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Inotropes and vasopressors

LENKO SARIC[1], IVANA PRKIC[1],NENAD KARANOVIC[1,2]

[1]Department of Anesthesiology, Reanimatology and Intensive Medicine, University Hospital Center Split, Split, Croatia
[2]University of Split, School of Medicine

Corresponding author:
Nenad Karanović
Department of Anesthesiology, Reanimatology and Intensive Medicine
University Hospital Center Split
Spinciceva 1, 21000 Split, Croatia
Phone: 091 51 77 880
e-mail: nenad.karanovic@gmail.com

ABSTRACT

Inotropic agents are used to increase myocardial contraction while vasopressors are used to increase vascular tone. They are often used for treatment of patients whose tissue perfusion is insufficient to meet metabolic requirements. Therefore, these agents are usually administered in intensive care units where continuous and invasive monitoring of cardiac function can be applied.
Inotropic agents can be divided into those that increase cAMP levels and those that do not. Adrenergic receptor agonists and phosphodiesterase inhibitors (PDEi) increase cAMP levels and are currently the mainstay of positive inotropic therapy. Levosimendan acts as calcium sensitizer and increases myocardial contraction force without increasing intracellular calcium levels. In addition to existing inotropic agents, new promising inotropes are being developed. These include sarcoplasmic reticulum calcium pump (istaroxime), cardiac myosin activators (omecamtivmecarbil), gene therapy, nitroxyl donors and ryanodine receptor stabilizers.
Current treatments of heart failure are aimed at prolonging survival and not just alleviating symptoms. This review provides a short description of the physiology of myocardial contraction and adrenergic receptors. We also provide a short description of commonly used inotropic agents and vasopressor drugs as well as a short review of agents that are expected are in use in the future.

Inotropes are agents used to increase myocardial contractility, while vasopressors are administered to increase vascular tone (1). Their use ismostly confined to critically ill patients whose hemodynamic impairment is such that tissue perfusion is insufficient to meet metabolic requirements (2). Patients in need of inotropic or vasopressor support are often presented with septic or cardiogenic shock and severe heart failure, and are victims of major trauma or undergoing major surgery.These drugs are therefore administered usually to patients treated in intensive care settings where continuous monitoring of cardiac rhythm, arterial oxygenation, urine output and other invasive hemodynamic monitoring can be applied.Inotropic and vasopressor drugs should be administered through a central venous catheter via infusion pumps that can deliver precise flow rates. These agents are mostly short acting with rapid onset and offset of action. Therefore, they can be used without an initial bolus and can be titrated frequently. Abrupt discontinuation should be avoided because of possible hypotension.

Key words: Inotropes, Vasopressor Agents, Intensive Care, Heart Failure

PHYSIOLOGY OF CONTRACTION

The contraction of cardiac muscle fibers is a result of interactions between actin and myosin filaments that form cross-bridge links. During depolarization of myocytes, voltage-gated calcium L-type channels open and intracellular concentration of Ca2+ increases. That also leads to further release of calcium ions from the sarcoplasmic reticulum. Calcium ions bind to troponin C that leads to conformational changes within myosin. Those changes expose actin-binding sites, allowing cross-bridge formation with myosin heads (1). At the end of contraction when repolarization occurs, calcium ions are pumped back into the sarcoplasmic reticulum and eliminated outside the cell by the sodium-calcium exchanger (NCX), allowing myocardial relaxation (3).
Inotropy depends upon the amount of calcium available to bind to troponin C, affinity of troponin C for calcium and alterations at the level of cross-bridge formation. Since one molecule of ATP is hydrolyzed during formation of one individual cross-bridge cycle, the most efficient way of increasing contractile strength would be prolongation of cross-bridge attachment time (4).
The most important regulation mechanism of basal contractile force is length-dependent activation of cross-bridges by increasing the length of individual sarcomere (Frank-Starling mechanism). This activation occurs without an increase of Ca2+. Other regulation mechanisms include frequency-dependent activation of contractile force and catecholamine-mediated inotropy (4).

ADRENERGIC RECEPTORS

Adrenergic receptors are classified into α-adrenoreceptors and β-adrenoreceptors. Both of those are further divided into subtypes (1, 5).
α1 receptors are mostly found in blood vessels and their activation is mainly responsible for vasoconstriction. Their presence has also been demonstrated in the myocardium where their activation results in a positive inotropic effect (6). α2 adrenoreceptors are mostly found on presynaptic neuron membranes and in the central nervous system, predominantly in

the cerebral cortex and medulla. Activation of these receptors results in inhibition of noradrenaline release and in a decrease in sympathetic tonus which leads to hypotension and bradycardia (6). Inotropy is provided predominantly by β adrenergic receptor mechanisms. β1 adrenoreceptors are the predominant adrenergic receptors in the heart and their activation results in a positive inotropic, chronotropic and lusitropic effect. Activation of β2 receptors leads to relaxation of smooth muscles in bronchial, gastrointestinal and uterine muscle, as well as vasodilation in skeletal muscle. β3-adrenergic receptors, which are located mainly in adipose tissue, are involved in the regulation of lipolysis and thermogenesis and do not play a role in hemodynamic stability (6). Other relevant receptors are dopaminergic receptors (DA) and vasopressin receptors. There are five types of DA which are divided into two groups, DA1 and DA2 receptors (1, 5, 7). Both groups are G-protein related receptors. Activation of DA1 receptors results in increased levels of intracellular cAMP, while activation of DA2 results in decreased levels of cAMP.DA1 receptors mediate renal, coronary, cerebral and mesenteric vasodilation (1, 7), while DA2 receptors are found in the central nervous system and may mediate nausea and vomiting (6).

Vasopressin type 1 receptors (V1) are found in vascular smooth muscle cells and platelets (1, 8). Their activation results in an increase in intracellular calcium levels, leading to vasoconstriction (8). Type 2 receptors (V2) are located in the renal medulla and have a role in regulation of water retention, while type 3 receptors (V3) are found in the pituitary gland and their role in heart failure is still unknown (8).

Adrenoreceptors α1, β1 and β2 are of importance for vasopressor and inotropic agents. Adrenergic receptors are coupled positively to adenylate cyclase and their activation leads to increase in intracellular cAMP levels and protein kinase A (PKA) activity. Increases of cAMP open Na+ channels, while PKA increases L-type Ca2+ channel activity and enhances sarcoplasmic reticulum Ca2+ uptake. Those are cellular mechanisms of chronotropy, dromotropy and lusitropy. Furthermore, increased sarcoplasmic reticulum Ca2+ content and L-type Ca2+ channel activation increases myocardial Ca2+ transients, resulting in greater contractile strength and inotropy (1).

INOTROPES

These agents can be divided into those that increase cAMP levels as their mechanisms of action and those that do not (9).

Drugs that exert their action by increasing cAMP levels are β-adrenoreceptor agonists and phosphodiesterase inhibitors (PDEi) (4). These agents are the mainstay of positive inotropic drug therapy (9). Their beneficial effect is a result of their ability to increase intracellular Ca2+ levels, which is also a mechanism of these agents' adverse effects (4).

β -receptor agonists increase intracellular cAMP levels in themyocardium, which leads to increased activation of PKA and increased myocardial contractility (as explained above). Most of the inotropic effect is mediated by β1 receptors. Since practically all adrenergic receptor agonists also have an effect on other adrenoreceptors, various effects on heart rate, rhythm and myocardial metabolism, as well as effect on peripheral vasculature can be expected (6). Disadvantages of these agents include increased myocardial oxygen consumption, tachycardia, arrhythmias, excessive peripheral vasoconstriction, coronary vasoconstriction and β receptor downregulation leading to decreased drug efficacy (1, 10).

PDEi increase levels of cAMP by inhibiting phosphodiesterase III, an enzyme responsible for degradation of cAMP. Their positive inotropic effects are independent of β1 adrenergic receptors. Therefore, since the number of β adrenoreceptors is reduced in patients with heart failure, PDEi are theoretically more effective in treatment of those patients (1, 11). PDEi also have unique vasodilatory actions independent of endothelial function or nitrovasodilators (12). Vasodilatory effect is present in arterial as well as in venous beds, leading to decreased mean arterial pressure (13). Increased cardiac output produced by PDEi is a result of positive inotropy and afterload reduction. Net effect is a decrease in myocardial wall tension, which is an important contrast with most sympathomimetic agents (11).

Inotropic agents that do not depend on cAMP form a diverse group of which the most important are cardiac glycosides and calcium sensitizers.Cardiac glycosides (digoxin) improve myocardial contractility by inhibiting Na+/K+ ATPase. That leads to reduced activity of the Na+/Ca2+ exchanger, thereby increasing intracellular levels of calcium (14). Their use today is limited to patients with atrial fibrillation to control ventricular rate. It has limited efficacy and a narrow margin of safety (15).

Calcium sensitizers increase contractile force without increasing intracellular calcium levels. Representative of this group of drugs is levosimendan.Levosimendan has a triple mechanism of action (16). It binds to troponin C which causes conformational changes leading to increased affinity of actin to myosin (17). Since it does not increase calcium levels, it does not impair diastolic function (4). Levosimendan also has an effect on ATP-K channels which leads to peripheral and coronary vasodilation (18, 19). The opening of ATP-K channels in cardiac mitochondria is believed to result in thecardioprotective effects of levosimendan such as preconditioning, postconditioning and anti-ischemic effects (16). All of these effects result in improved myocardial contractility without an increase in myocardial oxygen consumption. Furthermore, the effects of levosimendan are not diminished by β blockade (18).

COMMONLY USED INOTROPES AND VASOPRESSORS

Sympathomimetic agents

Sympathomimetic agents include dopamine, epinephrine, norepinephrine, dobutamine, isoproterenol, phenylephrine and ephedrine.

Dopamine is a precursor of norepinephrine. It has mixed direct and indirect effects. It acts on both adrenergic and dopaminergic receptors giving it a complex cardiovascular response profile (1). It has a direct effect on α adrenergic, β adrenergic and on dopaminergic receptors and it releases norepinephrine. It is rapidly metabolized by monoamine oxidase inhibitors (MAOi) and catechol-O-methyltransferase (COMT) and has a half-life of about 1 minute (6). It is administered as a continuous intravenous infusion without a loading dose. Its effect is dose dependent. At doses 0.5-0.2 μg/kg/min dopamine acts predominantly on dopaminergic (DA1) receptors and causes vasodilation of renal and mesenteric vasculature (6). It increases glomerular filtration rate and sodium excretion (17). With infusion rates of 2-10 μg/kg/min, dopamine stimulates β1 receptors, which leads to increased myocardial contractility and increased cardiac output.

At infusion rates greater than 5 μg/kg/min it stimulates release of endogenous norepinephrine from sympathetic nerve terminals in the myocardium and vasculature (10). At high doses (10-20 μg/kg/min) dopamine stimulates both α and β1 receptors. At these high doses α adrenergic effect predominates, resulting in generalized vasoconstriction and leading to an increase in mean arterial pressure and systemic vascular resistance. Renal blood flow decreases and urine output may decline (6). Because of its beneficial effect on renal perfusion and glomerular filtration, dopamine has long been used in patients with shock in order to preserve their renal function. Results of recent studies have called routine use of dopamine in those patients into question (20-22), and new guidelines suggest that low-dose dopamine should not be used as a renal protection strategy (23). Dopamine is frequently combined with other inotropic or vasodilator agents (17). In patients with cardiogenic shock higher doses of dopamine are used to increase systemic vascular resistance. When used in patients with acute decompensated heart failure, exacerbation of pulmonary edema can occur due to increased venous tone and pulmonary arterial pressure. In those cases venodilating agents may be added (17). It can also be useful to add dobutamine to augment the level of positive inotropic support (17). When used in treatment of patients with septic shock, dopamine can adversely affect splanchnic perfusion, and can also lead to splanchnic shunting, impairment of gastric mucosal oxygenation and increased risk of gastrointestinal bleeding (24). In patients with advanced heart failure inotropic responses to dopamine can be attenuated because of desensitization of β receptors (17). Adverse effects of dopamine include tachycardia, tachyarrhytmias and excessive vasoconstriction. In patients with ischemic heart disease increased myocardial oxygen consumption occurring with higher dopamine doses can result in myocardial ischemia (10).

Epinephrine is a potent agonist of all adrenoreceptors. Its effects are manifested as increase in inotropy, chronotropy and conduction in heart, smooth muscle relaxation in bronchial tree and vasoconstriction (6). It can be administered intravenously as a bolus or by a continuous infusion. As a bolus, epinephrine is usually administered in the states of cardiovascular collapse, asystole, ventricular fibrillation, electromechanical dissociation or anaphylactic shock. When used by a continuous infusion, rates of 1-2 μg/min should theoretically predominantly activate β2 receptors resulting in relaxation of bronchial smooth muscles. Infusion rate of 2-10 μg/min increases heart rate, contractility and myocardial conduction. Infusion rates greater than 10 μg/min results in generalized vasoconstriction. In some cases reflex bradycardia can be seen due to sudden and marked increase in blood pressure resulting from peripheral vasoconstriction (10). Because of its metabolic effects, prolonged infusions can lead to hyperglycemia and increased serum lactate levels which can be of clinical importance as lactate levels are used as a marker of tissue hypoperfusion in critically ill patients (1, 10). Continuous infusion of epinephrine may cause restlessness, tremor, headache and palpitations. It can also cause myocardial ischemia in patients with coronary artery disease. Epinephrine should be avoided if possible in patients taking β adrenergic antagonists because unopposed α adrenergic vasoconstriction may cause severe hypertension and cerebral hemorrhage (6). Other adverse effects include tachycardia, arrhythmias and oliguria from renal vasoconstriction (17).

Norepinephrineis vasopressor of choice in treatment of patients with sepsis (23, 25). It acts as agonist for α and β adrenoreceptors, but it is usually used for its potent α-adrenoreceptor agonism. It has short half-life of 2.5 minutes, which makes its administration via continuous infusion preferable (6). At infusion rates less than 2 μg/min β1 effects predominate, but norepinephrine is rarely used in these doses. Usual doses of greater than 3 μg/min cause peripheral vasoconstriction. It leads to increased arterial pressure and may cause reflex bradycardia. Pulmonary vascular resistance can also be increased so norepinephrine should be used with caution in patients with pulmonary hypertension. Cardiac output is usually unchanged or decreased, while oxygen consumption is increased (6). Norepinephrine also causes vasoconstriction of renal and mesenteric vasculature, which can lead to renal failure, mesenteric infarction and peripheral hypoperfusion (1). Despite the effect on renal perfusion, when norepinephrine is used to increase mean arterial pressure to more than 70 mmHg in sepsis, increased urine output and creatinine clearance rate usually occur after 24 hours (10). When PDEi are added to norepinephrine therapy, they attenuate arterial vasoconstrictive effects (10). Use of norepinephrine may be limited by arrhythmias, myocardial ischemia, renal impairment or tissue necrosis (17).

Dobutamine is a synthetic analog of dopamine (1). In contrast to dopamine, it has no effect on dopaminergic receptors and it does not release endogenous norepinephrine. At clinical doses it acts predominantly on β1 receptors (6). It is usually started with an initial dose of 2 μg/kg/min without a loading dose, and afterward it is titrated upward by 1-2 μg/kg/min every 15-30 minutes until unsatisfactory hemodynamic goal is achieved or until dose-limited events occur (17). Since its effect does not depend on norepinephrine stores it can be effective in patients with chronic heart failure. Nevertheless, in these patients its effectiveness can be hampered by downregulation of β receptors (6). Dobutamine is often used as first line agent for increasing cardiac output in patients with septic shock, but in this scenario it is usually combined with vasoconstrictors (1). As it increases myocardial oxygen demand, it can be used as a stressor in cardiac assessment (1). Theprimary adverse effect of dobutamine is tachycardia, but it is not often seen with doses lower than 20 μg/kg/min. Because of downregulation of β receptors, tolerance to its hemodynamic effects is significant after three days, necessitating an increase in the rate of infusion (6, 17). Chronic dobutamine infusions can lead to development of hypersensitivity myocarditis, which should be suspected if a patient develops worsening hemodynamics or peripheral eosinophilia (17).

Isoproterenolis a nonselective β adrenergic agonist with stronger β1 adrenergic effect (6). Because of β2 agonism, reduction in systemic and pulmonary vascular resistance occurs. It causes a fall in mean arterial and diastolic blood pressure while systolic pressure remains unchanged or rises modestly due to increased cardiac output (17). Its clinical use has declined over the years because of significant adverse effects such as tachycardia and arrhythmias. Today its primary use is as chronotropic agent in patients after heart transplantation. Those patients are unable to generate an endogenous sympathetic response because their sympathetic fibers are divided when their native heart is removed (6). It can also be useful in patients with torsades de pointes that is refractory to magnesium (17). Infusion rates start at 0.0075-0.1 mg/kg/min.

Its duration of action is somewhat longer than that of natural catecholamines (6). Isoproterenol can also, like other sympathomimetics, lead to ischemia due to increased myocardial oxygen consumption.

Dopexamine is a synthetic analog of dopamine that may be of use in patients with chronic heart failure. It has more potent effects on β2 and weaker effects on dopaminergic receptors than dopamine (6). It has no α adrenergic effects and almost no β1 adrenergic effects. Because of β2 agonism, dopexamine causes systemic vasodilation as well as indirect inotropic activity through inhibition of norepinephrine uptake. Stimulation of dopaminergic receptors produces selective vasodilation of renal and splanchnic blood vessels and increases glomerular filtration rate, diuresis and natriuresis (6). Combined inotropic, vasodilatory and diuretic effects are useful in patients with chronic heart failure. It is usually given in doses 1-6 μg/kg/min, but doses higher than 4 μg/kg/min cause tachycardia (6).

Ephedrine is anoncatecholaminedrug with mixed direct and indirect sympathomimetic effects. It enters nerve terminals where it displaces noradrenaline from vesicles and nerve terminals causing α adrenoreceptor effects (1). It increases blood pressure and has a positive inotropic effect. It is widely used as a vasopressor in hypotensive parturient patients as it does not have a significant effect on uterine blood flow (6). Due to its β1 adrenergic effects, it is useful in the treatment of moderate hypotension, particularly if it is associated with bradycardia. The usual dose is 2.5- 25 mg given intravenously, or 25-50 mg if given intramuscularly. Intravenous boluses can be repeated every 5 to 10 minutes. Total daily dose should not exceed 150 mg (6). Adverse effects include myocardial ischemia and excessive vasoconstriction.

Phenylephrine is selective α1 agonist. It is commonly used when cardiac output is adequate but peripheral vasoconstriction is needed, which is the case with hypotension accompanying spinal anesthesia or in patients with coronary artery disease or aortic stenosis when anincrease in coronary perfusion pressure is needed but with no chronotropic side effects (6). Due to vasoconstricitve effects, a reduction in renal and splanchnic blood flow can occur as well as reflex bradycardia (1). Phenylephrine has a fast onset and relatively short duration of action (5-10 min). It can be given by intravenous boluses of 40-100 μg or by continuous infusion at rate 0.05-1.5 μg/kg/min (6).

Vasopressin is an endogenous hormone released from the posterior pituitary in response to osmotic, chemoreceptor and baroreceptor stimuli. It causes vasoconstriction by activating V1 and oxytocin receptors in vascular smooth muscles (1, 8). Activation of those receptors is NO-dependent (1). Vasopressin can be used in patients with septic shock to reverse vasodilatation, but only in addition to norepinephrine (26). In addition, vasopressin may have positive effects when administered during cardio-pulmonary resuscitation (CPR) (27). However, due to insufficient evidence, its routine use during CPR is still not recommended (28). It is usually given in doses 0.01-0.04 U/min (23, 25). Adverse effects of vasopressin include end-organ ischemia, myocardial infarction and hyponatremia. Terlipressin is a synthetic analog of vasopressin with a longer duration of action. Compared to norepinephrine and vasopressin, it was associated with less rebound hypotension upon discontinuation of treatment (1). Adverse effect include hypertension, bradycardia and reduction in platelet count.

Phosphodiesterase inhibitors

As mentioned above, PDEi have positive inotropic as well as lusitropic effect. They are also potent systemic and pulmonary vasodilators (1). These agents are usually used for treatment of patients with heart failure characterized by low cardiac output, high filling pressures and elevated or normal systemic vascular resistance (17). They can also be useful in the treatment of patients with pulmonary hypertension. Positive inotropic effects of PDEi may be synergistic with those of sympathomimetics such as dobutamine (17).

Amrinone is the first PDEi used for treatment of heart failure and after cardiac surgery. It has half-life of around 3.5 hours (10). When administered, it is given as a continuous infusion at rates of 5-20 μg/kg/min. If used for a prolonged time, thrombocytopenia may occur (10). Amrinone has recently been mostly replaced by milrinone.

Milrinoneis an analog of amrinone and has inotropic activity that is almost 20 times more potent than that of amrinone (10). It is administered as a continuous infusion at rates of 0.375-0.75 μg/kg/min (17). In comparison with amrinone, milrinone has shorter context sensitive time and has no adverse effect on platelet function. It is mainly excreted unchanged in urine (10). It increases heart rate to a lesser extent than dobutamine despite a greater tendency to decrease systemic vascular resistance (1). Administration of milrinone may be limited in relatively volume-depleted patients due to its vasodilator effects (14, 17).

Enoximone is another PDEi. It is administered as a loading dose of 0.5-1 mg/kg followed by infusion of 5-10 μg/kg/min (10). It shows less inotropic and chronotropic effects, but more lusitropic effects when compared to milrinone (1). Enoximone is metabolized by saturable enzyme systems and has active metabolites that are renally excreted (1). It should be kept in mind that all of PDEi have prolonged half-lives in patients with renal failure, which is common among critically ill patients.

Calcium sensitizers

Levosimendan has positive inotropic, vasodilatory and anti-inflammatory effects. It exerts positive inotropic effects by increasing the affinity of myofilaments in cardiac myocites to calcium (16). Vasodilation is caused by decreasing the myofilaments sensitivity in smooth muscles to calcium and by activating ATP-dependent potassium channels which results in hyperpolarization, decreased Ca2+entry and vasodilation (16). These effects occur without an increase in intracellular cAMP or calcium (29, 30). Therefore, it does not impair diastolic relaxation and cardiac rhythm (1, 30). It has beneficial effects on myocardial energetics as its effects occur without an increase in myocardial oxygen consumption (30). Anti-inflammatory effects of levosimendan are manifested as areduction of circulating proinflammatory cytokines and reduction of mediators of apoptosis (31).

Since it does not act through adrenergic receptors, β blockade does not influence the hemodynamic effects of levosimendan(10). Although it is primarily used for treatment of patients with heart failure, there is growing evidence of its benefit in patients undergoing cardiac surgery (16, 32). In a recently published article, it is recommended that levosimendan be used in the preoperative setting in cardiac surgery (16). Applied preoperatively, it signifi-

cantly increases stroke volume and cardiac output and also decreases pulmonary capillary wedge pressure, mean arterial pressure, mean pulmonary artery pressure, mean right atrial pressure and total peripheral vascular resistance (16).

In addition to its use in the treatment of heart failure and cardiac surgery, there is growing evidence of beneficial effect when levosimendan is used in other settings. Although there is strong evidence of its renoprotective effect, there are still some conflicting results (31, 32). Furthermore, there is evidence that levosimendan reduces mortality in patients with severe sepsis and septic shock (33). However, a large clinical trial recently showed that levosimendan does not improve organ function nor does it lower mortality in patients with sepsis (34). Further studies are necessary and large clinical trials are currently being conducted in order to investigate the role of levosimendan in the treatment of severely ill patients other than those with heart failure and those undergoing cardiac surgery where the role of this drug is already well determined.

Levosimendan has a short elimination half-life, but its metabolite OR-1896, which has similar calcium-sensitizing effect as levosimendan, hasa much longer elimination half-life of around 96 hours (18, 29). It is administered as a continuous infusion, mostly without a loading dose, over 24-hours. After discontinuation of the 24-hour infusion, due to accumulation of its metabolite, hemodynamic effects last for up to 7 to 9 days (1). Effects of levosimendan are dose-dependent. It is administered at infusion rates of 0.05-0.6 μg/kg/min (14, 29). At rates higher than 0.2 μg/kg/min, there is a greater incidence of side effects such as headache, nausea and hypotension (30). In case of significant hypotension, use of norepinephrine or vasopressin is recommended (16). If additional inotropic support is necessary, dobutamine should be the inotrope of choice (16).

FUTURE DIRECTIONS

In addition to existing inotropic agents, new inotropes are being developed.

Istaroxime is a Na+/K+ ATPase inhibitor and activator of the sarcoplasmic reticulum calcium pump(14). Inhibition of Na+/K+ ATPase increases intracellular concentration of Na+ which reduces the driving force for the Na+/Ca2+ exchanger (4). Therefore, calcium elimination outside the cell is decreased. Moreover, increased intracellular Na+ may stimulate the Na+/Ca2+ exchanger to work in reverse mode resulting in increased intracellular Ca2+ concentration (4, 14). On the downside, increased Ca2+ concentration in the cytosol may be harmful in a failing heart, causing impaired diastolic relaxation and cardiac arrhythmias (4). Because istaroxime has an effect on the sarcoplasmic reticulum Ca2+ pump, it also stimulates Ca2+ uptake into the sarcoplasmic reticulum resulting in accelerated diastolic relaxation (14). Furthermore, istaroxime does not increase myocardial oxygen consumption (4). The overall effect of istaroxime is a positive inotropic and lusitropic effect, but with no vasodilatory properties (4).

Omecamtivmecarbil is a compound that acts as a cardiac myosin activator. Its effect is increase in contractile force due to more cross-bridges entering the force-producing state and more cross-bridges being activated per unit of time (14, 35). Myosin activators stimulate myosin ATPase and increase myocyte shortening without increasing intracellular calcium transients (14, 35). Improvements in cardiac function were not associated with increased myocardial oxygen consumption when tested on dogs (36). In human studies omecamtivmecarbil showed dose- and concentration-dependent increases in systolic ejection time, stroke volume and ejection fraction (37, 38). While the characteristic prolongation of systolic ejection time may be of concern, as long as relaxation is not prolonged and heart rate is not too high, this increased systolic ejection time should be well tolerated (4).

One of the possible inotropic interventions in the future could be gene therapy focused on increasing sarcoplasmic reticulum calcium pump activity. Most of the approaches are related to reduced sarcoplasmic reticulum calcium uptake and abnormal sarcoplasmic leak (4). Up-regulating SERCA2a (isoform of sarcoplasmic reticulum calcium ATPase) showed improvement in systolic and diastolic functions in different animal models of heart failure (14). Problems related to gene therapy include immunological reactions, duration of gene expression, control of gene expression and unknown toxic effects related to the vectors used to transfer a gene (4).

Nitroxyl (HNO) is gaseous signaling molecule very similar to nitric oxide (NO). HNO has unique signaling pathways and mechanisms of action independent of NO (4). In animal and in vitro studies, HNO showed potent arterio- and veno-dilating effects without tolerance or tachyphylaxis (30).Additional effects that were observed include inhibition of platelet aggregation and limiting vascular smooth muscle proliferation (4). Of more clinical importance is the potential positive inotropic and lusitropic effects observed in animal studies. These effects seem to be independent of cAMP and protein kinase A, and are a result of enhanced ryanodine receptor and SERCA2a activity (30, 39). Clinical utility of HNO is limited by poor pharmacological properties of available HNO donors (4, 30). Further clinical studies are currently being conducted.

Since calcium leak from sarcoplasmic reticulum through ryanodine receptors (RyRs) contributes significantly to abnormal calcium cycling in human heart failure, RyRs stabilizers have emerged as potential new inotropic agents (4). Calcium leak from the sarcoplasmic reticulum decreases SR calcium load and its availability for systolic contraction. Furthermore, it can lead to diastolic dysfunction as well as cardiac arrhythmias (4). Several agents that could influence RyRs are currently being evaluated (4, 40).

CONCLUSION

A variety of drugs are available for the treatment of hemodynamically unstable patients. The choice of medication depends on the hemodynamic disorder, understanding of drugs' mechanism of action, experience of the physician, and limitations to its use. Current treatments of heart failure are aimed to prolong survival, not just relief of symptoms. There are a number of new agents currently being developed and evaluated for clinical use. It is very important not to stop inotropic and vasopressor medications abruptly, but slowly, after step by step decrease in order to avoid complications.

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