinephrine tartrate. Expert recommendations suggest expressing doses in terms of norepinephrine base to standardize reporting and improve comparability across studies.³⁴ Therefore, the formulation and mode of dose expression should be clearly reported to ensure accurate interpretation of norepinephrine dosing.

Norepinephrine stimulates β_1 -adrenergic receptors, enhancing contractility, and activates α_1 and α_2 adrenergic receptors, leading to arterial and venous vasoconstriction, with recruitment of unstressed venous volume³⁵ and an increase in mean systemic filling pressure. Consequently, it is a potent vasoconstrictive catecholamine with inotropic and chronotropic properties. In addition to its hemodynamic effects, norepinephrine primarily exerts anti-inflammatory actions by lowering levels

of TNF-alpha and IL-2 and -6, while increasing IL-10 levels through β -receptor pathways. This could theoretically help to reduce the host's inflammatory response to stress or injury.³

In experimental endotoxemic models, the administration of norepinephrine leads to an increase in MAP, cardiac output, and myocardial contractility.³⁶ It improves hepatic blood flow in parallel with the increase in cardiac output, without compromising renal function.^{37,38}

In healthy individuals, even at low doses (starting at 0.1 µg/kg/minute), norepinephrine administration increases systolic, diastolic, and MAP¹⁴ through a rise in systemic vascular resistance. Norepinephrine is a systemic vasoconstrictor that affects the splanchnic, renal, and pulmonary circulations. In nonseptic animal models, norepinephrine decreases cortical renal blood flow while leaving medullary blood flow unchanged.^{39,40}

Norepinephrine in patients with septic shock

In patients with septic shock, norepinephrine increases MAP by increasing peripheral vascular resistance⁴¹ and enhancing cardiac output through its inotropic effects.⁴² Similarly to hypovolemic shock, norepinephrine also increases venous return by mobilizing unstressed blood volume, leading to an elevation in mean systemic filling pressure⁴³ and improved cardiac preload.^{44,45} Additionally, norepinephrine improves right ventricular function⁴⁶ (Figure 2).

Increasing norepinephrine doses within the range studied in experimental and clinical settings do not appear to impair cutaneous microcirculation or splanchnic perfusion, as suggested by stable capillary refill time and regional perfusion markers.^{47,48} In some patients, an improvement in cutaneous microcirculatory parameters has been reported.^{48,49} However, these findings should be interpreted in the context of the relatively moderate doses evaluated and cannot be extrapolated to the higher doses, where regional perfusion may be differently affected.

The effect of norepinephrine on the kidney remains controversial, with both experimental and clinical data showing heterogeneous responses. In endotoxemic shock models, conflicting findings have been reported regarding medullary perfusion, with studies showing either decreased or increased medullary blood flow and oxygenation,^{50,51} likely reflecting differences in dosing, duration, timing of administration, and experimental conditions.

In patients with septic shock, increasing MAP with norepinephrine is associated with variable effects on microcirculation and organ function, with marked interindividual variability: while some patients experience improved microcirculation as norepinephrine and MAP increase, others may show deterioration.^{48,52,53}

Regarding kidney function, norepinephrine has been associated with increased urine output and decreased creatinine levels in patients with septic shock, an effect not observed in nonseptic patients.⁵⁴ Increasing MAP to a higher level (i.e., 80–85 mmHg) through norepinephrine reduces the need for renal replacement therapy, but this effect is observed only in patients with a history of hypertension⁵⁵ and must be balanced against an increased risk of atrial fibrillation in patients without history of hypertension.

When compared with dopamine in septic shock, norepinephrine is associated with lower mortality in meta-analyses,⁵⁶ and a similar trend was observed in randomized controlled trials, although it did not reach statistical significance, along with significantly fewer rhythm-related side effects.⁵⁷ Currently, norepinephrine is the first-line vasopressor for septic and distributive shock (Table 2). Early norepinephrine administration helps to reduce fluid requirements,⁵⁸ the incidence of acute pulmonary edema, and allows for faster blood pressure control.^{59,60} Consequently, the initiation of norepinephrine should not be delayed by waiting for central venous catheter placement and can be started through a peripheral intravenous line.²⁷

Norepinephrine in cardiogenic shock

Due to its β -adrenergic activity, which provides a positive inotropic effect, and its α -adrenergic activity, which induces vasoconstriction to maintain MAP, norepinephrine also plays a central role in the management of cardiogenic shock.³²

In the cardiogenic shock subgroup of the sepsis occurrence in acutely ill patients study, which compared norepinephrine and dopamine in shock states, the use of norepinephrine was associated with a significant reduction in 28-day mortality compared with dopamine.⁵⁷

Furthermore, in patients with cardiogenic shock secondary to ST-segment elevation myocardial infarction, norepinephrine was associated with a lower incidence of tachycardia and fewer cases of refractory cardiogenic shock compared with epinephrine.²⁹ The trial was stopped early due to major safety concerns in the epinephrine group.

Consequently, in cases of severe arterial hypotension in patients with cardiogenic shock, current guidelines recommend using norepinephrine in combination with dobutamine to optimize hemodynamic support.^{31,32}

Norepinephrine in postresuscitation syndrome

An observational study using propensity score analysis showed that the use of norepinephrine in postresuscitation shock was associated with a lower risk of mortality compared with continuous intravenous epinephrine.⁶¹ However, no randomized controlled trials have yet compared norepinephrine with other first-line vasopressors in the management of patients with postresuscitation shock.

European guidelines recommend maintaining a MAP > 65 mmHg using norepinephrine in the management of patients with postresuscitation shock.⁶² Notably, studies targeting a higher MAP during postresuscitation shock, which required higher doses of norepinephrine, did not report an increased risk of ischemic or arrhythmic complications. These findings support the safety profile of norepinephrine in this clinical context.^{63,64}

Vasopressin

Pharmacology and mechanism of action

Vasopressin (also known as arginine vasopressin or antidiuretic hormone) is a 9-amino-acid peptide synthesized in the hypothalamus and transported to the posterior pituitary via magnocellular neurons. Its release is primarily triggered by increased osmolarity (indicating water deficit). Additionally, significant hypovolemia and hypotension activate atrial volume receptors and carotid baroreceptors, which further stimulate vasopressin secretion.⁶⁵

Vasopressin secretion is much more sensitive to changes in osmolarity than to variations in blood pressure.⁶⁶ This hormone has a short half-life (5–15 minutes) and is metabolized by renal and hepatic vasopressinases.⁶⁷ Vasopressin exerts its effects through six transmembrane G-protein-coupled receptors, each of which has distinct actions (Table 1).

The distribution of V1a receptors in kidney vessels is heterogeneous. The vasoconstrictive effect of low-dose vasopressin primarily targets renal efferent arterioles, with minimal impact on afferent arterioles. This mechanism is associated with a local phenomenon involving the release of nitric oxide.⁶⁸ Vasoconstriction of the efferent arterioles theoretically increases glomerular renal perfusion pressure, which in turn may lead to enhanced glomerular filtration.

The effects of vasopressin on pulmonary vascular resistance remain heterogeneous and context-dependent. Experimental studies suggest that vasopressin may induce pulmonary vasodilation in precontracted or hypoxic conditions^{69–72} through a nitric oxide-dependent mechanism.^{69,70,73,74} However, human data are

inconsistent. In patients with vasodilatory shock (post cardiac surgery), most studies report no significant change in pulmonary vascular resistance, regardless of dose.^{75–79} Conversely, limited data from specific populations, such as neonates with pulmonary hypertension or isolated case reports in pulmonary arterial hypertension, suggest a potential reduction in pulmonary vascular resistance in specific cases. Overall, the effects of vasopressin on the pulmonary circulation appear variable, and its impact in patients with pulmonary arterial hypertension or right ventricular dysfunction remains uncertain.

Experimental data suggest that vasopressin may exert modest immunomodulatory effects, including modulation of cytokine production and endothelial function, primarily through V1a receptor-mediated pathways.⁸⁰ However, these findings are mainly derived from preclinical studies, and clinical evidence remains limited.

Vasopressin in Septic Shock

In experimental models, the administration of vasopressin has produced different effects depending on the shock model and the dose used. In a hypodynamic endotoxemic shock model, vasopressin administration was linked to a reduction in cardiac output and myocardial ischemia.^{81,82} In a hyperdynamic shock model, the effects of vasopressin depended on the dose administered. High doses of vasopressin (>0.15 IU/minute) resulted in decreased cardiac output, oxygen consumption, and regional organ blood flow.⁸³ When lower doses of vasopressin analogue (<0.1 IU/minute) were administered, MAP increased without affecting cardiac output.⁸⁴ From a physiological standpoint, vasopressin is expected to exert some degree of venoconstriction to maintain coherence between arterial and venous tone and preserve venous return. However, clinical data specifically assessing its effects on the venous compartment in patients with septic shock are lacking. Table 3 summarizes the effects of vasopressin on intra-abdominal organs.

In clinical studies, higher doses of vasopressin (>0.03 IU/minute) have been associated with a decrease in cardiac output in patients with septic shock,⁸⁷ although this effect is not consistently observed across studies, as illustrated by a trial comparing 0.03 and 0.06 IU/minute that did not report significant changes in cardiac output.⁸⁸ At lower doses, cardiac output remains unchanged, although this was achieved at the expense of increased dobutamine use, while heart rate decreases⁸⁹ (Figure 2). Three potential mechanisms may explain the reduction in heart rate with vasopressin administration: first, the increase in vascular resistance raises blood pressure, and when baroreflexes are intact, heart rate decreases to maintain stable blood pressure. Second, vasopressin may exert a “ α ” effect, allowing a reduction in norepinephrine exposure and consequently decreasing β -adrenergic stimulation.⁶⁵ Third, an alteration or

Table 3

Effects of vasopressin on intra-abdominal organs in experimental models of septic shock.

Parameter	Endotoxemia models	Fecal peritonitis models of septic shock
Renal artery blood flow	↘ ⁸³	→ ⁸⁵
Urine output	-	→ ⁸⁶
Mesenteric artery blood flow	↘ ⁸²	↗ ⁸⁵ → ⁸⁶
Portal blood flow	-	↘ ⁸⁵ → ⁸⁴
Hepatic artery blood flow	↗ ⁸²	→ ⁸⁵ ↗ ⁸⁴
Pancreatic artery blood flow	-	↘ ⁸⁶

Arrows indicate the direction of change in comparison with baseline or control conditions: ↑ increase; ↓ decrease; → no significant change; - no data available.

impairment of baroreflex function may modulate this response. Experimental data in conscious dogs have shown that, in animals with intact baroreceptor reflexes, vasopressin induces a decrease in heart rate and cardiac output, whereas after baroreflex denervation, vasopressin increases arterial pressure without reducing heart rate, resulting in preserved cardiac output.⁹⁰ Vasopressin decreases cardiac output without impairing cardiac function.^{82,84,85} Reductions in troponin levels, serum creatinine, and liver cytolysis markers have also been observed.⁸⁴

The effect of vasopressin on renal blood flow is controversial, with some studies showing a decrease in renal blood flow, particularly in endotoxemic models.⁸³ Within the renal parenchyma, vasopressin seems to cause redistribution by reducing medullary renal blood flow.⁸⁸

The impact of vasopressin on portal vein flow seems to depend on cardiac output and fluid resuscitation status. In Krejci's study,⁸⁵ a marked decrease in portal flow was observed in parallel with a significant drop in cardiac output. In contrast, Simon et al⁸⁴ reported stable or slightly increased portal flow despite vasopressin administration, in a context of preserved cardiac output. These findings suggest that vasopressin may reduce portal flow primarily when cardiac output decreases.

Vasopressin decreases mesenteric blood flow in porcine endotoxemia models⁸³ but increases it in septic shock models induced by peritonitis.⁸⁵ Additionally, it reduces blood flow in the portal vein.⁸⁵

As vasopressin is purely a vasoconstrictive agent without inotropic effects, its use in septic shock can be theoretically justified. At the same level of MAP, plasma vasopressin concentrations are lower in septic shock patients compared with those in cardiogenic shock.⁹¹ In patients with septic shock, vasopressin secretion follows a biphasic profile, with an initial increase followed by a marked decrease over time, likely reflecting depletion of neurohypophyseal stores.⁹² Plasma vasopressin concentrations are even lower in more severe cases of septic shock.⁹⁰

Three randomized trials have compared the addition of vasopressin to norepinephrine in patients with septic shock (Table 4).

The addition of vasopressin does not reduce mortality in the overall population with septic shock. Meta-analyses combining individual data⁹⁶ from the three aforementioned studies and the study by Dunser et al⁷⁶ (targeting patients in distributive shock) do not show a reduction in mortality. However, they do demonstrate a decreased risk of arrhythmia, particularly atrial fibrillation, at the cost of an increased risk of digital ischemia.^{96,97} Notably, data regarding the antiarrhythmic effects of vasopressin remain heterogeneous. While some analyses focusing on septic shock populations suggest a reduction in arrhythmias,⁹⁶ other studies, including broader populations with distributive shock, report less consistent results.⁹⁸

A potential interaction between vasopressin and corticosteroids has been suggested. In a post hoc analysis of the VASST trial,⁹⁹ the use of vasopressin in combination with hydrocortisone was associated with a signal toward improved survival. However, this finding was not confirmed in a subsequent factorial randomized trial comparing norepinephrine versus vasopressin and hydrocortisone versus placebo.⁹⁴ In clinical practice, corticosteroids are generally considered in patients requiring increasing doses of norepinephrine, a context in which vasopressin is also frequently introduced.¹⁰⁰ Nevertheless, current evidence does not support a clear impact of their combination on patient-centered outcomes.

Current guidelines suggest adding vasopressin to norepinephrine rather than increasing norepinephrine doses in patients with septic shock²⁷ (Table 2). Nevertheless, if vasopressin is introduced, current data—primarily retrospective or based on subgroup analyses—suggest potential benefits from its early use.^{93,101,102}

Vasopressin in vasoplegic shock states in cardiac surgery

The efficacy of adding vasopressin has also been tested in vasoplegic shock following cardiopulmonary bypass in cardiac

Table 4
Randomized controlled trials on the effect of vasopressin in patients with septic shock.

Study	Patient type	Number of patients	Mortality	Renal function	Adverse event
Russell et al ⁸³ VASST	-Septic shock (Sepsis 2) ->5 µg/minute norepinephrine base for ≥6 hours, within max 24 hours before randomization -And ongoing at ≥5 µg/minute base	778	-No significant difference -Lower mortality in patients with low doses of norepinephrine at inclusion (<15 µg/minute base)	No difference	No difference
Gordon et al ⁸⁴ VANISH	-Septic shock within 6 hours after onset of shock -85% were already receiving open-label catecholamines at inclusion	421	No significant difference	-No difference in the number of days without acute kidney injury -Reduced use of renal replacement therapy, but influenced by the group of deceased patients	No difference
Hajjar et al ⁸⁵ VANCS II	Cancer patients with septic shock; randomized at vasopressor initiation (vasopressin or norepinephrine as first-line therapy)	250	No difference	No difference	No difference

surgery. A study (VANCS I) involving 300 patients with persistent hypotension despite at least 1,000 ml of crystalloid fluid resuscitation and preserved cardiac output (>2.2 L/min/m²) randomized patients to receive either vasopressin or norepinephrine.¹⁰³ Patients in the vasopressin group experienced less atrial fibrillation, less acute kidney injury, and a lower incidence of a composite endpoint combining mortality and severe postoperative complications within the first 30 days compared with the norepinephrine group. However, the results of this study should be interpreted with caution, as they originate from a single-center trial. So far, the role of vasopressin in cardiac surgery has not been addressed in multicenter studies. Consistently, in a meta-analysis including several interventional studies, the use of vasopressin in distributive shock following cardiac surgery was associated with a lower incidence of arrhythmias.⁹⁸ However, the evidence specific to cardiac surgery remains limited and is largely driven by a small number of trials (particularly the single-center VANCS I trial).¹⁰³

The use of vasopressin appears promising in patients with distributive shock. However, the role of this non-catecholaminergic vasopressor hormone remains to be clarified through future studies.

In current intensive care practice, vasopressin is most often administered via central venous access and at low doses (from 0.01 to 0.03 or 0.06 IU/minute). Higher doses increase the risk of ischemic complications without enhancing efficacy.

In clinical practice, the initiation of vasopressin is heterogeneous and not solely based on a fixed norepinephrine threshold. It is commonly introduced in response to increasing norepinephrine requirements, but also according to clinical indicators such as persistent hypotension, tachycardia or atrial fibrillation, signs of impaired peripheral perfusion, or inadequate lactate clearance.¹⁰⁰ Overall, vasopressin is mainly used as a catecholamine-sparing strategy tailored to the patient's hemodynamic profile rather than triggered by a single predefined threshold.

Vasopressin is generally initiated at low fixed doses, most commonly between 0.01 and 0.04 U/minute, with 0.03 U/minute frequently used. It is usually administered as a fixed-dose infusion, although titration based on hemodynamic targets may be performed.¹⁰⁰ The maximum dose typically ranges between 0.03 and 0.06 U/minute, consistent with major trials such as VASST⁹³ and VANISH,⁹⁴ which used doses of 0.03 and 0.06 U/minute, respectively.

Vasopressin in cardiac arrest

In experimental model, the beneficial effect of vasopressin in cardiac arrest is suggested by a theoretical improvement in coronary perfusion through increased diastolic pressure, resulting in increase of the left ventricular myocardial blood flow with the use of vasopressin.¹⁰⁴

In experimental models of cardiac arrest with ventricular fibrillation, a synergistic effect of a combination of vasopressin and epinephrine, compared with vasopressin alone or epinephrine alone, was shown both on the improvement of left ventricular myocardial blood flow^{105,106} and coronary perfusion pressure,^{107–109} and return of spontaneous circulation (ROSC)¹⁰⁸ and cerebral blood flow during CPR.^{105,106}

In porcine models of pulseless electrical activity cardiac arrest with prolonged CPR, when compared with epinephrine, early and late administration of vasopressin alone was associated with a significantly increased rate of ROSC.¹¹⁰ The superiority of vasopressin to epinephrine in achieving ROSC was shown in a meta-analysis of 33 comparative animal studies but only in the subgroup of cardiac arrest with ventricular fibrillation.¹¹¹

In clinical studies involving patients in cardiac arrest, the comparison of vasopressin alone as a first-line treatment to epinephrine alone failed to show any difference in survival (Table 5). These results suggest that adding vasopressin as a first-line agent, rather than using epinephrine, may be more

effective in achieving return ROSC in patients with a nonshockable rhythm. However, this had no impact on mortality nor neurological outcomes.

Finally, a large randomized controlled trial (N = 2894 patients) failed to show any difference in ROSC, mortality at hospital discharge, or neurological outcome when vasopressin plus epinephrine was compared with epinephrine alone.¹¹⁵ Results were similar in the subgroup of patients with initial asystolic cardiac arrest (N = 2,396)¹¹⁵

Since the addition of glucocorticoids promotes an increase in blood pressure when administered to intensive care unit patients, the use of vasopressin combined with hydrocortisone has been tested during cardiopulmonary arrest (Table 6). Three studies reported a higher rate of ROSC with the combined administration of vasopressin and corticosteroids alongside adrenaline.^{116–118} However, the largest study (N = 500) did not show any improvement in neurological outcome or survival at hospital discharge,¹¹⁸ nor in the long-term survival.¹¹⁹

Consequently, to date, both the European Resuscitation Council guidelines^{62,120} and the American Heart Association guidelines¹²¹ do not support the use of vasopressin during cardiac arrest.

An interventional randomized trial (NCT04591990) is ongoing to evaluate the benefits (survival and neurological outcome) of combining arginine vasopressin and hydrocortisone compared with norepinephrine in postresuscitation shock.

Vasopressin during hemorrhagic shock

The rationale for the use of vasopressin in hemorrhagic shock is based on two distinct phenomena: severe blood loss is associated with nitrite oxide-mediated vascular hyporeactivity to both endogenous and exogenous norepinephrine,¹²² and a relative AVP deficiency (<10 pg/ml) has been described within the first 48 hours of severe trauma with hemorrhagic shock, possibly linked to an increased need for blood product transfusions.¹²³

In experimental models of uncontrolled hemorrhagic shock (MAP < 20 mmHg), vasopressin was shown to not only increase MAP but also improve short-term survival when compared with fluid resuscitation by crystalloids^{124,125} and epinephrine.¹²⁶ Similarly, in a rat model of uncontrolled hemorrhagic shock, early administration of low-dose AVP (0.4 IU/kg) in association with norepinephrine improved survival when compared with either AVP or norepinephrine alone.¹²⁷

Two small randomized clinical trials have assessed the effect of vasopressin in patients with acute traumatic injury and hypotension.^{128,129} Both studies reported a reduction in fluid or blood product requirements in the vasopressin group, but no significant impact on mortality or other secondary outcomes. A trend toward less acute kidney injury was observed, but did not reach statistical significance.¹²⁹

Currently, based on the available data, the recommendations do not support the use of vasopressin in hemorrhagic shock.

Terlipressin

Terlipressin is a prodrug that is converted into lysine-vasopressin by endothelial peptidases. Its release is slow, and its half-life is approximately 6 hours. Terlipressin has a higher specificity for V1 receptors, with an affinity approximately six times greater than for V2 receptors.¹³⁰

When combined with norepinephrine, the addition of terlipressin, compared with norepinephrine alone, did not affect either mortality or the progression of organ failures in patients with septic shock. However, its use significantly increases adverse effects, particularly the risk of digital ischemia.¹³¹ This concern is further heightened by its long half-life, which may prolong or worsen adverse events when they occur. As a result, terlipressin is not recommended for the management of septic shock.

Table 5**Vasopressin versus epinephrine in first line of cardiac arrest: results of the randomized controlled studies.**

Study	Patient type	Number of patients	Methods	Mortality	Other results
Stiell et al ¹¹²	In-hospital cardiac arrest (78% nonshockable rhythm)	200	-Randomization: vasopressin 40 IU or epinephrine 1 mg -If there was no return of pulse: epinephrine 1 mg every 3–5 minutes	-No significant difference at 1 hour and hospital discharge	-No difference in ROSC -No difference in neurological outcome
Lindner et al ¹¹³	Out-hospital cardiac arrest with ventricular fibrillation resistant to electrical defibrillation	40	-Vasopressin 40 IU or epinephrine 1 mg. -If there was no return of pulse: standard of care treatment	-No significant difference in survival at hospital discharge -Higher rate of survival at 24 hours in the vasopressin group	-Trend to higher rate of successful resuscitation (70% in vasopressin group vs. 35% in epinephrine group; $P = 0.06$) -No difference in neurological outcome
Wenzel et al ¹¹⁴	Out-hospital cardiac arrest	1,186	-Vasopressin 40 IU or epinephrine 1 mg -If there was no return of pulse: second injection of the drug study -If there was no return of pulse: standard of care treatment	-In patients with asystole: higher survival rate at hospital discharge in the vasopressin group -No statistically significant difference in survival at hospital discharge in ventricular fibrillation or pulseless electrical activity	-No difference in neurological outcome -Higher rate of successful resuscitation in patients who failed to achieve ROSC in the vasopressin group and received additional epinephrine. ROSC was significantly higher in the arginine vasopressin group than epinephrine alone
Gueugniaud et al ¹¹⁵	Out-hospital cardiac arrest (81% with initial asystole)	2,894	Randomization: vasopressin 40 IU plus epinephrine 1 mg vs. epinephrine 1 mg alone	-No significant difference in survival was observed at hospital discharge, nor in the subgroup of patients with initial asystole	-No difference in ROSC in the overall population, including in patients with initial asystole -Higher rate of ROSC with the addition of vasopressin in a small subgroup of patients with pulseless electrical activity ($n = 231$) -No difference in neurological outcome

Table 6**Vasopressin, epinephrine, and corticosteroid versus epinephrine and placebo in-hospital cardiac arrest: results of the randomized controlled trial.**

Study	Patient type	Number of patients	Methods	Mortality	Other results
Mentzelopoulos et al ¹⁶	In-hospital cardiac arrest	100	Vasopressin 20 UI (after each epinephrine dose, maximum 5 doses) with epinephrine (1 mg) and methylprednisolone (40 mg, first cycle) vs. placebo and epinephrine	Higher survival rate at hospital discharge in the study group (19% vs. 4%)	Higher rate of ROSC in the vasopressin group (81% vs. 52%)
Mentzelopoulos et al ¹⁷	Monocentric study In-hospital cardiac arrest	300	Patients who survived 4 hours after cardiac arrest in the vasopressin group received intravenous hydrocortisone for less than 7 days	Higher probability of survival with a good cerebral performance category in the vasopressin group	Higher neurological outcome in vasopressin group at hospital discharge
Andersen et al ¹⁸	Multicentric study In-hospital cardiac arrest	501	Vasopressin 20 UI (after each epinephrine dose, maximum 4 doses) with epinephrine (1 mg) and methylprednisolone (40 mg, first cycle) vs. placebo and epinephrine No protocol injection of hydrocortisone	No significant difference in mortality between the two groups	Higher rate of ROSC in the vasopressin group (42% vs. 33%) No difference in neurological outcome between the two groups

Angiotensin

Angiotensin II exhibits a short plasma half-life (approximately 30 seconds)¹³² due to rapid enzymatic degradation into active metabolites such as angiotensin III and Ang (1–7), with no significant accumulation, requiring continuous infusion. Its distribution is primarily intravascular, although tissue effects may persist longer.^{132,133}

Angiotensin II is an endogenous octapeptide that increases blood pressure through peripheral vasoconstriction, stimulation of adrenocorticotrophic hormone secretion, and stimulation of postganglionic sympathetic fibers.

The effects of angiotensin II on the venous compartment remain less well characterized than those of norepinephrine. Experimental studies suggest that angiotensin II may induce venoconstriction and reduce venous capacitance,¹³⁴ potentially increasing venous return. However, clinical data in critically ill patients are lacking.

Angiotensin II has been shown to exert predominantly proinflammatory effects through activation of AT1 receptors, leading to increased cytokine production, oxidative stress, and endothelial dysfunction.^{135,136} However, these effects appear to be context-dependent, and experimental data in septic shock suggest that angiotensin II may also modulate the inflammatory response and could be associated with reduced myocardial inflammation compared with catecholamines.¹³⁷

Administration of angiotensin II increases MAP in patients with vasoplegic shock^{138–140} (Figure 2). This effect is maintained in patients previously treated with angiotensin-converting enzyme inhibitors, but not in those on angiotensin receptor antagonists.¹⁴¹ Patients requiring the lowest doses of norepinephrine at inclusion (<0.25 µg/kg/minute), with acute kidney injury (Kidney Disease: Improving Global Outcomes 3) or higher angiotensin I/II ratio appeared to benefit from angiotensin II administration.^{142–144}

Patients with vasodilatory shock and elevated renin concentrations may represent a biologically relevant phenotype of relative renin–angiotensin system failure, characterized by impaired conversion of angiotensin I to angiotensin II. High renin levels have been associated with increased vasopressor requirements, higher severity of shock, and worse clinical outcomes.¹⁴³ In this context, renin has been proposed as a potential biomarker to identify patients more likely to respond to exogenous angiotensin II, as suggested by post hoc analyses of the ATHOS-3 trial.¹⁴⁵ However, this approach remains hypothesis-generating and requires prospective validation before being implemented in clinical practice.

Currently, clinical data are insufficient to support the routine use of angiotensin II in clinical practice^{27,32} (Table 2).

Inodilators therapies

Dobutamine

Pharmacology and mechanism of action

Dobutamine is a synthetic catecholamine, consisting of a racemic mixture of dextrorotatory and levorotatory forms. The levorotatory form acts as an α1 agonist, while the dextrorotatory form primarily functions as an agonist for both β-receptor types and an antagonist at α1 receptors. Its half-life is between 2 and 3 minutes. After methylation and conjugation, its metabolites are predominantly eliminated through the biliary and urinary systems.

The hemodynamic effects of dobutamine are driven by its direct action on these receptors, coupled with a reduction in sympathetic tone linked to an increase in cardiac output. In healthy individuals, cardiac output increases in direct proportion to the dose (and serum concentration) of dobutamine.¹⁴⁶ Stroke volume increases with low doses of dobutamine but reaches a plateau at higher doses. At these higher doses, the increase

Hemodynamic effects of inotropic agents			
	Catecholamine	Ca ²⁺ -sensitizer	PDE 3 inhibitors
	Dobutamine	Levosimendan	Milrinone & Enoximone
Heart Rate	↑	→	→ or ↑ ¹
Inotropism	↑	↑	↑
Cardiac Output	↑	↑	↑
Right Ventricular Systolic Function	↑	↑	↑
Mean Arterial Pressure	↓	↓	→
Coronary Blood Flow	↑	↑	↑
Splanchnic Blood Flow	↑ ²	↑ ²	unknown

Figure 3. Hemodynamic effects of inotropic agents. ¹Moderate or no increase depending on the study. ²The increase in splanchnic blood flow under inotropes may reflect a regional effect or result from a global rise in cardiac output.

in cardiac output is primarily attributed to the rise in heart rate^{146,147} (Figure 3). According to some authors, the decrease in vascular resistance is attributed to a reflex reduction in sympathetic tone caused by the increased cardiac output, rather than a direct effect of dobutamine.¹⁴⁸ Dobutamine exhibits opposing effects on vascular resistance: vasodilation due to its dextrorotatory form and vasoconstriction from its levorotatory form.

Dobutamine in patients with septic shock

In patients with septic shock, as in healthy individuals, adding dobutamine increases stroke volume even at low doses (from 5 µg/kg/minute) without raising blood pressure. Heart rate elevation is mainly observed at higher doses (i.e., ≥10 µg/kg/minute)^{149,150} but it can also occur at low doses in clinical practice. The increase in cardiac output is associated with a rise in arterial oxygen delivery (DO₂).^{149,150}

The effects on oxygen consumption (VO₂) vary across studies. Some studies report an increase in VO₂ with rising DO₂ after dobutamine administration,¹⁴⁹ while another study did not observe an increase in VO₂ despite higher DO₂.¹⁵⁰ This increase in VO₂ can be explained either by DO₂-dependent VO₂, reflecting tissue oxygen debt, or by a direct thermogenic effect of dobutamine, which causes VO₂ to rise independently of DO₂.

Patients with septic shock who experience an improvement in VO₂ with dobutamine administration have better survival rates compared with those who do not show such an improvement.^{151,152} This may reflect preserved mitochondrial oxygen extraction capacity, together with the identification of patients whose oxygen consumption remains at least partially dependent on DO₂, representing the component that can be improved by inotropic therapy.

A strategy of increasing DO₂ to supraphysiological levels by adding dobutamine in patients admitted to intensive care for acute respiratory failure or sepsis did not improve VO₂ compared with standard care. This interventional approach resulted in higher hospital mortality and increased drug doses, highlighting the potential harm of strategies aiming at supraphysiological oxygen delivery. However, the study population was not selected (e.g., no heart failure or low DO₂ at inclusion), and dobutamine doses were increased up to 200 µg/kg/minute,

which does not reflect typical clinical practice and increases the risk of side effects.¹⁵³

For adults with septic shock and persistent hypoperfusion associated with cardiac dysfunction despite adequate fluid resuscitation and arterial blood pressure, the Surviving Sepsis Campaign suggests adding dobutamine to norepinephrine or using epinephrine alone.²⁷ However, no studies have specifically evaluated the effect of dobutamine in patients with septic shock and impaired oxygen delivery.

Dobutamine in patients with cardiogenic shock

In cardiogenic shock, the combination of dobutamine and norepinephrine was associated with fewer arrhythmias and a faster correction of hyperlactatemia compared with epinephrine.²⁴ It is important to note that the use of dobutamine in end-stage chronic heart failure is associated with increased long-term mortality, despite improvements in hemodynamic parameters and quality of life.^{154,155} Therefore, its use should be considered in acute settings where clinical reversibility is deemed possible.

For its use in intensive care, due to its hypotensive effect, dobutamine should not be used alone in cases of severe arterial hypotension or with the goal of correcting MAP. Instead, it should be used in combination with norepinephrine.^{31,32} Before using dobutamine, it is essential to correct hypovolemia to ensure that the patient is no longer preload-dependent. In addition, its use requires gradual titration of the dosage, with close monitoring of both efficacy—such as tissue perfusion (e.g., capillary refill time, mottling, urine output), central venous oxygen saturation (ScVO₂), and lactate levels—and tolerance, including the occurrence of arrhythmias or arterial hypotension.

An increase in cardiac index with dobutamine does not necessarily indicate an increase in DO₂ or in VO₂,¹⁵² and since microcirculation improvement under dobutamine can occur independently of macro-hemodynamic parameters,¹⁵⁶ reassessing SvO₂ or ScVO₂ alongside cardiac output after administering or escalating dobutamine doses is important. Adding dobutamine to patients who are already highly tachycardic does not appear appropriate due to the risk of worsening symptoms.

The Surviving Sepsis Campaign currently recommends the use of dobutamine as an inotropic agent in shock states with

myocardial dysfunction and persistent organ hypoperfusion, despite corrected hypovolemia and arterial hypotension.²⁷ A strategy of administering dobutamine when cardiac output is reduced, combined with norepinephrine in septic shock, has not shown an increased risk of adverse effects compared with a strategy using epinephrine alone.²²

An interventional, randomized trial (NCT04166331) is ongoing to evaluate the benefits of dobutamine in septic shock associated with heart failure.

Levosimendan

Pharmacology and mechanism of action

Levosimendan is an inodilator that belongs to the class of calcium-sensitizing myofilament agents. By binding to troponin C, it stabilizes the troponin C–calcium complex, which enhances and prolongs contraction. Its highly specific and compartmentalized inhibition of PDE3 may explain its beneficial diastolic effects. Levosimendan can open sarcolemmal and mitochondrial ATP-dependent potassium channels, which provide venous and arterial vasodilatory effects, including on coronary arteries. Unlike dobutamine, its inotropic and vasodilatory actions do not increase VO_2 .¹⁵⁷

Levosimendan is metabolized in the liver. Some of its metabolites, such as OR-1896 and OR-1855, have a long half-life and remain active, leading to clinical effects that can last several days, even after a 24-hour infusion of levosimendan.^{158,159}

In patients with heart failure, levosimendan increases cardiac output by enhancing stroke volume^{160–163} without significantly increasing heart rate,¹⁵⁹ reduces pulmonary arterial occlusion pressure,^{159–162} and improves right ventricular contractility¹⁶⁴ (Figure 3). Levosimendan decreases systemic vascular resistance, leading to lower arterial pressure.^{161,162} A double-blind randomized study including 1327 patients with acute heart failure without shock compared levosimendan to dobutamine. The use of levosimendan did not affect survival, neither in the overall population nor in patients on beta-blockers.¹⁶⁵ However, levosimendan use was associated with arrhythmia complications (such as atrial fibrillation and ventricular extrasystoles) and hypokalemia.¹⁶⁵

Levosimendan has been suggested to exert potential anti-inflammatory effects,¹⁶⁶ with some studies reporting a reduction in proinflammatory cytokines such as IL-6.¹⁶⁷ However, these findings remain inconsistent¹⁶⁸ and are mainly derived from small clinical or experimental studies, limiting firm conclusions.

Levosimendan in patients with cardiogenic shock

In cardiogenic shock, levosimendan also increases cardiac output^{169–171} without a significant rise in heart rate. Its action results in a reduction in MAP due to decreased vascular resistance.^{169,171} Compared with dobutamine, levosimendan leads to a more pronounced increase in cardiac output.¹⁷⁰ However, the only study comparing levosimendan to dobutamine was underpowered to evaluate any potential effects on mortality. The LevoHeartShock trial (NCT04020263) is currently ongoing and aims to compare levosimendan with dobutamine to address this question.

Levosimendan in patients with septic shock

In septic shock, calcium myofilament desensitization plays an important role in the pathophysiology of septic myocardial dysfunction, making levosimendan a potentially valuable option in the context. A study involving 28 patients with persistent heart failure due to sepsis-induced cardiomyopathy, after 48 hours of dobutamine treatment, randomized participants to

either continue dobutamine (without dose escalation) or receive levosimendan in a blinded fashion. The results demonstrated a greater increase in cardiac index, DO_2 , and VO_2 in the levosimendan group.¹⁷² However, addition of levosimendan in an unselected population of patients with septic shock did not reduce mortality compared with placebo (LEOPARDS study).¹⁷³

Meta-analyses comparing dobutamine to levosimendan in septic shock have shown conflicting results regarding the improvement of mortality with dobutamine use.^{174,175} No large-scale study has compared levosimendan to dobutamine in septic myocarditis patients with septic shock. Current evidence and international recommendations do not support the routine use of levosimendan in patients with septic shock, even in cases of septic myocarditis.²⁷

Milrinone and enoximone

Milrinone and enoximone are phosphodiesterase inhibitors classified as noncatecholaminergic inotropes. They work by inhibiting type III phosphodiesterase, which is predominantly found in the heart and vascular smooth muscle. This inhibition increases intracellular cAMP levels, which, independent of surface receptor activation, stimulates protein kinase and raises sarcoplasmic calcium concentrations. The half-life of milrinone and enoximone is longer than that of dobutamine, with milrinone ranging from 90 to 150 minutes and enoximone from 240 to 420 minutes. Their elimination is primarily renal for milrinone and hepatic for enoximone. These drugs are typically administered as a continuous infusion following a loading dose. Due to their pharmacokinetic profile, there is a risk of accumulation during prolonged administration, particularly in critically ill patients or those with renal insufficiency.

In healthy individuals and in chronic heart failure, both milrinone and enoximone increase cardiac contractility and, to a lesser extent, heart rate. Their systemic and pulmonary vasodilatory effects are significant, but MAP generally remains within the normal range due to a concomitant increase in cardiac output. Milrinone specifically reduces right ventricular afterload¹⁷⁶ (Figure 3). Milrinone exerts pronounced pulmonary vasodilatory effects, leading to a reduction in pulmonary vascular resistance and right ventricular afterload, which may be advantageous in patients with right ventricular dysfunction and elevated pulmonary pressures.^{177,178} All these effects are dose-dependent.

In cases of acute decompensated chronic heart failure without shock, milrinone does not improve survival compared with placebo.¹⁷⁹ In patients with severe chronic heart failure, oral milrinone is associated with increased mortality.¹⁸⁰

In cardiogenic shock, milrinone has been compared with dobutamine and does not affect composite outcomes, including mortality and cardiovascular complications.¹⁸¹

Currently, there is no experimental or clinical data evaluating the use of milrinone in patients with septic shock. Moreover, based on current evidence, milrinone is not recommended for the management of patients with septic shock.²⁷

Conclusions

Inotropic and vasopressor therapies are crucial in the management of critically ill patients in the intensive care unit, especially for those in shock. Their effects are closely linked to underlying physiological mechanisms, requiring thoughtful application of available evidence to optimize their use. While norepinephrine remains the first-line vasopressor for most cases of septic and distributive shock, adjunct therapies such as vasopressin, dobutamine, and emerging treatments like angiotensin II may offer benefits in specific contexts. The choice and titration of these therapies must be individualized, balancing efficacy and tolerance. Although high-quality evidence remains limited, the

concept of individualized hemodynamic management is gaining traction and may represent a promising avenue to optimize patient outcomes. Future studies should focus on refining patient selection, exploring therapeutic combinations, and clarifying the optimal timing and duration of interventions to improve outcomes in this complex patient population.

Conflicts of interest

N.F. declares having stock investments in the company Air Liquide®. The other authors have no conflicts to report.

Author contributions

N.F., M.B., P.R., and P.A. wrote the manuscript. All authors read and approved the final manuscript.

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