Review and update on inotropes and vasopressors: Evidence-based use in cardiovascular diseases

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Patients in the intensive care unit frequently develop low-output syndromes due to cardiac dysfunction, myocardial injury and activation of inflammatory cascades. Pharmacological agents, including vasodilators, inotropes and vasopressors, are frequently used in the critical care setting for the management of unstable cardiac patients. These medications are used to elicit varying effects on vascular resistance, myocardial contractility and heart rate to achieve desired hemodynamic and clinical end points. Conventional inotropic agents appear to be useful in restoring hemodynamic parameters and improving peripheral organ perfusion, but they can increase short-term and long-term mortality in these patients. Novel inotropes may be promising in the management of cardiogenic shock patients without serious adverse effects. The present review summarizes the current knowledge about the pathophysiology and evidence-based use of conventional and novel inotropic agents in various clinical scenarios associated with cardiovascular diseases.

Key Words: *Heart failure; Inotrope; Vasopressor*

Shock is a state of inadequate perfusion in which oxygen delivery to the tissues fails to meet oxygen demands. This serious clinical entity may be a result of several clinical pathologies. Shock state may emerge from a reduction in oxygen delivery to tissues, or an increase in oxygen demands (1). Global oxygen delivery is determined by the oxygen content of the arterial blood and the body's ability to circulate this oxygen-rich blood throughout the body. Cardiac patients are vulnerable to impaired cardiac output (CO) and peripheral tissue hypoperfusion. Theoretically, inotropic agents can improve hemodynamic parameters by increasing CO, and reducing left and right ventricular filling pressures. Therefore, inotropes are indicated for the treatment of all cardiac patients with clinical conditions characterized by peripheral hypoperfusion and fluid retention resulting from impaired cardiac contractility. Although these agents benefit cardiac patients by improving CO, they have been also associated with arrhythmogenesis, increased myocardial oxygen demands, myocardial ischemia and damage (2).

Hemodynamic instability is a common cause of morbidity and mortality in cardiac patients. In clinical practice, hemodynamic instability is routinely defined as a systolic blood pressure <90 mm Hg. However, when considering hemodynamic instability, clinicians should be more concerned with organ hypoperfusion rather than a fixed blood pressure. In most patients with hemodynamic instability, administration of intravenous fluids is initially used as an attempt to improve hemodynamics. This may not alleviate the hemodynamic instability completely in some cases and, in these instances, the use of vasoactive medications, including vasopressors and/or inotropes, is warranted.

The choice of which vasoactive medication to use will depend on the etiology of the hemodynamic instability. Patients with hemodynamic instability resulting from distributive shock typically present with decreased systemic vascular resistance (SVR), leading to a decrease in blood pressure. Distributive shock is noted in patients with sepsis or those in anaphylactic shock. In these patients, pharmacological agents to increase SVR, such as vasopressors, are often used (3). Unlike patients with distributive shock, those with cardiogenic shock have markedly decreased CO, resulting in hemodynamic instability. Patients with heart failure typically are most prone to developing cardiogenic shock when they decompensate. Strategies to improve hemodynamics include the use of pharmacological agents, such as inotropes, to increase cardiac contractility and CO (4).

Inotropes and vasopressors increase myocardial contractility and modify vascular tone through the activation of adrenergic pathways. The effects vary depending on the interaction with the specific receptors in the myocardium and the vascular smooth muscle. Table 1 provides a summary of locations and responses of common adrenergic reseptors. β1-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. β2-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. Activation of α1-adrenergic receptors on arterial vascular smooth muscle cells results in smooth muscle contraction and an increase in SVR. Finally, stimulation of D1 dopaminergic receptors in the kidney and splanchnic vasculature results in renal and mesenteric vasodilation through activation of complex second messenger systems. Regarding mechanisms of action, all inotropes improve cardiac contractility through different pathways. In most cases, these agents increase intracellular cyclic adenylate monophosphate (cAMP) levels, which in turn induce an augmentation in calcium release from the sarcoplasmatic reticulum and, hence, enhance the contractile force generation by the contractile apparatus (5). A thorough understanding of the relative differences between the receptor profiles of inotropes can help clinicians decide which agent is best in specific situations. The actions and hemodynamic effects of various inotropes and vasopressors are summarized in Table 2.

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TABLE 1
Summary of locations and responses of common adrenergic receptors

Receptor	Location	Response to stimulation
β1	Heart	Positive inotropic effect
β2	Vascular and bronchial smooth muscle	Vasodilation, bronchodilation
α1	Heart, vascular smooth muscle	Positive inotropy, vasoconstriction
α2	Vascular smooth muscle	Vasoconstriction
D1	Renovascular smooth muscle	Renal vasodilation
V1	Vascular smooth muscle	Vasoconstriction
V2	Renal collecting ducts	Antidiuresis

CATECHOLAMINES

A large group of endogenous and synthetic catecholamines have been described in the fields of pharmacology and physiology since the initial discovery of epinephrine as the principal active substance from the adrenal gland. The catecholamines or sympathomimetic agents all act on receptors of the sympathetic nervous system. Stimulation of the β1 receptor in the heart results in positive inotropic (increase in contractility), chronotropic (increase in heart rate), and dromotropic (increase in conduction of impulse) effects. Stimulation of β2 receptors results in smooth muscle relaxation including arterioles, which can result in vasodilation and a decrease in SVR. Stimulation of α receptors results in vasoconstriction and an increase in SVR and blood pressure (5).

Dopamine, an endogenous central neurotransmitter, is the immediate precursor to norepinephrine and epinephrine in the synthetic pathway of catecholamines. When administered therapeutically, it acts on dopaminergic and adrenergic receptors. Dopamine produces dose-dependent hemodynamic effects. At low doses (<3 μg/kg/min), stimulation of dopaminergic D1 receptors concentrated in the coronary, renal, mesenteric, and cerebral beds promotes vasodilation and increased blood flow to these tissues (6). Dopamine also has direct natriuretic effects through its action on renal tubules (7). The clinical significance of 'renal-dose' dopamine is somewhat controversial. Low doses of dopamine cause vasodilation, and an increase in renal blood flow in healthy volunteers, which leads to an increase in urine output. However, there are no well-designed studies, especially in critically ill patients, that demonstrate benefits such as renal protection or improved mortality. The Renal Optimization Strategies Evaluation (ROSE) study demonstrated that low-dose dopamine in patients with acutely decompensated heart failure did not result in reduced incidence of renal dysfunction or other clinical outcomes compared with nesiritide or placebo (8). In addition, some studies have demonstrated harm, due to arrhythmias such as postoperative atrial fibrillation after cardiac surgery (9). As the dose is increased, at intermediate doses (3 μg/kg/min to 5 μg/kg/min), dopamine predominantly stimulates the β1 and β2 receptors causing positive chronotropic and inotropic effects. At higher doses (5 mg/kg/min to 15 mg/kg/min), α-adrenergic stimulation occurs, with peripheral arterial and venous constriction (6).

Dobutamine is a synthetic catecholamine with potent inotropic and modest vasodilatory properties. Its pharmacological effects are mediated primarily through β1 (inotropy) and β2 receptor (vasodilatory) stimulation. Dobutamine produces a dose-dependent increase in myocardial contractility and reduction in cardiac filling pressures. Despite increases in CO, blood pressure may be reduced or unchanged because of reduction in SVR through β2 receptor-mediated vasodilation (10). In comparison with other inotropes, such as dopamine, dobutamine produces a strong inotropic response without a significant increase in heart rate. The favourable inotropic and vasodilatory effects of dobutamine make it a preferred agent for the management of low-output states including acute decompensated heart failure (ADHF) and cardiogenic shock. The usual dose range of dobutamine is 5 μg/kg/min to 20 μg/kg/min given as a continuous IV infusion. After 72 h of infusion, however, tachyphylaxis may develop due to β receptor downregulation. Despite its mild chronotropic effects at low to medium doses, dobutamine significantly increases myocardial oxygen consumption, which can precipitate and accelerate tachyarrhythmias, worsen myocardial ischemia and increase mortality (10). This exercise-mimicking phenomenon is the basis on which dobutamine may be used as a pharmacological stress agent for diagnostic perfusion imaging. Doses >20 μg/kg/min are generally not advised because of an increased risk for hypotension and tachycardia, which can worsen myocardial ischemia. Dobutamine remains a cornerstone of therapy for low-output states with elevated cardiac filling pressures including ADHF and cardiogenic shock. For acute management of these patients, the clinical outcomes of dobutamine appear to be comparable with milrinone (11).

Norepinephrine, the major endogenous neurotransmitter liberated by postganglionic adrenergic nerves, is a potent α1-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. Coronary flow is increased due 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). The recommended starting dose is from 0.01 mg/kg/min to 0.03 mg/kg/min; maximum suggested dose is 0.1 mg/kg/min (14). Norepinephrine is considered a first-line drug in the management of hypotension related to sepsis. The use of norepinephrine was strongly related to a favourable outcome in a prospective, observational study enrolling 97 adult patients with septic shock. Patients treated with norepinephrine had significantly lower hospital mortality rates (62% versus 82%; P<0.001) than those who did not have norepinephrine as part of their hemodynamic support regimen (15).

Epinephrine is a nonspecific α and β adrenergic agonist. β-Adrenergic effects are more pronounced at low doses and α1-adrenergic effects at higher doses. Clinical effects include an increase in CO and profound peripheral vasoconstriction. Its use results in the elevation of systemic blood pressure through positive inotropic effect, positive chronotropic effect and vasoconstriction in the cutaneous and renal vascular beds. The recommended starting dose is 0.01 mg/kg/min to 0.03 mg/kg/min; maximum suggested doses are 0.1 mg/kg/min to 0.3 mg/kg/min (14). Because epinephrine increases myocardial oxygen consumption, it is rarely used for the management of acute decompensated heart failure. Epinephrine should not be considered as the initial vasopressor for the management of hypotension in septic shock because of side effects such as impaired gastric blood flow and increased lactate levels (16). Use of epinephrine in this setting should be reserved for extreme cases of cardiovascular collapse if other catecholamines fail. Epinephrine is commonly used after cardiac surgery to overcome myocardial stunning and raise systemic blood pressure.

Phenylephrine with a potent α-adrenergic activity and virtually no affinity for β-adrenergic receptors increases peripheral vascular resistance and blood pressure. The elevation in blood pressure stimulates baroreceptors with activation of the vagal reflex with significant bradycardia. Because of the decreased heart rate, the cardiac output also decreases. Due to its negative effect on cardiac output, utilization in cardiogenic shock is rare and it is more frequently utilized for vasodilatory shock. The recommended dose is 40 mg/min to 60 mg/min (17). It is used primarily as a rapid bolus for immediate correction of sudden severe hypotension. It can be used to raise mean arterial pressure 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.

TABLE 2
Summary of mechanisms of action, therapeutic dose and hemodynamic effects of various inotropes and vasopressors

Inotropic agent	Mechanism/receptor	Therapeutic dose	BP	HR	CO	SVR
Dopamine (low dose)	D1	<3 µg/kg/min	0	0	0	0
Dopamine (medium dose)	β	3–10 µg/kg/min	↑↑	↑	↑↑	0/↓
Dopamine (high dose)	α	10–20 µg/kg/min	↑↑	↑↑	↑	↑↑
Dobutamine	β1> β2>α	5–20 µg/kg/min	↓	↑	↑↑	↓
Epinephrine	β1=β2>α	0.01–0.03 µg/kg/min	↑	↑	↑↑↑	↓
Norepinephrine	β1>α>β2	0.01–0.03 µg/kg/min	↑↑	0/↑	0	↑↑
Phenilephrine	α1	40–60 µg/min	↑↑	↓	↓	↑
Vasopressin	V1	0.01–0.04 ünits/min	↑↑	0	0	↑↑
Milrinone	PDE-3 inhibition	0.375–0.75 µg/kg/min	↓↓	↑	↑↑	↓↓
Levosimendan	Calcium-sensitizing effect	0.05–0.2 µg/kg/min	0	0	↑↑	↓↓

↑ Increase; ↓ Decrease; BP Blood pressure; HR Heart rate; CO Cardiac output; SVR Systemic vascular resistance

Isoproterenol is a potent, nonselective, synthetic β-adrenergic agonist with very low affinity for α-adrenergic receptors. It has powerful chronotropic and inotropic properties, with potent systemic and mild pulmonary vasodilatory effects. The recommended dose is 2 µg/min to 10 µg/min. It is mainly used for treatment of bradiarrhythmias (5).

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. These agents are potent inotropes and vasodilators and also improve diastolic relaxation (lusitropy), thus reducing preload, afterload and SVR.

Milrinone is a phosphodiesterase-3 inhibitor that prevents the degradation of cAMP. In patients with heart failure, milrinone increases heart rate, stroke volume and cardiac output. It is also likely to decrease mean arterial pressures, SVR and left ventricular filling pressures (10). Unlike other catecholamines, the effects of milrinone are independent of β-adrenergic receptors, a result of bypassing the receptor complex. Therefore, tachyphylaxis due to β receptor downregulation is not a clinical concern. Milrinone has shown a greater vasodilatory effect than dobutamine, as demonstrated by further reductions in mean pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP) and SVR. In fact, dobutamine may need to be combined with nitroprusside to exert a similar degree of vasodilation (11). On the other hand, dobutamine may increase CO to a greater extent than milrinone, but at the expense of greater increases in heart rate and myocardial oxygen consumption. Milrinone increases myocardial oxygen consumption, but to a lesser degree than dobutamine (18).

Milrinone may be administered as an intravenous loading dose of 50 µg/kg over 10 min, followed by a continuous infusion of 0.25 µg/kg to 0.75 µg/kg per minute. Lower doses should be initiated for patients with renal failure due to reduced milrinone elimination in these patients. Because bolus administration may exacerbate hypotension, many clinicians have initiated milrinone without the loading dose, particularly when a rapid effect is not required (19).

Although milrinone improves hemodynamics acutely, there are concerns regarding its safety as far as longer-term outcomes. In a prospective trial randomising milrinone versus placebo in 951 patients with decompensated heart failure, there was no significant difference in the primary endpoint of cumulative days of hospitalisation; however, there was a nonsignificant increase in in-hospital mortality in the milrinone group versus the placebo group (3.8% versus 2.3%; P=0.19). There were also more adverse events in the milrinone group compared with placebo, including new atrial fibrillation or flutter, and sustained hypotension (20).

Despite the potentially more favourable hemodynamic profile of milrinone compared with dobutamine, clinical outcomes between the two agents have not differed. In a large retrospective comparative study of these agents for advanced heart failure, no differences in hospital mortality or hospital complications were observed (11). The OPTIME-CHF study found that routine use of milrinone for patients with ADHF did not decrease days of hospitalization compared with placebo, but did result in a significant increase in adverse events related to hypotension and atrial arrhythmias (21). The results of this trial reinforce the role of milrinone as an alternative inotropic strategy for patients with ADHF. An important consideration for use of milrinone over dobutamine in ADHF, however, is for patients admitted on β-blocker therapy. The use of a β agonist with a β-blocker would be largely counterproductive.

Amrinone is an other phosphodiesterase-3 inhibitor that is used less often because of important side effects, which include dose-related thrombocytopenia.

VASOPRESSIN

Vasopressin, also known as antidiuretic hormone, is stored primarily in granules in the posterior pituitary gland and is released after increased plasma osmolality or hypotension. It exerts its circulatory effects through V1 (V1a in vascular smooth muscle, V1b in the pituitary gland) and V2 receptors (renal collecting duct system). V1a receptor stimulation mediates constriction of vascular smooth muscle, whereas V2 receptors mediate water reabsorption by enhancing renal collecting duct permeability. In many settings, vasopressin acts as a vasoconstrictor; however, low concentrations in pulmonary vessels activate V1 receptors and cause nitric oxide release and vasodilation. A relative vasopressin deficiency has been described in the setting of septic shock (22); thus, it is most commonly used in the context of vasodilatory septic shock, in which it has been best studied (23).

CALCIUM-SENSITIZING AGENTS

Calcium sensitizers are a recently developed class of inotropic agents. 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. The opening of K^+ channels on vascular smooth muscle leads to arteriolar and venous vasodilation (24). The combination of improved contractile performance and vasodilation is particularly beneficial during acute and chronic heart failure states, for which they have been used with increasing frequency in the last decade (25).

Levosimendan is a calcium-sensitizing agent that binds to cardiac troponin C in a calcium-dependent manner and also has a vasodilatory effect in the vascular smooth muscle. Several trials have evaluated the effects of levosimendan in severe ADHF. The recommended dose is 0.05 mg/kg/min to 0.2 mg/kg/min, but levosimendan is not recommended in patients with systolic blood pressure <90 mmHg (26). The SURVIVE trial compared levosimendan with dobutamine

in 1327 patients with decompensated heart failure. After 180 days, there was no difference in all-cause mortality (27). In another randomized trial, levosimendan was compared with placebo in 600 patients and the levosimendan group had improved symptoms, lower serum B-type natriuretic peptide levels and shorter length of hospital stay compared with the placebo group. However, at 90 days after randomization, patients assigned to levosimendan experienced more hypotension, cardiac arrhythmias and higher mortality (28).

Levosimendan may be administered as a 6 mg/kg to 24 mg/kg loading dose delivered in 10 min followed by a 24 h infusion at 0.05 mg/kg/min to 0.2 mg/kg/min. Hovewer, the results of recent clinical studies and the experience of many users suggest omission of the loading dose, especially in the context of a low blood pressure before start of the infusion. Also, the dose should be reduced in patients with severe renal insufficiency because the half-life of the levosimendan metabolites is prolonged (29).

NEW INOTROPIC AGENTS AND FUTURE DIRECTIONS

Unfortunately, current inotropic drugs have consistently failed to show beneficial effects beyond short-term hemodynamic improvement in patients with heart failure. To address these limitations, new agents targeting novel mechanisms are being developed including sodium-potassium-ATPase inhibitors, sarcoplasmic reticulum calcium pump (SERCA) stimulators, cardiac myosin activators, nitroxyl donors, ryanodine receptor stabilizers, metabolic energy modulators and gene therapies.

Istaroxime has been developed as a nonglycoside inhibitor of the sodium-potassium-ATPase with additional stimulatory effects on the SERCA, and has shown lusitropic and inotropic properties in experimental and early clinical studies. Inhibition of sodium-potassium ATPase increases intracellular sodium, which reduces the driving force for the sodium-calcium exchanger, decreasing calcium elimination outside the cell. The HORIZON trial (30) evaluated the hemodynamic, echocardiographic and neurohormonal effects of intravenous istaroxime in 120 patients hospitalized with heart failure and reduced ejection fraction. In this randomized, double-blinded, placebo-controlled, dose-escalating study, three doses of istaroxime or a placebo were given as intravenous infusions to patients with a history of heart failure and a PCWP of 20 mmHg. A reduction in PCWP was the primary endpoint, which was attained in all three dose groups during the entire observation period. There was an increase in systolic blood pressure and a transient increase in cardiac index with the highest dose, and a decrease in heart rate and diastolic and systolic volume, without a change in ejection fraction. Thus, the hemodynamic profile of istaroxime reflects inotropic and lusitropic effects without any indication of vasodilatory properties. The limitation of this study is related to the fact that the included patients presented with milder forms of acute heart failure, not requiring inotropic interventions according to current guidelines.

Omecamtiv mecarbil is a cardiac myosin activator which represent a new class of compounds, which directly influence the cross-bridge cycle. These molecules accelerate the rate of actin-dependent phosphate release of the weakly bound acto-myosin cross-bridge. As a consequence, more cross-bridges enter the force-producing state, more cross-bridges are activated per unit of time, and contractile force increases. Omecamtiv mecarbil has advanced into clinical studies. The first-in-human study assessed the effect of omecamtiv mecarbil in ascending dose cohorts of healthy volunteers (n=34) and demonstrated dose- and concentration-dependent increases in the left ventricle systolic ejection time, stroke volume, fractional shortening and ejection fraction (31).

ADVERSE REACTIONS TO INOTROPES AND VASOPRESSORS

Myocardial ischemia

Determinates of myocardial oxygen consumption include heart rate, ventricular wall tension and contractility. Beta-agonists and PDIs can increase myocardial oxygen demand as a result of increased heart rate and contractility. Alpha-agonists and vasopressin can increase myocardial oxygen consumption by increasing vascular resistance and systolic blood pressure, thus increasing ventricular wall tension. Vasoconstrictors can also cause vasoconstriction of coronary vessels and decreased myocardial oxygen supply. In addition, PDIs may cause a reflex tachycardia that can induce myocardial ischemia. Therefore, patients receiving any of these agents should be monitored for signs of myocardial ischemia.

Arrhythmia

Sympathomimetic amines that stimulate the β-receptors, such as dobutamine and isoproterenol, can directly cause atrial and ventricular tachyarrythmias, and pure alpha agents, such as phenylephrine, will cause a reflex bradycardia secondary to an increase in blood pressure.

Metabolic effects

Sympathomimetic amines can increase serum glucose levels due to increased glycolysis and gluconeogensis. β2-agonists, such as isoproterenol and dobutamine, can decrease serum potassium levels, which may also induce arrhythmias. Therefore, serum potassium and glucose levels should also be monitored. In addition catecholamines may cause nausea, tremors, restlessness, and even confusion and psychosis as a result of central nervous system stimulation.

Decreased splanchnic blood flow

Excessive vasoconstriction caused by vasopressors may decrease blood flow to vital organs including kidneys and the gastrointestinal tract. Theoretically, these effects may have several adverse consequences, including acute renal failure, gastrointestinal tract ischemia or necrosis, which can cause translocation of bacteria from the gastrointestinal tract into the blood stream.

Hematological effects

Sympathomimetic amines can cause an increase in white blood cell counts as a result of stress response. Amrinone, which is a PDI, may cause dose-related thrombocytopenia.

Tissue ischemia and necrosis

All vasoconstrictors can cause severe tissue necrosis if they extravasate. Therefore, vasopressors should be administered via a central line when possible. For α-agonists, such as norepinephrine, phenylephrine and dopamine, tissue necrosis from extravasation may be prevented by injecting the α-blocker phentolamine subcutaneously into the area of infiltrate. Vasoconstrictors can also induce peripheral ischemia due to the decrease in blood flow, especially in patients with peripheral vascular disease.

EVIDENCE-BASED INOTROPE USE IN DIFFERENT CARDIOVASCULAR SCENARIOS

Cardiogenic shock due to acute myocardial infarction

Cardiogenic shock is a clinical state of organ hypoperfusion due to cardiac failure. The definition of cardiogenic shock is based on hemodynamic parameters, such as systolic blood pressure (SBP) <90 mmHg or mean arterial pressure (MAP) 30 mmHg lower than baseline, severe reduction in cardiac index <1.8 L/min/m^2 and adequate left ventricular filling pressures (left ventricular end-diastolic pressure >20 mmHg) (32). The incidence of cardiogenic shock is approximately 7% (5% to 8%) in ST-elevation myocardial infarction and 2.5% in non-ST-elevation myocardial infarction patients (33).

Although left ventricular dysfunction is the primary reason, it is now accepted that systematic inflammatory response syndrome, neurohormones, inflammatory and apoptotic mediators and tissue microcirculation may contribute to the pathogenesis of cardiogenic shock (34). Despite early vascularization, mortality rates due to cardiogenic shock remain >50% in most studies (35). According to the GUSTO-I trial, 30-day survivors of cardiogenic shock have a similar prognosis to

that of patients with MI uncomplicated with shock (36). This finding underlines the importance of reperfusion, mechanical and pharmacological support in the acute phase.

Pharmacological support in cardiogenic shock includes inotropes and vasopressors. These agents are used in the early stabilization of patients with cardiogenic shock to increase cardiac output and MAP and decrease PCWP. Despite their hemodynamic benefits, inotropes increase oxygen demand in a failing heart with limited supply and, therefore, may provoke arrhythmias and lead to necrosis (37). Thus, the lowest doses of inotropes should be used in cardiogenic shock patients.

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of hypotension complicating acute myocardial infarction (AMI) suggest the use of dobutamine as a first-line agent if systolic blood pressure ranges between 70 mmHg and 100 mmHg 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. 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 mmHg, the use of norepinephrine has been recommended (38). Combined therapy with both dopamine and dobutamine, at doses of 7.5 μg/kg/min each, was shown to improve hemodynamic profile with fewer side effects compared with each agent alone at 15 μg/kg/min. Moderate doses of these agents maximize inotropy and avoid excessive α1-adrenergic stimulation that can result in end-organ ischemia (39).

During early shock, endogenous vasopressin levels are elevated significantly to help maintain end-organ perfusion (40). 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. Vasopressin therapy may thus be effective in norepinephrine-resistant vasodilatory shock. 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 PCWP (41).

Observational studies have shown that levosimendan, compared with dobutamine, improved LV hemodynamic function in patients with cardiogenic shock, especially in patients with cardiogenic shock after percutaneous coronary intervention (42,43). However, additional large, randomized trials with long-term outcomes are needed to establish the use of levosimendan in cardiogenic shock. PDE inhibitors have been shown to increase cardiac index, but there are no data supporting superiority of these agents in comparison with catecholamines in patients with cardiogenic shock.

Acute decompensated heart failure

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 renin-angiotensin-aldosterone system. In this setting, reversal of systemic vasoconstriction is often achieved through the use of vasodilators and inotropes with peripheral vasodilatory properties to improve hemodynamic parameters and clinical symptoms.

The use of positive inotropes in chronic HF has been consistently demonstrated to increase mortality (44). As a result, the ACC/AHA guidelines for diagnosis and management of chronic HF in adults 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) (45). The European Society of Cardiology acute heart failure guideline points out that in an appropriate clinical setting of hypotension and peripheral hypoperfusion, particular agents may be indicated with slightly different levels of recommendation (dobutamine and levosimendan, class IIa; PDIs and dopamine, class IIb) (46).

PDIs, such as milrinone, cause 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 demonstrated similar clinical outcomes in decompensated heart failure patients (18).

Several major clinical trials have evaluated the safety and efficacy of levosimendan in HF syndromes. The RUSSLAN (Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure Due to an Acute Myocardial Infarct) and LIDO (Levosimendan Infusion versus Dobutamine) studies demonstrated a mortality benefit in heart failure patients given levosimendan versus placebo or dobutamin respectively (47,48). However, in larger multicentre randomized trials in the setting of acute decompensated heart failure (REVIVE II [Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy] and SURVIVE [Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support]) levosimendan use significantly improved symptoms but not survival (49,50).

Septic shock

Septic shock is characterized by organ hypoperfusion due to systemic inflammatory response to infection. Severe sepsis and septic shock are among the most important causes of morbidity and mortality in patients admitted to the ICU. Despite hemodynamic measurements showing increased cardiac output, variable degrees of left ventricular dysfunction have been observed in septic shock patients (51).

According to 2008 Surviving Sepsis Guidelines, noradrenaline and dopamine are recommended as first choice agents for the maintenance of MAP ≥65 mmHg. Dobutamine is indicated in states of low cardiac output despite fluid administration and inotropic therapy. Second-line agents, such as phenylephrine and vasopressin, may be used when adrenaline or dopamine fail to restore an adequate organ perfusion (52).

A systematic review of seven randomized trials that compared the action of inotropes in septic shock, published in 2004, was unable to determine superiority of a vasopressor agent (53). A study from the 1990s has shown improvement in hemodynamic parameters for patients with septic shock receiving noradrenaline versus dopamine (54). Investigators from the SOAP (Sepsis Occurrence in Acutely Ill Patients) study, a multicentre European observational study, reported higher ICU and hospital mortality rates with dopamine administration in a subgroup of patients with septic shock (55). A recent randomized trial tried to evaluate the choice of norepinephrine over dopamine as the first-line agent among patients with septic shock and did not reveal significant differences in the 28-day mortality rates (56).

Vasopressin, an endogenously released peptide hormone, is recommended for patients with severe septic shock as an adjunct to catecholamines, since a relative vasopressin deficiency is apparent in patients with sepsis (57). Evidence for the use of vasopressin in septic shock has been described in two small randomized trials that showed improvement in hemodynamic parameters and renal function in patients treated with vasopressin (58,59). However, recently completed VASST trial which was a multicentre, randomized double-blinded trial compared vasopressin with norepinephrine in sepsis and found no significant difference in 90-day mortality rate or rate of organ dysfunction (60).

Phenylephrine, a pure alpha-adrenergic agonist, may be useful when use of beta-adrenergic inotropes is restricted due to tachycardia or arrhythmia. A prospective randomized trial that compared phenylephrine with noradrenaline, as a first-line agent in septic shock, found no differences in terms of hemodynamic parameters and cardiopulmonary performance; however, larger randomized trials are needed regarding the use of phenylephrine in sepsis (61).

Cardiopulmonary arrest

Inotropic and vasopressor agents are a mainstay of resuscitation therapy during cardiopulmonary arrest. Epinephrine, with its potent vasopressor and inotropic properties, can rapidly increase diastolic blood pressure to facilitate coronary perfusion and help restore organized myocardial contractility (62). 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 (63). Repeated high-bolus doses (5 mg) appear to be no more effective than repeated standard doses (1 mg) at restoring circulation (64).

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 (65). Clinically, its use has been associated with a higher rate of short-term survival in patients experiencing out-of-hospital ventricular fibrillation (66). However, in a larger trial of 1186 patients with out-of-hospital cardiac arrest who were randomized to vasopressin versus epinephrine, only 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 (67).

Low CO syndrome after cardiac surgery

Pharmacological support may be necessary during and after weaning from cardiopulmonary bypass in patients who have developed a low CO syndrome. Causes of low CO syndrome include cardioplegia-induced myocardial dysfunction, precipitation of cardiac ischemia during aortic cross-clamping, reperfusion injury, activation of inflammatory and coagulation cascades. Pharmacological support therapy should be instituted promptly in addition to optimization of volume status, reduction of SVR with propofol infusion, temporary pacing and intraaortic 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 (68).

CONCLUSION

Inotropes and vasopressors play an essential role in the supportive care of a number of important cardiovascular diseases. Short-term use of inotropic agents is recommended for the alleviation of symptoms, restoration of peripheral organ perfusion and reduction of abnormal filling pressures in patients with low output syndromes. The use of inotropes in serious clinical conditions such as ADHF, post-AMI cardiogenic shock, postcardiac surgery low CO syndrome and septic shock may be beneficial at the lowest necessary doses but require more clinical data. New drugs with novel mechanisms of inotropic action may be more safe, but ongoing trials will confirm their safety and efficacy in daily clinical practice. A better understanding of the physiology and important adverse effects of these medications is necessary for clinicians to make appropriate decisions regarding when and which vasopressors or inotropes are indicated in specific situations.

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