

Inotropes and Vasopressors

Review of Physiology and Clinical Use in Cardiovascular Disease

Christopher B. Overgaard, MD; Vladimír Džavík, MD

Inotropic and vasopressor agents have increasingly become a therapeutic cornerstone for the management of several important cardiovascular syndromes. In broad terms, these substances have excitatory and inhibitory actions on the heart and vascular smooth muscle, as well as important metabolic, central nervous system, and presynaptic autonomic nervous system effects. They are generally administered with the assumption that short- to medium-term clinical recovery will be facilitated by enhancement of cardiac output (CO) or vascular tone that has been severely compromised by often life-threatening clinical conditions. The clinical efficacy of these agents has been investigated largely through examination of their impact on hemodynamic end points, and clinical practice has been driven in part by expert opinion, extrapolation from animal studies, and physician preference. Our aim is to review the mechanisms of action of common inotropes and vasopressors and to examine the contemporary evidence for their use in important cardiac conditions.

Cardiovascular Effects of Common Inotropes and Vasopressors

Catecholamines

Since the initial discovery of epinephrine, the principal active substance from the adrenal gland,¹ the pharmacology and physiology of a large group of endogenous and synthetic catecholamines or “sympathomimetics” have been characterized.² Catecholamines mediate their cardiovascular actions predominantly through α_1 , β_1 , β_2 , and dopaminergic receptors, the density and proportion of which modulate the physiological responses of inotropes and pressors in individual tissues. β_1 -Adrenergic receptor stimulation results in enhanced myocardial contractility through Ca^{2+} -mediated facilitation of the actin-myosin complex binding with troponin C and enhanced chronicity through Ca^{2+} channel activation (Figure 1). β_2 -Adrenergic receptor stimulation on vascular smooth muscle cells through a different intracellular mechanism results in increased Ca^{2+} uptake by the sarcoplasmic reticulum and vasodilation (Figure 1). Activation of α_1 -adrenergic receptors on arterial vascular smooth muscle cells results in smooth muscle contraction and an increase in systemic vascular resistance (SVR; Figure 2). Finally, stimulation of D_1 and D_2 dopaminergic receptors in the kidney and

splanchnic vasculature results in renal and mesenteric vasodilation through activation of complex second-messenger systems.

A continuum exists between the effects of the predominantly α_1 -stimulation of phenylephrine (intense vasoconstriction) to the β -stimulation of isoproterenol (marked increase in contractility and heart rate; Table). Specific cardiovascular responses are further modified by reflexive autonomic changes after acute blood pressure alterations, which impact heart rate, SVR, and other hemodynamic parameters. Adrenergic receptors can be desensitized and downregulated in certain conditions, such as in chronic heart failure (HF).⁴ Finally, the relative binding affinities of individual inotropes and vasopressors to adrenergic receptors can be altered by hypoxia⁵ or acidosis,⁶ which mutes their clinical effect.

Dopamine

Dopamine, an endogenous central neurotransmitter, is the immediate precursor to norepinephrine in the catecholamine synthetic pathway (Figure 3A). When administered therapeutically, it acts on dopaminergic and adrenergic receptors to elicit a multitude of clinical effects (Table). At low doses (0.5 to $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), stimulation of dopaminergic D_1 postsynaptic receptors concentrated in the coronary, renal, mesenteric, and cerebral beds and D_2 presynaptic receptors present in the vasculature and renal tissues promotes vasodilation and increased blood flow to these tissues. Dopamine also has direct natriuretic effects through its action on renal tubules.⁷ The clinical significance of “renal-dose” dopamine is somewhat controversial, however, because it does not increase glomerular filtration rate, and a renal protective effect has not been demonstrated.⁸ At intermediate doses (3 to $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), dopamine weakly binds to β_1 -adrenergic receptors, promoting norepinephrine release and inhibiting reuptake in presynaptic sympathetic nerve terminals, which results in increased cardiac contractility and chronotropy, with a mild increase in SVR. At higher infusion rates (10 to $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), α_1 -adrenergic receptor-mediated vasoconstriction dominates.

Dobutamine

Dobutamine is a synthetic catecholamine with a strong affinity for both β_1 - and β_2 -receptors, which it binds to at a 3:1 ratio (Table; Figure 3B). With its cardiac β_1 -stimulatory

From the Division of Cardiology, Peter Munk Cardiac Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada.

Correspondence to Dr Vladimír Džavík, Division of Cardiology, Toronto General Hospital, 200 Elizabeth St, EN6-246, Toronto, Ontario, Canada M5G 2C4. E-mail vlad.dzavik@uhn.on.ca

(*Circulation*. 2008;118:1047-1056)

© 2008 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.107.728840

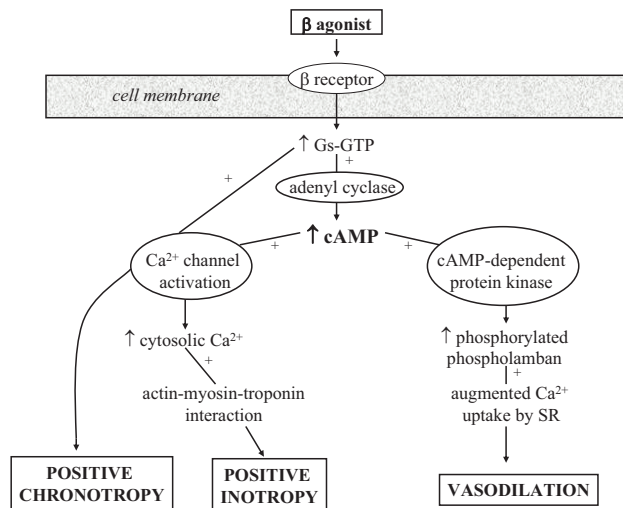


Figure 1. Simplified schematic of postulated intracellular actions of β -adrenergic agonists. β -Receptor stimulation, through a stimulatory Gs-GTP unit, activates the adenylyl cyclase system, which results in increased concentrations of cAMP. In cardiac myocytes, β_1 -receptor activation through increased cAMP concentration activates Ca^{2+} channels, which leads to Ca^{2+} -mediated enhanced chronotropic responses and positive inotropy by increasing the contractility of the actin-myosin-troponin system. In vascular smooth muscle, β_2 -stimulation and increased cAMP results in stimulation of a cAMP-dependent protein kinase, phosphorylation of phospholamban, and augmented Ca^{2+} uptake by the sarcoplasmic reticulum (SR), which leads to vasodilation. Adapted from Gillies et al⁹ with permission of the publisher.

effects, dobutamine is a potent inotrope, with weaker chronotropic activity. Vascular smooth muscle binding results in combined α_1 -adrenergic agonism and antagonism, as well as β_2 -stimulation, such that the net vascular effect is often mild vasodilation, particularly at lower doses ($\leq 5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Doses up to $15 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ increase cardiac contractility without greatly affecting peripheral resistance, likely owing to the counterbalancing effects of α_1 -mediated vasoconstriction and β_2 -mediated vasodilation. Vasoconstriction progressively dominates at higher infusion rates.⁹

Despite its mild chronotropic effects at low to medium doses, dobutamine significantly increases myocardial oxygen consumption. This exercise-mimicking phenomenon is the basis upon which dobutamine may be used as a pharmacological stress agent for diagnostic perfusion imaging,¹⁰ but conversely, it may limit its utility in clinical conditions in which induction of ischemia is potentially harmful. Tolerance can develop after just a few days of therapy,¹¹ and malignant ventricular arrhythmias can be observed at any dose.

Norepinephrine

Norepinephrine, the major endogenous neurotransmitter liberated by postganglionic adrenergic nerves (Table; Figure 3A), is a potent α_1 -adrenergic receptor agonist with modest β -agonist activity, which renders it a powerful vasoconstrictor with less potent direct inotropic properties. Norepinephrine primarily increases systolic, diastolic, and pulse pressure and has a minimal net impact on CO. Furthermore, this agent has minimal chronotropic effects, which makes it attractive

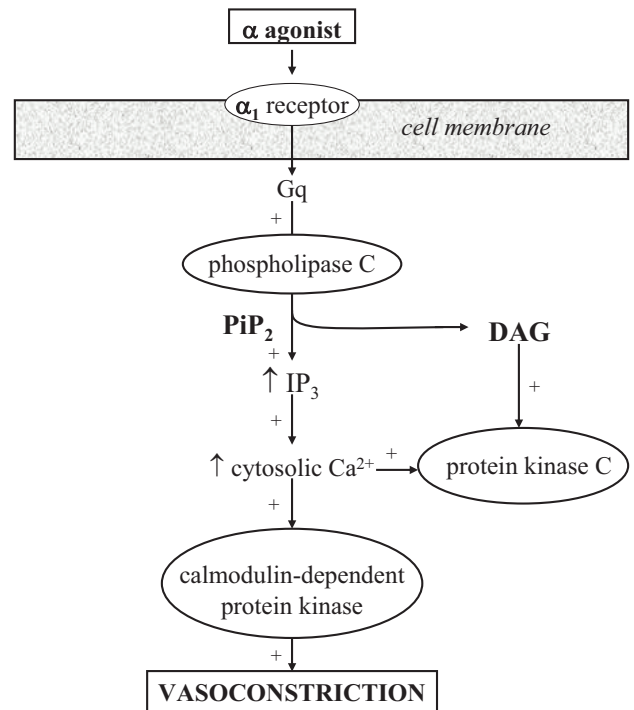


Figure 2. Schematic representation of postulated mechanisms of intracellular action of α_1 -adrenergic agonists. α_1 -Receptor stimulation activates a different regulatory G protein (Gq), which acts through the phospholipase C system and the production of 1,2-diacylglycerol (DAG) and, via phosphatidylinositol-4,5-bisphosphate (PIP_2), of inositol 1,4,5-trisphosphate (IP_3). IP_3 activates the release of Ca^{2+} from the sarcoplasmic reticulum (SR), which by itself and through Ca^{2+} -calmodulin-dependent protein kinases influences cellular processes, leading in vascular smooth muscle to vasoconstriction. Adapted from Gillies et al⁹ with permission of the publisher.

for use in settings in which heart rate stimulation may be undesirable. Coronary flow is increased owing to elevated diastolic blood pressure and indirect stimulation of cardiomyocytes, which release local vasodilators.¹² Prolonged norepinephrine infusion can have a direct toxic effect on cardiac myocytes by inducing apoptosis via protein kinase A activation and increased cytosolic Ca^{2+} influx.¹³

Epinephrine

Epinephrine is an endogenous catecholamine with high affinity for β_1 -, β_2 -, and α_1 -receptors present in cardiac and vascular smooth muscle (Figure 3A; Table). β -Adrenergic effects are more pronounced at low doses and α_1 -adrenergic effects at higher doses. Coronary blood flow is enhanced through an increased relative duration of diastole at higher heart rates and through stimulation of myocytes to release local vasodilators, which largely counterbalance direct α_1 -mediated coronary vasoconstriction.¹⁴ Arterial and venous pulmonary pressures are increased through direct pulmonary vasoconstriction and increased pulmonary blood flow. High and prolonged doses can cause direct cardiac toxicity through damage to arterial walls, which causes focal regions of myocardial contraction band necrosis, and through direct stimulation of myocyte apoptosis.¹⁵

Isoproterenol

Isoproterenol is a potent, nonselective, synthetic β -adrenergic agonist with very low affinity for α -adrenergic receptors

Table. Inotropic and Vasopressor Drug Names, Clinical Indication for Therapeutic Use, Standard Dose Range, Receptor Binding (Catecholamines), and Major Clinical Side Effects

Drug	Clinical Indication	Dose Range	Receptor Binding				Major Side Effects
			α_1	β_1	β_2	DA	
Catecholamines							
Dopamine	Shock (cardiogenic, vasodilatory) HF Symptomatic bradycardia unresponsive to atropine or pacing	2.0 to 20 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (max 50 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	+++	++++	++	+++++	Severe hypertension (especially in patients taking nonselective β -blockers) Ventricular arrhythmias Cardiac ischemia Tissue ischemia/gangrene (high doses or due to tissue extravasation)
Dobutamine	Low CO (decompensated HF, cardiogenic shock, sepsis-induced myocardial dysfunction) Symptomatic bradycardia unresponsive to atropine or pacing	2.0 to 20 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (max 40 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	+	+++++	+++	N/A	Tachycardia Increased ventricular response rate in patients with atrial fibrillation Ventricular arrhythmias Cardiac ischemia Hypertension (especially nonselective β -blocker patients) Hypotension
Norepinephrine	Shock (vasodilatory, cardiogenic)	0.01 to 3 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	+++++	+++	++	N/A	Arrhythmias Bradycardia Peripheral (digital) ischemia Hypertension (especially nonselective β -blocker patients)
Epinephrine	Shock (cardiogenic, vasodilatory) Cardiac arrest Bronchospasm/anaphylaxis Symptomatic bradycardia or heart block unresponsive to atropine or pacing	Infusion: 0.01 to 0.10 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ Bolus: 1 mg IV every 3 to 5 min (max 0.2 mg/kg) IM: (1:1000): 0.1 to 0.5 mg (max 1 mg)	+++++	++++	+++	N/A	Ventricular arrhythmias Severe hypertension resulting in cerebrovascular hemorrhage Cardiac ischemia Sudden cardiac death
Isoproterenol	Bradycardia (especially torsade des pointes) Brugada syndrome	2 to 10 $\mu\text{g}/\text{min}$	0	+++++	+++++	N/A	Ventricular arrhythmias Cardiac ischemia Hypertension Hypotension
Phenylephrine	Hypotension (vagal mediated, medication-induced) Increase MAP with AS and hypotension Decrease LVOT gradient in HCM	Bolus: 0.1 to 0.5 mg IV every 10 to 15 min Infusion: 0.4 to 9.1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	+++++	0	0	N/A	Reflex bradycardia Hypertension (especially with nonselective β -blockers) Severe peripheral and visceral vasoconstriction Tissue necrosis with extravasation
PDIs							
Milrinone	Low CO (decompensated HF, after cardiotomy)	Bolus: 50 $\mu\text{g}/\text{kg}$ bolus over 10 to 30 min Infusion: 0.375 to 0.75 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (dose adjustment necessary for renal impairment)			N/A		Ventricular arrhythmias Hypotension Cardiac ischemia Torsade des pointes
Amrinone	Low CO (refractory HF)	Bolus: 0.75 mg/kg over 2 to 3 min Infusion: 5 to 10 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$			N/A		Arrhythmias, enhanced AV conduction (increased ventricular response rate in atrial fibrillation) Hypotension Thrombocytopenia Hepatotoxicity
Vasopressin	Shock (vasodilatory, cardiogenic) Cardiac arrest	Infusion: 0.01 to 0.1 U/min (common fixed dose 0.04 U/min) Bolus: 40-U IV bolus		V ₁ receptors (vascular smooth muscle) V ₂ receptors (renal collecting duct system)			Arrhythmias Hypertension Decreased CO (at doses >0.4 U/min) Cardiac ischemia Severe peripheral vasoconstriction causing ischemia (especially skin) Splanchnic vasoconstriction
Levosimendan	Decompensated HF	Loading dose: 12 to 24 $\mu\text{g}/\text{kg}$ over 10 min Infusion: 0.05 to 0.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$			N/A		Tachycardia, enhanced AV conduction Hypotension

α_1 indicates α -1 receptor; β_1 , β -1 receptor; β_2 , β -2 receptor; DA, dopamine receptors; 0, zero significant receptor affinity; + through +++++, minimal to maximal relative receptor affinity; N/A, not applicable; IV, intravenous; IM, intramuscular; max, maximum; AS, aortic stenosis; LVOT, LV outflow tract; HCM, hypertrophic cardiomyopathy; and AV, atrioventricular.

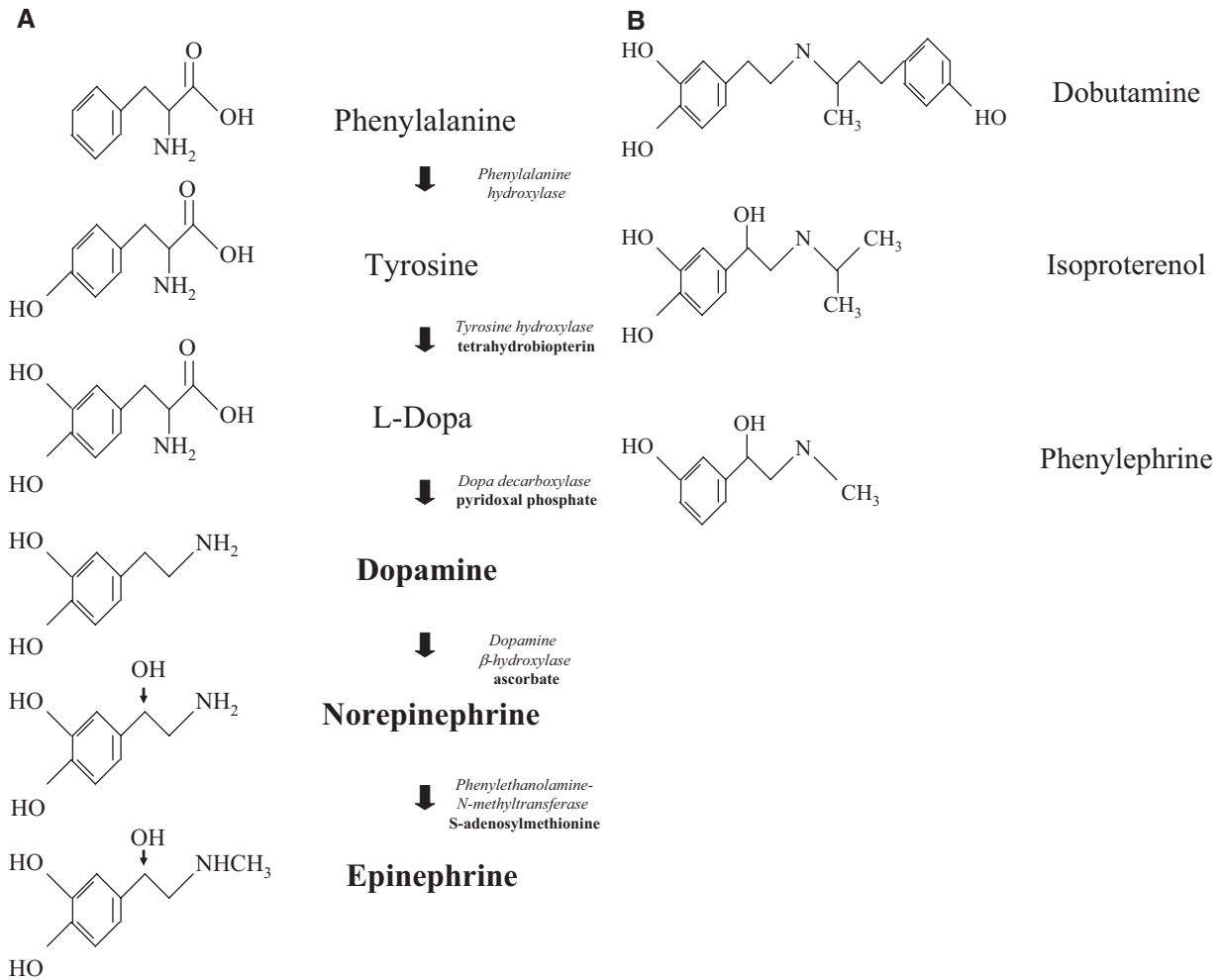


Figure 3. A, Endogenous catecholamine synthesis pathway. Left, chemical structures; Right, names of compounds with conversion enzymes (*italics*) and cofactors (**bold**). B, Chemical structures and names of common synthesized catecholamines.

(Table; Figure 3B). It has powerful chronotropic and inotropic properties, with potent systemic and mild pulmonary vasodilatory effects. Its stimulatory impact on stroke volume is counterbalanced by a β_2 -mediated drop in SVR, which results in a net neutral impact on CO.

Phenylephrine

With its potent synthetic α -adrenergic activity and virtually no affinity for β -adrenergic receptors (Table; Figure 3B), phenylephrine is used primarily as a rapid bolus for immediate correction of sudden severe hypotension. It can be used to raise mean arterial pressure (MAP) in patients with severe hypotension and concomitant aortic stenosis, to correct hypotension caused by the simultaneous ingestion of sildenafil and nitrates, to decrease the outflow tract gradient in patients with obstructive hypertrophic cardiomyopathy, and to correct vagally mediated hypotension during percutaneous diagnostic or therapeutic procedures. This agent has virtually no direct heart rate effects, although it has the potential to induce significant baroreceptor-mediated reflex rate responses after rapid alterations in MAP.

Phosphodiesterase Inhibitors

Phosphodiesterase 3 is an intracellular enzyme associated with the sarcoplasmic reticulum in cardiac myocytes and

vascular smooth muscle that breaks down cAMP into AMP. Phosphodiesterase inhibitors (PDI) increase the level of cAMP by inhibiting its breakdown within the cell, which leads to increased myocardial contractility (Figure 4). These agents are potent inotropes and vasodilators and also improve

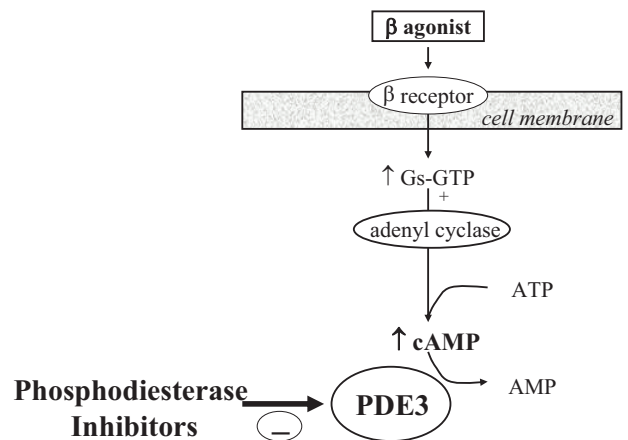


Figure 4. Basic mechanism of action of PDI. PDI lead to increased intracellular concentration of cAMP, which increases contractility in the myocardium and leads to vasodilation in vascular smooth muscle.

diastolic relaxation (lusitropy), thus reducing preload, afterload, and SVR.

Milrinone is the PDI most commonly used for cardiovascular indications (Table). In its parenteral form, it has a longer half-life (2 to 4 hours) than many other inotropic medications. This drug is particularly useful if adrenergic receptors are downregulated or desensitized in the setting of chronic HF, or after chronic β -agonist administration. Amrinone is used less often because of important side effects, which include dose-related thrombocytopenia.

Vasopressin

Isolated in 1951,¹⁶ the nonapeptide vasopressin or “antidiuretic hormone” is stored primarily in granules in the posterior pituitary gland and is released after increased plasma osmolality or hypotension, as well as pain, nausea, and hypoxia. Vasopressin is synthesized to a lesser degree by the heart in response to elevated cardiac wall stress¹⁷ and by the adrenal gland in response to increased catecholamine secretion.¹⁸ It exerts its circulatory effects through V_1 (V_{1a} in vascular smooth muscle, V_{1b} in the pituitary gland) and V_2 receptors (renal collecting duct system; Table). V_{1a} stimulation mediates constriction of vascular smooth muscle, whereas V_2 receptors mediate water reabsorption by enhancing renal collecting duct permeability.

Vasopressin causes less direct coronary and cerebral vasoconstriction than catecholamines and has a neutral or inhibitory impact on CO, depending on its dose-dependent increase in SVR and the reflexive increase in vagal tone. A vasopressin-modulated increase in vascular sensitivity to norepinephrine further augments its pressor effects. The agent may also directly influence mechanisms involved in the pathogenesis of vasodilation, through inhibition of ATP-activated potassium channels,¹⁹ attenuation of nitric oxide production,²⁰ and reversal of adrenergic receptor downregulation.²¹ The pressor effects of vasopressin are relatively preserved during hypoxic and acidotic conditions, which commonly develop during shock of any origin.

Calcium-Sensitizing Agents

Calcium sensitizers are a recently developed class of inotropic agents, levosimendan being the most well known (Table).²² These agents have a dual mechanism of action that includes calcium sensitization of contractile proteins and the opening of ATP-dependent potassium (K^+) channels. Calcium-dependent binding to troponin C enhances ventricular contractility without increasing intracellular Ca^{2+} concentration or compromising diastolic relaxation, which may favorably impact myocardial energetics relative to traditional inotropic therapies. The opening of K^+ channels on vascular smooth muscle leads to arteriolar and venous vasodilation and may confer a degree of myocardial protection during ischemia.²³ The combination of improved contractile performance and vasodilation is particularly beneficial during acute and chronic HF states, for which levosimendan is being used with increasing frequency in some countries.

Evidence for Use of Inotropes and Vasopressors in Cardiovascular Disease

Cardiogenic Shock Complicating Acute Myocardial Infarction

Inotropes and vasopressors are used routinely in the setting of cardiogenic shock complicating acute myocardial infarction (AMI). These agents all increase myocardial oxygen consumption and can cause ventricular arrhythmias, contraction-band necrosis, and infarct expansion. However, critical hypotension itself compromises myocardial perfusion, leading to elevated left ventricular (LV) filling pressures, increased myocardial oxygen requirements, and further reduction in the coronary perfusion gradient. Thus, hemodynamic benefits usually outweigh specific risks of inotropic therapy when used as a bridge to more definitive treatment measures.

Inotropic agents may improve mitochondrial function in noninfarcted myocardium that has become deranged during AMI complicated by shock.²⁴ However, free cytosolic Ca^{2+} , which is significantly elevated in postischemic cardiac myocytes, is further increased with the administration of dopamine, which leads to activation of proteolytic enzymes, proapoptotic signal cascades, mitochondrial damage, and eventual membrane disruption and necrosis.²⁵ Thus, the lowest possible doses of inotropic and pressor agents should be used to adequately support vital tissue perfusion while limiting adverse consequences, some of which may not be immediately apparent.

The American College of Cardiology/American Heart Association guidelines for management of hypotension complicating AMI suggest the use of dobutamine as a first-line agent if systolic blood pressure ranges between 70 and 100 mm Hg in the absence of signs and symptoms of shock. Dopamine is suggested in patients who have the same systolic blood pressure in the presence of symptoms of shock.²⁶ However, definitive evidence supporting use of specific agents in this setting is lacking. Moderate doses of these agents maximize inotropy and avoid excessive α_1 -adrenergic stimulation that can result in end-organ ischemia. The deliberate combination of dopamine and dobutamine at a dose of $7.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ each was shown to improve hemodynamics and limit important side effects compared with either individual agent administered at $15 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.²⁷ Moderate doses of combinations of medications may potentially be more effective than maximal doses of any individual agent.

When response to a medium dose of dopamine or dopamine/dobutamine in combination is inadequate, or the patient's presenting systolic blood pressure is <70 mm Hg, the use of norepinephrine has been recommended.²⁶ With an antithrombotic effect in addition to its pressor qualities, norepinephrine may be the optimal choice under these conditions compared with epinephrine, which can exacerbate lactic acidosis and promote thrombosis in coronary vasculature.²⁸

During early shock, endogenous vasopressin levels are elevated significantly to help maintain end-organ perfusion.²⁹ As the shock state progresses, however, plasma vasopressin levels fall dramatically, which contributes to a loss of

vascular tone, worsening hypotension, and end-organ perfusion. Proposed mechanisms to explain this phenomenon include depletion of neurohypophyseal stores,³⁰ baroreceptor and generalized autonomic dysfunction during prolonged shock,³¹ and endogenous norepinephrine-induced inhibition of vasopressin release.³² Vasopressin therapy may thus be effective in norepinephrine-resistant vasodilatory shock, improving MAP, cardiac index, and LV stroke work index and reducing the need for norepinephrine, resulting in decreased cardiotoxicity and malignant arrhythmias.³³ Vasopressin may also attenuate interleukin-induced generation of nitric oxide, have a modest inotropic effect on the myocardium via V_{1a}-mediated increases in intracellular Ca²⁺, and improve coronary blood flow due to catecholamine sparing.³⁴

In the only study to date that examined vasopressin use in cardiogenic shock after AMI, this agent was found to increase MAP without adversely impacting cardiac index and wedge pressure.³⁵ Cardiac power index, an important determinant of outcome in cardiogenic shock after AMI, was not adversely affected by vasopressin but decreased when norepinephrine was used. Further studies to validate the use of vasopressin in this setting are needed.

Congestive HF

Inotropic therapy is used in the management of decompensated HF to lower end-diastolic pressure and improve diuresis, thus allowing traditional medical therapy (eg, angiotensin-converting enzyme inhibitors, diuretics, and β -blockers) to be reinstated gradually. Patients with decompensated HF unresponsive to diuresis often have diminished concomitant peripheral perfusion, clinically apparent as cool extremities, narrowed pulse pressure, and worsening renal function. They may have markedly elevated SVR despite hypotension due to the stimulation of the renal-angiotensin-aldosterone system, as well as release of endogenous catecholamines and vasopressin. In this setting, reversal of systemic vasoconstriction is often achieved through the use of vasodilators (such as sodium nitroprusside) and inotropes with peripheral vasodilatory properties to improve hemodynamic parameters and clinical symptoms.

The use of positive inotropes (parenteral inotropes and oral PDI) in chronic HF has been consistently demonstrated to increase mortality.^{36,37} A proposed central mechanism involves a chronic increase in intracellular Ca²⁺, which contributes to altered gene expression and apoptosis and an increased likelihood of malignant ventricular arrhythmias.³⁸ As a result, the current American College of Cardiology/American Heart Association guidelines for diagnosis and management of chronic HF in the adult do not recommend the routine use of intravenous inotropic agents for patients with refractory end-stage HF (class III recommendation) but do state that they may be considered for palliation of symptoms in these patients (class IIb recommendation).³⁹ The European Society of Cardiology acute HF guidelines also stress that few controlled trials with intravenous inotropic agents have been performed.⁴⁰ However, these guidelines do point out that in an appropriate clinical setting of hypotension and peripheral hypoperfusion, particular agents may be indicated with slightly different levels of recommendation (do-

butamine and levosimendan, class IIa; PDI and dopamine, class IIb).⁴¹

The most commonly recommended initial inotropic therapies for refractory HF (dobutamine, dopamine, and milrinone) are used to improve CO and enhance diuresis by improving renal blood flow and decreasing SVR without exacerbating systemic hypotension. Dobutamine stimulation of β_1 - and β_2 -receptors can achieve this goal at low to medium doses by modestly increasing contractility with usually mild systemic vasodilation. Unfortunately, β -adrenergic receptor responses are often blunted in the failing human heart. A chronic increase in activation of the sympathetic nervous system and increased circulating catecholamine levels results in a phosphorylation signal that leads to uncoupling of the surface receptor from its intracellular signal transduction proteins (desensitization), as well as increased receptor targeting for endocytosis (decreased receptor density).⁴² PDI such as milrinone, acting through a non- β -adrenergic mechanism, are not associated with diminished efficacy or tolerance with prolonged use. This drug causes relatively more significant right ventricular afterload reduction through pulmonary vasodilation and less direct cardiac inotropy, which results in less myocardial oxygen consumption. Milrinone can cause severe systemic hypotension, necessitating the coadministration of additional pressor therapies. Direct randomized comparisons of milrinone and dobutamine have been small and have demonstrated similar clinical outcomes.^{43,44}

Several major clinical trials have evaluated the safety and efficacy of levosimendan in HF syndromes. Two early studies demonstrated a mortality benefit in patients given levosimendan versus placebo early (within 14 days) in the setting of LV failure complicating AMI (RUSSLAN [Randomized Study on Safety and Effectiveness of Levosimendan in Patients With Left Ventricular Failure due to an Acute Myocardial Infarct])⁴⁵ and at 180 days in the setting of chronic HF when compared with dobutamine therapy (LIDO [Levosimendan Infusion versus Dobutamine in Severe Low-Output Heart Failure]).⁴⁶ However, in larger multicenter randomized trials in the setting of acute decompensated HF (REVIVE II [Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy] and SURVIVE [Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support]),^{47,48} levosimendan use significantly improved symptoms but not survival.

In some patients, complete inotropic dependence manifested by symptomatic hypotension, recurrent congestive symptoms, or worsening renal function may develop after discontinuation of parenteral therapy. Inotropic support may become necessary until cardiac transplantation or implantation of an LV assist device can be instituted. Long-term therapy is also used as a "bridge to decision" in patients who are not presently destination-therapy candidates but may become so in the future. Inotrope-dependent HF patients who do not go on to definitive therapy have a poor prognosis, with 1-year mortality ranging from 79% to 94%.⁴⁹ Long-term inotropic therapy is associated with an increased risk of line sepsis, arrhythmias, accelerated functional decline due to worsening nutritional status, and direct acceleration of end-

organ dysfunction, such as the development of eosinophilic myocarditis from an allergic response to chronic dobutamine exposure.⁵⁰ Inotropic home therapy has been used effectively for palliation of symptoms in patients who are not candidates for LV assist device support or transplantation, enabling those individuals to die in the comfort of their own homes.⁵¹

The majority of HF patients can be weaned off inotrope infusions successfully after diuresis of excess volume and careful adjustment of concomitant oral medications. General recommendations have been to keep patients in the hospital and on a stable oral HF regimen for 48 hours before discharge to ensure adequacy of the initiated therapy.⁵²

Cardiopulmonary Arrest

Inotropic and vasopressor agents are a mainstay of resuscitation therapy during cardiopulmonary arrest.⁵³ Epinephrine, with its potent vasopressor and inotropic properties, can rapidly increase diastolic blood pressure to facilitate coronary perfusion and help restore organized myocardial contractility. However, it is not clear whether epinephrine actually facilitates cardioversion to normal rhythm, and its use has been associated with increased oxygen consumption, ventricular arrhythmias, and myocardial dysfunction after successful resuscitation.⁵⁴ Repeated high-bolus doses (5 mg) appear no more effective than repeated standard doses (1 mg) at restoring circulation.⁵⁵

The finding that endogenous vasopressin levels are greater in patients successfully resuscitated from sudden cardiac death than in nonsurvivors sparked interest in the use of vasopressin for this indication.⁵⁶ Experimentally, the use of vasopressin during cardiopulmonary collapse has demonstrated a more beneficial effect than epinephrine on cerebral and myocardial blood flow,⁵⁷ resulting in more sustained increases in MAP.⁵⁸ Clinically, its use has been associated with a higher rate of short-term survival in patients experiencing out-of-hospital ventricular fibrillation.⁵⁹ However, in a larger trial of 1186 patients with out-of-hospital cardiac arrest who were randomized to 2 injections of either 40 U of vasopressin or 1 mg of epinephrine (followed by additional treatment with epinephrine if needed), patients with asystole but not those with ventricular fibrillation or pulseless electrical activity were significantly more likely to survive to hospital admission with vasopressin administration.⁶⁰ The mechanism of benefit may stem from the ability of vasopressin to retain its potent vasoconstricting properties under severely acidotic conditions, in which catecholamines have limited efficacy. The current American Heart Association guidelines for adult cardiac life support have incorporated vasopressin as a 1-time alternative to the first or second dose of epinephrine (1-time bolus of 40 U) in patients with pulseless electrical activity or asystole and for pulseless ventricular tachycardia or ventricular fibrillation.⁵³

Postoperative Cardiac Surgery

Pharmacological support may be necessary during and after weaning from cardiopulmonary bypass in patients who have developed a low-CO syndrome, arbitrarily defined as a cardiac index $<2.4 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ with evidence of end-organ dysfunction.³ Causes of low CO include

cardioplegia-induced myocardial dysfunction, precipitation of cardiac ischemia during aortic cross-clamping, reperfusion injury, activation of inflammatory and coagulation cascades, and the presence of nonrepaired preexisting cardiac disease. Therapy should be instituted promptly in addition to other measures, including optimization of volume status, reduction of SVR with propofol infusion, temporary pacing, and intra-aortic balloon counterpulsation. Although no single agent is universally superior in this setting, dobutamine has the most desirable side-effect profile of the β -agonists, whereas PDIs increase flow through arterial grafts, reduce MAP, and improve right-sided heart performance in pulmonary hypertension.³ As is the case in HF, concomitant vasopressor therapy may be necessary.

Several studies have examined the role of prophylactic inotropic or vasopressor therapy in weaning from cardiopulmonary bypass or to improve hemodynamic status in general. Preemptive milrinone administration before separation from cardiopulmonary bypass was found to attenuate postoperative deterioration in cardiac function and reduce the need for additional inotropes.⁶¹ In off-pump bypass surgery patients, the use of preemptive milrinone significantly ameliorates increases in mitral regurgitation and improves hemodynamic indexes that often deteriorate with off-pump surgery.⁶² Milrinone and dobutamine were both found to be effective in improving general hemodynamic parameters compared with placebo in a European multicenter, randomized, open-label trial.⁶³

The development of a systemic inflammatory response during cardiopulmonary bypass may cause severe generalized vasodilation, known as “vasoplegia syndrome,” which can result in increased early mortality, especially in heart transplant recipients.⁶⁴ This syndrome is associated with prolonged cardiopulmonary bypass time, orthotopic heart transplantation, and LV assist device insertion and is characterized by severe persistent hypotension, metabolic acidosis, decreased SVR, and low intracardiac filling pressures, with normal or elevated CO. Preoperative risk factors include preoperative angiotensin-converting enzyme inhibitor, calcium channel blocker, or intravenous heparin use and poor LV function.^{64–66} Development of vasoplegia syndrome may be related to the release of vasodilatory inflammatory mediators, extensive complement activation, or vasoactive substance depletion, such as vasopressin. Although catecholamine therapy is often ineffective, methylene blue (through a nitric oxide–inhibition mechanism) and vasopressin have been shown to improve outcomes.^{65–67}

Right Ventricular Infarction

Significant right ventricular free-wall ischemia leads to immediate dilation of the right ventricle within a constrained pericardium. A rapid increase in intrapericardial pressure and intraventricular septal shift alters LV geometry, impairing LV filling and contractile performance.^{68,69} These combined effects result in a drop in CO that may exacerbate shock.⁷⁰ Excessive intravenous fluid beyond a right atrial pressure $>15 \text{ mm Hg}$ to improve a “preload-dependent” right ventricle can result in deterioration of LV performance. Dobutamine improves myocardial performance in this setting.⁷¹

Close observation is essential to monitor for exacerbation of hypotension and atrial arrhythmias, which can profoundly worsen hemodynamics.

Bradyarrhythmias

Owing to their chronotropic effects, β -adrenergic agonists can be useful for transient emergency treatment of bradyarrhythmias if atropine is ineffective.⁵³ The use of the β -agonists dobutamine, dopamine, or isoproterenol can stabilize the patient to allow time for a temporary pacemaker to be inserted. These agents are also useful under the same circumstances to treat bradycardia-induced torsade des pointes. Finally, isoproterenol has also been used to suppress the trigger for ventricular fibrillation in patients with the Brugada syndrome who do not wish to have cardioverter-defibrillator implantation to prevent sudden cardiac death.⁷²

Adjuvant Issues

Patient Monitoring During Parenteral Inotropic and Vasopressor Therapy

Patients requiring treatment with inotropes and vasopressors generally require monitoring in an intensive care or step-down setting because of the potential for development of life-threatening arrhythmias.

Invasive Blood Pressure Monitoring

In shock, continuous blood pressure monitoring with an arterial line is essential both to monitor the status of the underlying illness and because inotropes and vasopressors have the potential to induce life-threatening hypotension or hypertension. Chronic HF patients undergoing hemodynamic tailoring with a low-dose β -agonist or PDI can usually be monitored noninvasively.

Pulmonary Artery Catheter Use

Consensus on pulmonary artery catheter use during treatment with inotropic therapy is lacking. Although this tool can be helpful diagnostically, its routine use has never been shown to improve outcomes.⁷³ This may reflect an absence of effective evidence-based therapies to be used in response to pulmonary artery catheter data in the treatment of critically ill patients.⁷⁴ In the ESCAPE trial (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness), which examined pulmonary artery catheter use in patients with severe HF, catheter insertion was deemed safe but was not associated with improved rates of mortality or hospitalization.⁷⁵ Inotropic titration with pulmonary artery catheter data in isolation can result in inappropriate stimulation of CO, thus negatively impacting prognosis in heterogeneous intensive care unit patient populations.⁷⁶ Titration of inotropic therapy should be guided by the adequacy of end-organ perfusion, based on multiple clinical parameters.

Goals of Inotropic and Vasopressor Therapy

The use of inotropes and vasopressors has not been shown in randomized, controlled studies to ultimately lead to improved patient outcomes, at least in part because no clinical trials have been conducted with study size and power adequate to test their effect on improving survival. In the absence of such data, the definitive goals of therapy must be considered of

primary importance, and the role of inotropic therapy should be kept in a supportive context to allow treatment of the underlying disorder. Such therapy includes prompt percutaneous or surgical revascularization and the institution of mechanical support (intra-aortic balloon counterpulsation or LV assist device) to improve coronary perfusion, CO, or both.

Conclusions and Recommendations

In conclusion, inotropes and vasopressors play an essential role in the supportive care of a number of important cardiovascular disease processes. To date, prospective examination of their impact on clinical outcomes in randomized trials has been minimal, despite their widespread use in cardiovascular illness. However, the recently published TRIUMPH (Tilarginine Acetate Injection in a Randomized International Study in Unstable MI Patients With Cardiogenic Shock) international randomized trial of N^G -monomethyl L-arginine in cardiogenic shock has shown that such trials are not only feasible but necessary to validate findings of smaller studies.^{77,78} A better understanding of the physiology and important adverse effects of these medications should lead to directed clinical use, with realistic therapeutic goals. The following broad recommendations can be made:

Smaller combined doses of inotropes and vasopressors may be advantageous over a single agent used at higher doses to avoid dose-related adverse effects.

The use of vasopressin at low to moderate doses may allow catecholamine sparing, and it may be particularly useful in settings of catecholamine hyposensitivity and after prolonged critical illness.

In cardiogenic shock complicating AMI, current guidelines based on expert opinion recommend dopamine or dobutamine as first-line agents with moderate hypotension (systolic blood pressure 70 to 100 mm Hg) and norepinephrine as the preferred therapy for severe hypotension (systolic blood pressure <70 mm Hg).

Routine inotropic use is not recommended for end-stage HF. When such use is essential, every effort should be made to either reinstitute stable oral therapy as quickly as possible or use destination therapy such as cardiac transplantation or LV assist device support.

Large randomized trials focusing on clinical outcomes are needed to better assess the clinical efficacy of these agents.

Acknowledgments

We would like to thank Uchewnwa Genus for her assistance during the preparation of this article.

Disclosures

Dr Overgaard is supported by a Heart and Stroke Foundation of Canada (HSFC)/AstraZeneca Canada Inc fellowship award. Dr Džavík is supported in part by the Brompton Funds (Toronto, Canada) Professorship in Interventional Cardiology. Dr Džavík has received research funding from Arginox Inc and speaker's honoraria from Datascope Inc.

References

1. Abel JJ, Taveau RD. On the decomposition products of epinephrine hydrate. *J Biol Chem*. 1905;1:1–32.
2. Barger G, Dale HH. Chemical structure and sympathomimetic action of amines. *J Physiol*. 1910;41:19–59.

3. Gillies M, Bellomo R, Doolan L, Buxton B. Bench-to-bedside review: inotropic drug therapy after adult cardiac surgery: a systematic literature review. *Crit Care*. 2005;9:266–279.
4. Tilley DG, Rockman HA. Role of beta-adrenergic receptor signaling and desensitization in heart failure: new concepts and prospects for treatment. *Expert Rev Cardiovasc Ther*. 2006;4:417–432.
5. Li HT, Long CS, Rokosh DG, Honbo NY, Karliner JS. Chronic hypoxia differentially regulates α 1-adrenergic receptor subtype mRNAs and inhibits α 1-adrenergic receptor-stimulated cardiac hypertrophy and signaling. *Circulation*. 1995;92:918–925.
6. Modest VE, Butterworth JF IV. Effect of pH and lidocaine on beta-adrenergic receptor binding: interaction during resuscitation? *Chest*. 1995;108:1373–1379.
7. Denton MD, Chertow GM, Brady HR. “Renal-dose” dopamine for the treatment of acute renal failure: scientific rationale, experimental studies and clinical trials. *Kidney Int*. 1996;50:4–14.
8. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J; Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. *Lancet*. 2000;356:2139–2143.
9. Ruffolo RR Jr. The pharmacology of dobutamine. *Am J Med Sci*. 1987;294:244–248.
10. Patel RN, Arteaga RB, Mandawat MK, Thornton JW, Robinson VJ. Pharmacologic stress myocardial perfusion imaging. *South Med J*. 2007;100:1006–1014.
11. Unverferth DA, Blanford M, Kates RE, Leier CV. Tolerance to dobutamine after a 72 hour continuous infusion. *Am J Med*. 1980;69:262–266.
12. Tune JD, Richmond KN, Gorman MW, Feigl EO. Control of coronary blood flow during exercise. *Exp Biol Med (Maywood)*. 2002;227:238–250.
13. Communal C, Singh K, Pimentel DR, Colucci WS. Norepinephrine stimulates apoptosis in adult rat ventricular myocytes by activation of the β -adrenergic pathway. *Circulation*. 1998;98:1329–1334.
14. Jones CJ, DeFily DV, Patterson JL, Chilian WM. Endothelium-dependent relaxation competes with α 1- and α 2-adrenergic constriction in the canine epicardial coronary microcirculation. *Circulation*. 1993;87:1264–1274.
15. Singh K, Xiao L, Remondino A, Sawyer DB, Colucci WS. Adrenergic regulation of cardiac myocyte apoptosis. *J Cell Physiol*. 2001;189:257–265.
16. Turner RA, Pierce JG, du Vigneaud V. The purification and the amino acid content of vasopressin preparations. *J Biol Chem*. 1951;191:21–28.
17. Hupf H, Grimm D, Riegger GA, Schunkert H. Evidence for a vasopressin system in the rat heart. *Circ Res*. 1999;84:365–370.
18. Guillon G, Grazzini E, Andrez M, Breton C, Trueba M, Serradeil-LeGal C, Boccara G, Derick S, Chouinard L, Gallo-Payet N. Vasopressin: a potent autocrine/paracrine regulator of mammal adrenal functions. *Endocr Res*. 1998;24:703–710.
19. Salzman AL, Vromen A, Denenberg A, Szabo C. K(ATP)-channel inhibition improves hemodynamics and cellular energetics in hemorrhagic shock. *Am J Physiol*. 1997;272:H688–H694.
20. Kusano E, Tian S, Umino T, Tetsuka T, Ando Y, Asano Y. Arginine vasopressin inhibits interleukin-1 beta-stimulated nitric oxide and cyclic guanosine monophosphate production via the V1 receptor in cultured rat vascular smooth muscle cells. *J Hypertens*. 1997;15:627–632.
21. Hamu Y, Kanmura Y, Tsuneyoshi I, Yoshimura N. The effects of vasopressin on endotoxin-induced attenuation of contractile responses in human gastroepiploic arteries in vitro. *Anesth Analg*. 1999;88:542–548.
22. Hasenfuss G, Pieske B, Castell M, Kretschmann B, Maier LS, Just H. Influence of the novel inotropic agent levosimendan on isometric tension and calcium cycling in failing human myocardium. *Circulation*. 1998;98:2141–2147.
23. Lehtonen L, Poder P. The utility of levosimendan in the treatment of heart failure. *Ann Med*. 2007;39:2–17.
24. Mukae S, Yanagishita T, Geshi E, Umetsu K, Tomita M, Itoh S, Konno N, Katagiri T. The effects of dopamine, dobutamine and amrinone on mitochondrial function in cardiogenic shock. *Jpn Heart J*. 1997;38:515–529.
25. Stamm C, Friehs I, Cowan DB, Cao-Danh H, Choi YH, Duebener LF, McGowan FX, del Nido PJ. Dopamine treatment of posts ischemic contractile dysfunction rapidly induces calcium-dependent pro-apoptotic signaling. *Circulation*. 2002;106(suppl 1):I-290–I-298.
26. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Ornato JP. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *J Am Coll Cardiol*. 2004;44:E1–E211.
27. Richard C, Ricome JL, Rimailho A, Bottineau G, Auzepy P. Combined hemodynamic effects of dopamine and dobutamine in cardiogenic shock. *Circulation*. 1983;67:620–626.
28. Lin H, Young DB. Opposing effects of plasma epinephrine and norepinephrine on coronary thrombosis in vivo. *Circulation*. 1995;91:1135–1142.
29. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. *N Engl J Med*. 2001;345:588–595.
30. Sharshar T, Carlier R, Blanchard A, Feydy A, Gray F, Paillard M, Raphael JC, Gajdos P, Annane D. Depletion of neurohypophyseal content of vasopressin in septic shock. *Crit Care Med*. 2002;30:497–500.
31. Landry DW, Levin HR, Gallant EM, Ashton RC Jr, Seo S, D'Alessandro D, Oz MC, Oliver JA. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation*. 1997;95:1122–1125.
32. Day TA, Randle JC, Renaud LP. Opposing alpha- and beta-adrenergic mechanisms mediate dose-dependent actions of noradrenaline on supraoptic vasopressin neurones in vivo. *Brain Res*. 1985;358:171–179.
33. Dunser MW, Mayr AJ, Ulmer H, Knotzer H, Sumann G, Pajk W, Friesenecker B, Hasibeder WR. Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. *Circulation*. 2003;107:2313–2319.
34. Okamura T, Ayajiki K, Fujioka H, Toda N. Mechanisms underlying arginine vasopressin-induced relaxation in monkey isolated coronary arteries. *J Hypertens*. 1999;17:673–678.
35. Jolly S, Newton G, Horlick E, Seidelin PH, Ross HJ, Husain M, Dzavik V. Effect of vasopressin on hemodynamics in patients with refractory cardiogenic shock complicating acute myocardial infarction. *Am J Cardiol*. 2005;96:1617–1620.
36. Felker GM, O'Connor CM. Inotropic therapy for heart failure: an evidence-based approach. *Am Heart J*. 2001;142:393–401.
37. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML, Mallis GI, Sollano JA, Shannon J, Tandon PK, deMets DL; the PROMISE Study Research Group. Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med*. 1991;325:1468–1475.
38. Stevenson LW. Clinical use of inotropic therapy for heart failure: looking backward or forward? Part II: chronic inotropic therapy. *Circulation*. 2003;108:492–497.
39. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation*. 2005;112:e154–e235.
40. Thackray S, Easthaugh J, Freemantle N, Cleland JG. The effectiveness and relative effectiveness of intravenous inotropic drugs acting through the adrenergic pathway in patients with heart failure: a meta-regression analysis. *Eur J Heart Fail*. 2002;4:515–529.
41. Nieminen MS, Bohm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, Hasin Y, Lopez-Sendon J, Mebazaa A, Metra M, Rhodes A, Swedberg K, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie MR, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth OA, Garcia MA, Dickstein K, Albuquerque A, Conthe P, Crespo-Leiro M, Ferrari R, Follath F, Gavazzi A, Janssens U, Komajda M, Morais J, Moreno R, Singer M, Singh S, Tendera M, Thygesen K. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005;26:384–416.
42. Perrino C, Rockman HA, Chiariello M. Targeted inhibition of phosphoinositide 3-kinase activity as a novel strategy to normalize beta-adrenergic receptor function in heart failure. *Vascul Pharmacol*. 2006;45:77–85.

43. Karlsberg RP, DeWood MA, DeMaria AN, Berk MR, Lasher KP; Milrinone-Dobutamine Study Group. Comparative efficacy of short-term intravenous infusions of milrinone and dobutamine in acute congestive heart failure following acute myocardial infarction. *Clin Cardiol*. 1996; 19:21–30.
44. Aranda JM Jr, Schofield RS, Pauly DF, Cleeton TS, Walker TC, Monroe VS Jr, Leach D, Lopez LM, Hill JA. Comparison of dobutamine versus milrinone therapy in hospitalized patients awaiting cardiac transplantation: a prospective, randomized trial. *Am Heart J*. 2003;145:324–329.
45. Moiseyev VS, Poder P, Andrejevs N, Ruda MY, Golikov AP, Lazebnik LB, Kobalava ZD, Lehtonen LA, Laine T, Nieminen MS, Lie KI. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction: a randomized, placebo-controlled, double-blind study (RUSSLAN). *Eur Heart J*. 2002;23:1422–1432.
46. Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, Harjola VP, Mitrovic V, Abdalla M, Sandell EP, Lehtonen L. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet*. 2002;360:196–202.
47. Packer M. REVIVE II: multicentre placebo-controlled trial of levosimendan on clinical status in acutely decompensated heart failure. Presented at: 78th Scientific Sessions of the American Heart Association; November 13–16, 2005; Dallas, Tex.
48. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, Thakkar R, Padley RJ, Poder P, Kivikko M. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE randomized trial. *JAMA*. 2007;297:1883–1891.
49. Hershberger RE, Nauman D, Walker TL, Dutton D, Burgess D. Care processes and clinical outcomes of continuous outpatient support with inotropes (COSI) in patients with refractory endstage heart failure. *J Card Fail*. 2003;9:180–187.
50. Fernandez-Gonzalez AL, Panizo-Santos A. Eosinophilic myocarditis in heart transplant candidates. *J Heart Lung Transplant*. 1996;15:852–853.
51. Sindone AP, Keogh AM, Macdonald PS, McCosker CJ, Kaan AF. Continuous home ambulatory intravenous inotropic drug therapy in severe heart failure: safety and cost efficacy. *Am Heart J*. 1997;134:889–900.
52. Stevenson LW, Massie BM, Francis GS. Optimizing therapy for complex or refractory heart failure: a management algorithm. *Am Heart J*. 1998; 135:S293–S309.
53. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2005;112(suppl IV):IV-1–IV-203.
54. Paradis NA, Wenzel V, Southall J. Pressor drugs in the treatment of cardiac arrest. *Cardiol Clin*. 2002;20:61–78, viii.
55. Gueugniaud PY, Mols P, Goldstein P, Pham E, Dubien PY, Deweerdt C, Vergnion M, Petit P, Carli P; European Epinephrine Study Group. A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. *N Engl J Med*. 1998;339: 1595–1601.
56. Lindner KH, Strohmenger HU, Ensinger H, Hetzel WD, Ahnefeld FW, Georgieff M. Stress hormone response during and after cardiopulmonary resuscitation. *Anesthesiology*. 1992;77:662–668.
57. Morris DC, Dereczyk BE, Grzybowski M, Martin GB, Rivers EP, Wortsman J, Amico JA. Vasopressin can increase coronary perfusion pressure during human cardiopulmonary resuscitation. *Acad Emerg Med*. 1997;4:878–883.
58. Wenzel V, Lindner KH, Prengel AW, Maier C, Voelckel W, Lurie KG, Strohmenger HU. Vasopressin improves vital organ blood flow after prolonged cardiac arrest with postcountershock pulseless electrical activity in pigs. *Crit Care Med*. 1999;27:486–492.
59. Lindner KH, Dirks B, Strohmenger HU, Prengel AW, Lindner IM, Lurie KG. Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. *Lancet*. 1997;349:535–537.
60. Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med*. 2004;350:105–113.
61. Kikura M, Sato S. The efficacy of preemptive milrinone or amrinone therapy in patients undergoing coronary artery bypass grafting. *Anesth Analg*. 2002;94:22–30.
62. Omae T, Kakiyama Y, Mastunaga A, Tsuneyoshi I, Kawasaki K, Kanmura Y, Sakata R. Hemodynamic changes during off-pump coronary artery bypass anastomosis in patients with coexisting mitral regurgitation: improvement with milrinone. *Anesth Analg*. 2005;101:2–8.
63. Feneck RO, Sherry KM, Withington PS, Odoro-Dominah A. Comparison of the hemodynamic effects of milrinone with dobutamine in patients after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2001;15:306–315.
64. Byrne JG, Leacche M, Paul S, Mihaljevic T, Rawn JD, Sherman SK, Mudge GH, Stevenson LW. Risk factors and outcomes for “vasoplegia syndrome” following cardiac transplantation. *Eur J Cardiothorac Surg*. 2004;25:327–332.
65. Argenziano M, Chen JM, Choudhri AF, Cullinane S, Garfein E, Weinberg AD, Smith CR Jr, Rose EA, Landry DW, Oz MC. Management of the hemodynamic effects of milrinone with dobutamine in predisposing factors and use of a novel pressor agent. *J Thorac Cardiovasc Surg*. 1998;116:973–980.
66. Ozal E, Kuralay E, Yildirim V, Kilic S, Bolcal C, Kucukarslan N, Gunay C, Demirkilic U, Tatar H. Preoperative methylene blue administration in patients at high risk for vasoplegic syndrome during cardiac surgery. *Ann Thorac Surg*. 2005;79:1615–1619.
67. Morales DL, Garrido MJ, Madigan JD, Helman DN, Faber J, Williams MR, Landry DW, Oz MC. A double-blind randomized trial: prophylactic vasopressin reduces hypotension after cardiopulmonary bypass. *Ann Thorac Surg*. 2003;75:926–930.
68. Dell’Italia LJ. Reperfusion for right ventricular infarction. *N Engl J Med*. 1998;338:978–980.
69. Calvin JE Jr. Acute right heart failure: pathophysiology, recognition, and pharmacological management. *J Cardiothorac Vasc Anesth*. 1991;5: 507–513.
70. Goldstein JA. Pathophysiology and management of right heart ischemia. *J Am Coll Cardiol*. 2002;40:841–853.
71. Ferrario M, Poli A, Previtali M, Lanzarini L, Fetiveau R, Diotallevi P, Mussini A, Montemartini C. Hemodynamics of volume loading compared with dobutamine in severe right ventricular infarction. *Am J Cardiol*. 1994;74:329–333.
72. Marquez MF, Salica G, Hermsillo AG, Pastelin G, Cardenas M. Drug therapy in Brugada syndrome. *Curr Drug Targets Cardiovasc Haematol Disord*. 2005;5:409–417.
73. Summerhill EM, Baram M. Principles of pulmonary artery catheterization in the critically ill. *Lung*. 2005;183:209–219.
74. Shah MR, Hasselblad V, Stevenson LW, Binanay C, O’Connor CM, Sopko G, Califf RM. Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. *JAMA*. 2005;294: 1664–1670.
75. Binanay C, Califf RM, Hasselblad V, O’Connor CM, Shah MR, Sopko G, Stevenson LW, Francis GS, Leier CV, Miller LW. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA*. 2005;294:1625–1633.
76. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med*. 1994;330:1717–1722.
77. Alexander JH, Reynolds HR, Stebbins AL, Dzavik V, Harrington RA, Van de Werf F, Hochman JS. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: the TRIUMPH randomized controlled trial. *JAMA*. 2007;297:1657–1666.
78. Dzavik V, Cotter G, Reynolds HR, Alexander JH, Ramanathan K, Stebbins AL, Hathaway D, Farkouh ME, Ohman EM, Baran DA, Prondzinsky R, Panza JA, Cantor WJ, Vered Z, Buller CE, Kleiman NS, Webb JG, Holmes DR, Parrillo JE, Hazen SL, Gross SS, Harrington RA, Hochman JS. Effect of nitric oxide synthase inhibition on haemodynamics and outcome of patients with persistent cardiogenic shock complicating acute myocardial infarction: a phase II dose-ranging study. *Eur Heart J*. 2007;28:1109–1116.

KEY WORDS: drugs ■ heart failure ■ inotropic agents ■ shock ■ vasopressin