Inotropes

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Gary S. Francis, MD, Jason A. Bartos, MD, PhD, Sirtaz Adatya, MD

Minneapolis, Minnesota

Inotropes have been fundamental to resuscitation of acute cardiogenic shock for decades. Heart failure and cardiogenic shock, in severe cases, are syndromes characterized in many patients by a reduction in myocardial contractile force. While inotropes successfully increase cardiac output, their use has been plagued by excessive mortality due to increased tachycardia and myocardial oxygen consumption leading to arrhythmia and myocardial ischemia. There is a pressing need for new inotropic agents that avoid these harmful effects. This review describes the mechanism of action and the clinical utility of some of the older inotropic agents, which are still commonly used, and provides an update for physicians on the development of newer inotropic drugs. The field is rapidly changing, and it is likely that new agents will be designed that improve systolic performance without necessarily increasing the myocardial oxygen consumption.   (J Am Coll Cardiol 2014;63:2069–78) © 2014 by the American College of Cardiology Foundation

Positive inotropic agents have been used to treat patients with heart failure since 1775 when Withering introduced foxglove into practice. Inotropic drugs may be strictly defined as therapies that enhance myocardial contractile performance independent of changes in heart rate and loading conditions. However, loading conditions and heart rate are highly variable in patients with heart failure; they are subject to change, and may be altered by some inotropic drugs. Many inotropic drugs increase heart rate, and some have direct or indirect vasodilator properties. Therefore, some of the improved systolic performance generated by inotropic agents may also be due to changes in loading conditions and heart rate inherent to many of these drugs.

Today, positive inotropic drugs are typically used to stabilize patients with acute decompensated heart failure in the intensive care unit, as a bridge to heart replacement therapy, or a bridge-to-decision. Intravenous positive inotropic drugs are indicated when patients with acute systolic heart failure exhibit signs or symptoms of end-organ dysfunction due to hypoperfusion (1). The use of positive inotropic drugs has been plagued by serious concerns regarding increased morbidity and mortality. Problems include increased arrhythmia, induced myocardial ischemia, and in some cases, hypotension (2–7). The largest database demonstrating increased mortality with inotropes is the ADHERE (Acute Decompensated Heart Failure National Registry), where

short-term inotropic therapy was associated with increased in-hospital mortality (8).

Despite clear evidence that inotropic therapy increases mortality, there are clinical settings where inotropic support with dopamine, dobutamine, milrinone, or norepinephrine may be life-saving measures. For example, short-term use of intravenous positive inotropic drugs may have a clear therapeutic role in patients hospitalized with acute systolic heart failure, where hypoperfusion of vital organs is obvious and the need for improved perfusion is immediate. Although temporary mechanical circulatory support devices (intra-aortic balloon pumps, extracorporeal membrane oxygenation, impella, and others) are now available to augment cardiac output and blood pressure, these short-term and less durable devices are reserved for special circumstances such as bridge-to-heart replacement therapy or bridge-to-decision (9). In some cases, such as in the setting of acute myocardial infarction, short-term, less durable devices are also implanted for temporary support while awaiting revascularization, but stabilization therapy often begins with intravenous inotropic agents.

Some patients require sustained inotropic support, as they cannot be weaned from drugs such as dobutamine or milrinone without experiencing hypoperfusion. Such patients are believed to be "inotrope-dependent" when repeated attempts to wean result in symptomatic hypotension, worsening symptoms, and/or progressive organ dysfunction (usually renal). Further use of inotropic agents should not be based on hemodynamic parameters alone but on clinical deterioration. Inotropic therapy is appropriate in hospitalized patients with evidence of end-organ hypoperfusion until resolution of the acute cause occurs and in situations requiring chronic critical support until definitive therapy such as heart transplantation, mechanical circulatory support,

or bridge-to-decision. For those patients who are not candidates for advanced heart replacement therapy, intravenous inotropes may also be considered as palliation at the end of life.

With this in mind, cardiologists should be familiar with the pharmacology of conventional positive inotropic agents and how the drugs' use might be applied under various circumstances. For example, patients with ischemic cardiomyopathy and decompensated heart failure who are experiencing ongoing angina or rhythm disturbances would be poor candidates for pharmacologic inotropic support. Such patients are perhaps best managed by direct coronary revascularization in the cardiac catheterization laboratory when possible. Even patients with chronic ischemic cardiomyopathy without active symptoms of coronary artery disease are at substantial risk when given drugs that increase myocardial oxygen demand. Other strategies including mechanical circulatory devices such as an intra-aortic balloon pump may be more appropriate than using large doses of norepinephrine, dopamine, dobutamine, or milrinone. In addition, new inotropic agents that use noncatecholamine pathways are being developed, thereby adding positive inotropy without necessarily increasing myocardial oxygen consumption. In this article, we review the history of some of the older agents and provide an update for physicians on the development of new drugs.

Conventional Inotropic Agents

The positive inotropic drugs that are widely used in the United States include digoxin, dopamine, dobutamine, milrinone, and norepinephrine.

Digoxin. There is still considerable debate regarding the role of digoxin for the treatment of patients with systolic heart failure. Although digoxin is generally considered to be a positive inotropic agent, there is uncertainty regarding the precise mechanisms whereby digoxin improves heart failure. We know that digoxin improves hemodynamics without adversely affecting heart rate or blood pressure (10). It tends not to increase myocardial oxygen demand and does not reduce coronary perfusion. It further diminishes neurohormonal activation (11–13), does not impair kidney function, and is available in both intravenous and oral form. Perhaps most importantly, digoxin can improve symptoms and tends to reduce hospitalization rate (14). When digoxin is withdrawn from patients with stable heart failure, there is considerable risk that patients will clinically deteriorate (15,16). Digoxin also improves hemodynamics at rest and during exercise (17). Importantly, digoxin is cleared by renal

excretion, making accumulation problematic in patients with impaired renal function.

Despite the fact that we have known about molecular targets for cardiac glycosides for several decades, it remains uncertain whether the sympatholytic or positive inotropic effects are responsible for relief of symptoms in heart failure (18). Digoxin acts by inhibiting the sarcolemmal Na^+/K^+ ATPase pump, thereby impeding the transport of sodium from the intracellular to the extracellular space. The reduction in the transmembrane sodium gradient tends to further reduce the activity of the Na^+/Ca^{2+} exchanger, thereby raising the intracellular calcium levels (Fig. 1). It is now believed that the increase in activator calcium is responsible for both the inotropic and the arrhythmogenic effects of cardiac glycosides. Digoxin has been used to wean patients dependent on intra-aortic balloon pumps or inotropic support (19). Digoxin was once widely used to treat patients with systolic heart failure. However, in 1997, results from the DIG (Digitalis Investigation Group) study indicated that digoxin had a neutral effect on mortality, although reductions were seen in overall rates of hospitalization and heart failure progression (20). The 15 years that followed the DIG study have seen a substantial decrease in its use for the treatment of heart failure. However, we believe there is still a role for digoxin in patients with heart failure (21).

Digoxin is particularly useful for patients with heart failure and concomitant atrial fibrillation, where it helps to control the heart rate. Atrial fibrillation occurs in roughly 20% to 30% of patients with heart failure, but the prevalence varies widely. A lenient rate control strategy targeting a ventricular rate of <110 beats/min is a preferred therapeutic pathway (22). However, cardioversion is sometimes necessary in the case of hemodynamic instability or refractory symptoms. Although intravenous diltiazem or verapamil are widely used to slow rapid atrial fibrillation, these two drugs can be problematic in patients with moderate hypotension or severe left ventricular (LV) dysfunction. In this scenario, small repeated doses of intravenous digoxin may be preferred.

The DIG trial also demonstrated the importance of measuring digoxin levels. Digoxin levels ≥1.2 ng/ml may be harmful; whereas, levels in the range of 0.5 to 0.9 ng/ml may be optimal. In general, digoxin levels below 1.0 ng/ml are safer and may even be more effective (1,23–25). A post-hoc subgroup analysis of the DIG study indicated that the effects of digoxin vary between men and women (26). Digoxin was associated with an increase in all-cause mortality among women, but not men, with systolic heart failure. It is conceivable that women, because they tend to have lower body weight, may be more prone to harmful elevations of digoxin levels (≥1.2 ng/ml) (27).

Dopamine. Dopamine, the immediate precursor to norepinephrine in the catecholamine synthetic pathway, is an endogenous neurotransmitter with multiple clinically important effects (28). Use of exogenous dopamine was largely studied and developed in the laboratories of Leon Goldberg
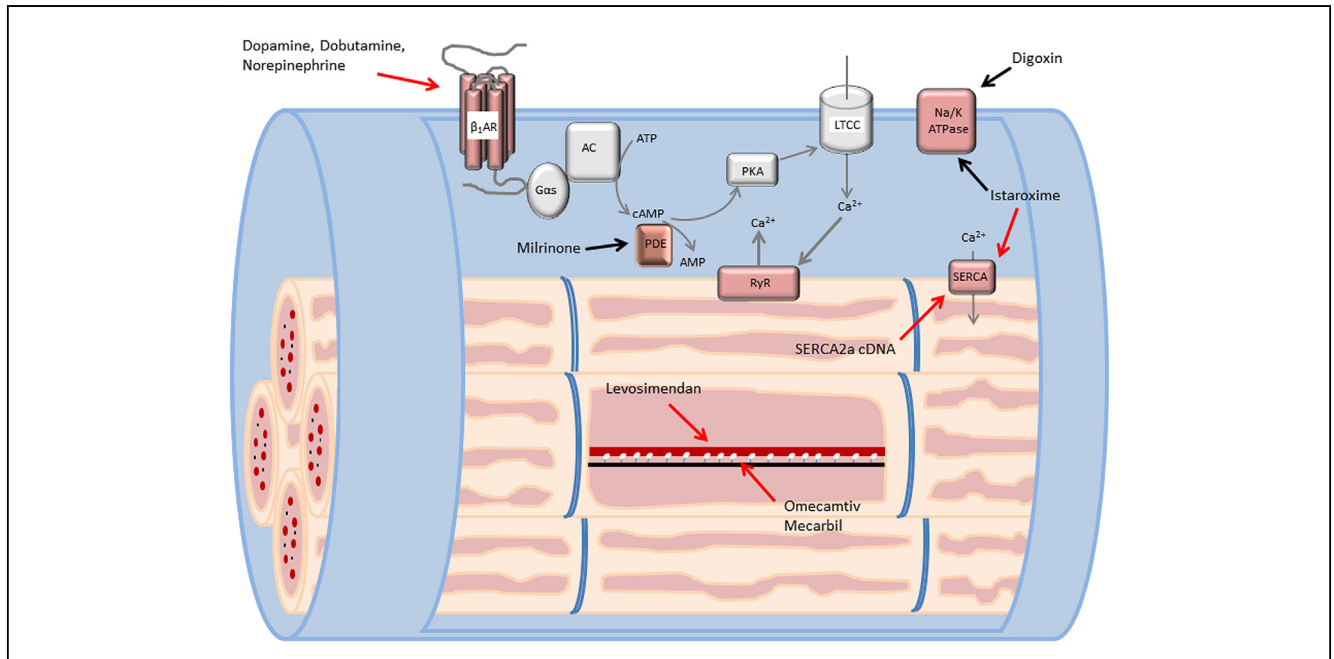
Figure 1   **Diagram of Intracellular Signaling Cascades Within Cardiomyocytes Altered by Inotropes**

Dopamine, dobutamine, and norepinephrine activate the β1-adrenergic receptor, which activates the G protein Gαs, which in turn, activates adenylyl cyclase. Adenylyl cyclase converts ATP to cAMP when activated. cAMP can activate PKA, which then phosphorylates the L-type calcium channel, among other targets. cAMP is converted to AMP by PDE. Milrinone inhibits PDE-3 thereby increasing the effective concentration of cAMP. Calcium influx through the L-type calcium channel induces activation of ryanodine receptors, leading to calcium-induced calcium release. Free intracellular calcium interacts with troponin C, which changes the binding properties of tropomyosin and allows the interaction between actin and myosin. Levosimendan potentiates the interaction between troponin and calcium. It may also have PDE-3 inhibitor activity as well. Omecamtiv mecarbil increases the rate of ATP turnover and slows the rate of ADP release thereby increasing the number of myosin molecules bound to actin at any given time. SERCA is responsible for uptake of calcium into the sarcoplasmic reticulum while the Na/K ATPase participates in resetting the membrane potential of the cell. Istaroxime inhibits Na/K ATPase while also potentiating SERCA. Digoxin inhibits the Na/K ATPase. **Red arrows** denote agonists, whereas **black arrows** signify antagonists. AC = adenylyl cyclase; ADP = adenosine diphosphate; ATP = adenosine triphosphate; B1AR = β1-adrenergic receptor; cAMP = cyclic adenosine monophosphate; LTCC = L-type calcium channel; PDE = phosphodiesterase; PKA = protein kinase A; RyR = ryanodine receptor; SERCA = sarco/endoplasmic reticulum Ca^{2+}-ATPase.

at the University of Chicago. It has been used intravenously to treat cardiogenic and septic shock since the 1970s. At low doses (<3 μg/kg/min), dopamine activates dopaminergic (D1) receptors that subserve vasodilation in various vascular beds, including the coronary and renal arteries. Despite the early observation demonstrating increased renal blood flow (28), the benefits of "renal doses" of dopamine have remained controversial. Estimated glomerular filtration rate does not improve with use of low-dose dopamine infusions, and there is no apparent renal protective effect (29). The ROSE AHF (Renal Optimization Strategies Evaluation in Acute Heart Failure) trial recently found that neither nesiritide nor low-dose dopamine was better than placebo when added to standard care (30). It is possible that some patients may experience inotropic effects even at low doses of dopamine. Intermediate doses of dopamine (3 to 10 μg/kg/min) activate β-adrenergic receptors that cause increased inotropy and heart rate and also promote release and inhibit reuptake of norepinephrine in presynaptic sympathetic nerve terminals (Fig. 1). At higher infusion rates (10 to 20 μg/kg/min), dopamine acts primarily as an α-adrenergic agonist resulting in peripheral vasoconstriction.

Dobutamine. Dobutamine was introduced in the late 1970s as a new, synthetic, intravenously administered catecholamine that had a direct agonist effect on β1- and β2-adrenergic receptors with no vasoconstrictor properties and less tachycardia (Fig. 1) (31). This drug was developed in the laboratories of Eli Lilly under the direction of Dr. Ron Tuttle. Many of the early human studies were performed in the laboratories of Dr. Carl Leier at Ohio State University. In principle, it was suggested that dobutamine might have an advantage over dopamine, as it does not increase sympathetic norepinephrine signaling or peripheral vasoconstriction (32). Dobutamine raises blood pressure solely by increasing cardiac output, whereas dopamine raises blood pressure via peripheral vasoconstriction (33). Both dobutamine and dopamine can reduce left ventricular enddiastolic pressure (LVEDP), although dopamine has the propensity to raise afterload when used in high doses and theoretically could increase filling pressure. Dobutamine can reduce blood pressure in some patients due to the peripheral vasodilatory properties, but the severity and importance of this effect varies widely among patients. Dobutamine can also cause idiosyncratic adverse effects including eosinophilia (34,35) and fever (36).

Dobutamine quickly became a popular drug to treat patients with severe heart failure, as it clearly improves cardiac output and lowers LVEDP with only a modest increase in heart rate (37). It exhibits a peripheral vasodilatory effect, most likely caused by β2-adrenergic stimulation in the peripheral vasculature in combination with reflex withdrawal of intense vasoconstriction. With time and experience, however, it became clear that dobutamine infusions lasting longer than 72 h were associated with pharmacodynamic tolerance (38). Tachycardia, myocardial ischemia, and arrhythmia can occur during dobutamine infusions, especially at doses of 15 μg/kg/min or higher. Generally, these outcomes are rapidly reversible, as the plasma half-life is 2.37 ± 0.7 min (32), indicating that >98% of the drug is eliminated within 10 to 12 min after cessation of the infusion.

Initial studies by Leier et al. (39) indicated that dobutamine improved regional blood flow to skeletal muscles and other regional beds. Subsequent metabolic studies by Mancini et al. (40) using phosphorous-31 magnetic resonance spectroscopy demonstrated that even though dobutamine improves the overall blood flow to the limb, it is unlikely to improve oxygen delivery to working skeletal muscle.

During the early stages of dobutamine use, a potential durable clinical benefit of short-term infusion was observed (41,42). Short-term infusion for 72 h selectively improves vascular endothelial function for ≥2 weeks (43). These observations led to the use of chronic home or outpatient infusions of dobutamine (44–46). However, the tide turned when it became clear that infusion of dobutamine for 7 to 52 days (median duration, 14 days) at an average dose of 9 μg/kg/min was associated with a much higher 6-month mortality compared with a vasodilator, epoprostenol (47). In the FIRST (Flolan International Randomized Survival Trial), dobutamine was associated with worse survival and poorer clinical outcomes and did not improve quality of life during or after the infusions. Although the data were observational, subsequent experience has verified that use of inotropic therapy for the treatment of severe heart failure is associated with reduced survival. Long-term infusions are still used as a bridge to heart replacement therapy and also in the palliative care setting.

Norepinephrine. Norepinephrine is an endogenous catecholamine normally synthesized, stored, and released from sympathetic neurons. Norepinephrine has potent α- and β-adrenergic receptor agonist properties including increased chronotropy, heightened inotropy, and increased peripheral vasoconstriction (Fig. 1). Synthetically manufactured norepinephrine has been available for decades for the treatment of severe septic and cardiogenic shock. Similar to high-dose dopamine, it should be given through a secure intravenous cannula or, preferably, a central venous catheter because of its potential to cause skin necrosis and sloughing of tissue. Typically, norepinephrine is infused at 0.2 to 1 μg/kg/min. As with all catecholamine-based therapies, it can be associated with tachycardia, myocardial ischemia, and arrhythmia. There is a large experience with the drug over many years. However, high doses of dopamine (>3 μg/kg/min) seem equivalent to those of norepinephrine with similar attributes and adverse effects. A comparator study published in 2010 indicated that a subset of patients with cardiogenic shock derived more survival benefit from norepinephrine than from dopamine (48). However, it should be noted that the study included patients with various types of shock, that the overall mortality rate was similar between dopamine and norepinephrine, and that there were more adverse effects with the use of dopamine than with the use of norepinephrine.

It has been noted that occasionally patients in cardiogenic shock present with vasodilation and hypotension. We have also commonly seen patients develop refractory vasodilation following mechanical circulatory assist device implantation. Such patients benefit from vasoconstricting agents such as norepinephrine, although intravenous arginine vasopressin has also been successfully used (49,50).

Nonadrenergic Inotropic Agents

Milrinone. Milrinone is a bipyridine, noncatecholamine, positive inotropic agent that can be given intravenously to patients with advanced systolic heart failure to improve cardiac performance (51). It is both a positive inotropic agent and a peripheral vasodilator. Milrinone also has lusitropic properties which are manifested by improvement in diastolic function. It raises heart rate, but not to the same extent as dobutamine. This is because dobutamine has direct β-adrenergic receptor activity. Milrinone, on the contrary, is a phosphodiesterase (PDE) inhibitor (Fig. 1). It inhibits PDE-3, an intracellular enzyme that breaks down cyclic adenosine monophosphate (cAMP). cAMP is a second messenger that modulates intracellular calcium. PDE-3 inhibitors thus increase cAMP, which increases calcium entry into the cardiac myocytes as well as the rate of removal, which in turn leads to increased myocardial contractility. In vascular smooth muscle, heightened cAMP primarily increases removal of calcium from the vascular smooth muscle cell, leading to cellular relaxation and vasodilation. Milrinone was introduced in the early 1990s for the treatment of severe systolic heart failure.

Based on the lack of head-to-head trials, there is no preference for milrinone versus dobutamine in most patients. Because activation of β1-receptors increases cAMP similar to milrinone, the downstream effects of the drugs are likely similar. However, milrinone may be the preferred inotropic drug for patients receiving β-adrenergic blocking drugs, as it does not use the β-adrenergic receptor to drive cardiac contractility, unlike dobutamine and dopamine. It is also favored in some patients who have markedly elevated pulmonary artery pressure. Milrinone, through its enhancement of cAMP, may reduce pulmonary artery pressure via a vasodilator mechanism and, therefore, may improve right

ventricular function. The use of PDE-5 inhibitors for pulmonary hypertension and right ventricular failure is currently under intense study, but these agents are considered vasodilators and not positive inotropic agents. Dobutamine and milrinone lead to similar increases in cardiac output and decreases of filling pressure, although milrinone may reduce LV filling pressure more than dobutamine. However, milrinone can lead to hypotension, especially in patients with low filling pressure. It should be avoided in patients with impaired renal function, as milrinone is renally cleared. It has a relatively long plasma elimination half-life (50 min, although this may be longer in severe heart failure). If hypotension or arrhythmia occurs, these adverse effects may persist for hours (52). A bolus infusion can sometimes cause hypotension and is not recommended. An initial continuous infusion dose of 0.125 μg/kg/min is generally reasonable.

In the OPTIME-CHF (Outcomes of Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure), there was no support for the use of intravenous milrinone as an adjunct to standard therapy for hospitalized patients treated with an exacerbation of chronic heart failure (5). Sustained hypotension with milrinone was more common than with placebo (10.7% vs. 3.2%), and occurrence of atrial arrhythmias was also more common (4.6% vs. 1.5%) (5). In-hospital mortality was similar between milrinone and placebo (3.8% vs. 2.3%). These findings run counter to earlier observational studies that were more favorable toward milrinone (53). Despite the fact that dobutamine increases myocardial oxygen consumption and milrinone may not (54), this seems not to be a distinguishing or clinically important attribute of milrinone. There is a belief that the harm of inotropic agents is not due solely to effects on myocardial oxygen consumption but may be related to the increase in intracellular calcium as a consequence of heightened cAMP in the cell. Although the 2 are linked, it is not absolutely clear that all of the harm is entirely related to heightened myocardial oxygen consumption. An increase in mortality was also seen with chronic use of oral milrinone in patients with severe chronic heart failure (55). Routine outpatient infusion of milrinone (and dobutamine) is to be discouraged. However, long-term use as a bridge to heart replacement therapy or as a form of palliative care when other therapies are insufficient may be appropriate. Milrinone remains widely used to treat patients with acute decompensated heart failure and in our view should be considered specifically for patients who have preserved renal function or pulmonary hypertension or patients who are receiving a β-adrenergic blocking agent.

Levosimendan. Levosimendan is a calcium sensitizing drug widely used in Europe but is not approved for use in the United States. The drug appears to enhance troponin C sensitivity to intracellular calcium, thereby enhancing cardiac inotropy and lusitropy (56). Levosimendan also causes peripheral vasodilation by opening smooth muscle adenosine triphosphate (ATP)-dependent potassium channels. It may also have some PDE-3 inhibitor activity (57).

Calcium sensitizing agents such as levosimendan exert positive inotropic effects on the heart by increasing the contractile apparatus' sensitivity to calcium (58). Therefore, such drugs have the theoretical advantage of driving contractile state without increasing cAMP or calcium itself, both of which have adverse effects. It appears that levosimendan's ability to enhance calcium responsiveness of myofilaments potentiates cross-bridge formation, thereby augmenting contractility and enhancing relaxation (59). Levosimendan causes a rapid dose-dependent improvement in the deranged hemodynamic profile of patients with severe heart failure (60). Typically the dose is titrated upward over 4 h from 0.1 μg/kg/min to 0.4 μg/kg/min and is maintained for several hours. Symptoms appear to improve.

There have been 2 randomized trials with levosimendan: REVIVE-II (Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy) (61) and SURVIVE (Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support) (7). The REVIVE-II study indicated no difference in mortality at 90 days, although survival was not a primary end point, and levosimendan was associated with more adverse effects. In SURVIVE, levosimendan was compared with dobutamine in a randomized, controlled trial involving 1,327 patients. In the trial, levosimendan did not significantly reduce all-cause mortality at 180 days and did not affect any secondary clinical outcomes (7). Levosimendan was associated with more peripheral vasodilation and hypotension than dobutamine. In a smaller hemodynamic study, levosimendan improved hemodynamic performance more effectively than dobutamine (6). Few data are available regarding oral levosimendan, but at least one study indicated improved quality of life scores with oral levosimendan (62).

New and Emerging Positive Inotropic Agents

The quest to develop more effective and safer positive inotropic drugs has continued despite numerous setbacks and disappointments. Some new agents do not target inotropy per se. Additional targets may include improved mitochondrial function through modulation of oxidative stress, iron handling, and biogenesis (63). Newer positive inotropic agents will also have greater advantages if they can be given orally.

Omecamtiv mecarbil. Formerly known as CK-1827452, omecamtiv mecarbil was developed by Malik et al. (64) at Cytokinetics, and it has emerged as an interesting new potential therapy for heart failure (65). Omecamtiv mecarbil is the first selective cardiac myosin activator to be studied in humans (66). It is under intense investigation in the laboratories of John Teerlink and others.

The small omecamtiv mecarbil molecule increases the efficiency of heart muscle contraction via selectivity for a subset of cardiac myosins. It does not affect fast isoforms of myosin in other organs. Myosin motors act on the thin filaments via the actin and troponin-tropomyosin complex.

The chemical energy necessary to drive myosin movement is derived from ATP hydrolysis. As a selective allosteric activator of cardiac myosin, omecamtiv mecarbil's action depends on "activation" rather than enzyme inhibition. Omecamtiv mecarbil selectively activates the S1 domain of cardiac myosin, the main component of the thick sarcomeric filament. Omecamtiv mecarbil increases the rate of ATP turnover by accelerating actin-dependent phosphate release and by slowing the rate of adenosine 5′-diphosphate (ADP) release. This increases the occupancy time of myosin on actin, leading to increased numbers of myosin molecules bound to actin, which causes prolongation of the contractile force without increasing left ventricular pressure development (dP/dt) (Fig. 2) (64,67,68). The calcium transient remains unchanged with omecamtiv mecarbil in contrast to conventional inotropic agents such as dobutamine, which increase intracellular cAMP and thereby increase the calcium transient. By this mechanism, it appears that omecamtiv mecarbil does not increase the heart's demand for energy, rather, it improves systolic performance by allowing the myocardium to make more efficient use of energy (67).

Sufficient data were provided from a phase II dose-ranging trial in 45 patients with stable heart failure to initiate a new trial, ATOMIC AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility–Acute Heart Failure; NCT01300013). The ATOMIC AHF trial results were recently presented at the European Society of Cardiology (Amsterdam, 2013), and the drug appears to avoid the usual adverse effects (e.g., tachycardia and arrhythmia) of traditional inotropic agents. Early experience demonstrated an increase in LV ejection fraction and stroke volume with decreased end-systolic and end-diastolic volumes. At high plasma concentrations, chest pain, tachycardia, and myocardial ischemia were noted (69).

On balance, the development of omecamtiv mecarbil is an example of highly creative biological engineering used to produce a molecule that can improve myocardial performance by prolonging systole rather than increasing the velocity of fiber-shortening, which is the mechanism typical of most positive inotropic agents. Omecamtiv mecarbil does not appear to drive oxygen consumption like more conventional agents, which is a unique attribute. In a sense, omecamtiv mecarbil may not be an inotrope, but it does improve myocardial systolic performance. Omecamtiv mecarbil has moved from the laboratory to clinical trials on a relatively rapid trajectory. We await the results of additional clinical studies with anticipation.

Sarcoplasmic Reticulum Ca^{2+}-ATPase Modulation

Calcium is critical in regulating the contraction and relaxation phases of the cardiac cycle. Sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) is an enzyme responsible for both myocardial relaxation by reuptake of calcium into the sarcoplasmic reticulum (SR) and contractility by controlling the amount of calcium in the SR (70). SERCA2a is downregulated in the failing human heart, resulting in contractile dysfunction and arrhythmia (71). Experimental animal models of heart failure have demonstrated an improvement in contractility, cardiac metabolism, and survival when SERCA2a expression is increased in cardiomyocytes leading to restoration of intracellular calcium cycling (72).

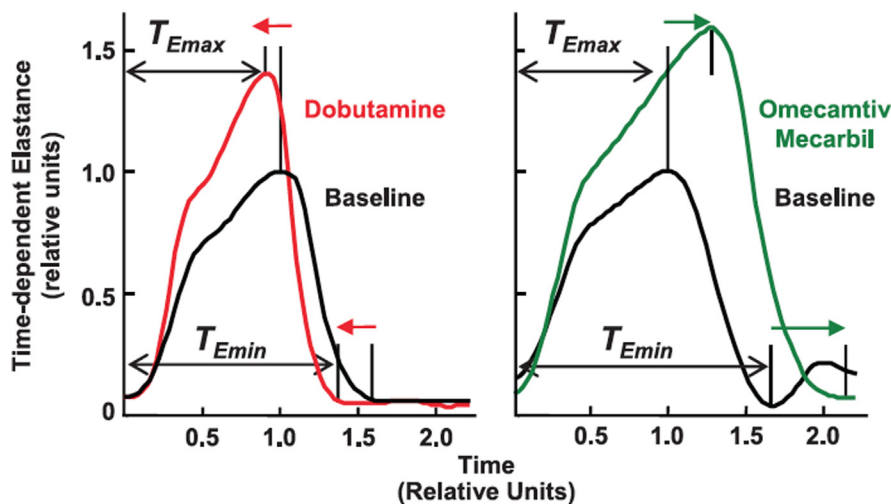**Figure 2**   **Time-Dependent LV End Systolic Elastance, a Load-Independent Measure of Cardiac Contractility Plot for Dobutamine and Omecamtiv Mecarbil**

The responses for each dog to dobutamine (10 μg/kg/min) and omecamtiv mecarbil (10 min following a 1 mg/kg bolus) were normalized to the magnitude and time of peak elastance at baseline to compare the shapes of the responses. From Malik et al. (64).

Table 1	Inotropic Drugs: Mechanisms and Outcomes		
Drug	**Mechanism**	**Effect on Mortality**	**Key Trials (Ref. #)**
Digoxin	Na-K pump inhibitor, raises SR calcium	Neutral, increased mortality if long-term therapy discontinued	DIG (15,20)
Dopamine	Dose-dependent D1, α1-, and β1-adrendergic receptor agonist	Increased	(48)
Norepinephrine	β1- and α1-adrenergic receptor agonist	Increased	(48)
Dobutamine	β1- and β2-adrenergic receptor agonist	Increased	FIRST (47)
Milrinone	PDE inhibitor, raises SR calcium	Increased	OPTIME-CHF (5)
Levosimendan	Myofilament calcium sensitizer, PDE-3 inhibitor	Neutral	REVIVE-II (61), SURVIVE (7)
Omecamtiv mecarbil	Potentiates the effects of myosin on actin to prolong systole	Unknown	ATOMIC AHF (underway), (66,69)
Istaroxime	Na-K pump inhibitor, PDE inhibitor	Unknown	HORIZON-HF (75)
SERCA2a gene therapy	Restoration of SERCA2a to improve calcium release and reuptake from the SR	Unknown	CUPID (70)

Studies: ATOMIC AHF = Study to Evaluate the Safety and Efficacy of IV Infusion Treatment With Omecamtiv Mecarbil in Subjects With Left Ventricular Systolic Dysfunction Hospitalized for Acute Heart Failure; CUPID = Calcium Up-regulation by Percutaneous administration of gene therapy In cardiac Disease; DIG = Digitalis Investigation Group; FIRST = Flolan International Randomized Survival Trial; HORIZON-HF = Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent: a Randomized Controlled Trial in Patients Hospitalized with Heart Failure; OPTIME-CHF = Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure; REVIVE-II = Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy; SURVIVE = Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support.

AC = adenylyl cyclase; ADP = adenosine diphosphate; ATP = adenosine triphosphate; B1AR = β1-adrenergic receptor; cAMP = cyclic adenosine monophosphate; LTCC = L-type calcium channel; PDE = phosphodiesterase; PKA = protein kinase A; RyR = ryanodine receptor; SERCA = sarco/endoplasmic reticulum Ca^{2+}-ATPase.

The first clinical trial of gene therapy for heart failure in the United States was CUPID (Calcium Up-regulation by Percutaneous administration of gene therapy In cardiac Disease). The trial was a multicenter open-label study designed to evaluate the safety profile and provide first-in-human data for the gene transfer of SERCA2a cDNA (adeno-associated virus [AAV1]/SERCA2a). The cDNA was delivered by intracoronary infusion. The phase I dose escalation portion of the study demonstrated an adequate safety profile in patients with advanced heart failure (73,74). In phase II of the CUPID study, 39 patients with advanced heart failure (estimated 1-year mortality rate of 25%) were randomly allocated to intracoronary AAV1-mediated SERCA2a gene delivery or placebo (70). Clinical efficacy was assessed using symptoms (New York Heart Association class and Minnesota Living With Heart Failure Questionnaire), walking distance (6-min walk test, maximal oxygen consumption [VO_{2max}]), biomarkers (N-terminal pro-brain natriuretic peptide), and LV function/remodeling (determined by echocardiography). In addition to the clinical outcomes, time to death or heart replacement therapy was assessed at 6 months (70). Three separate dosing regimens of AAVI/SERCA2a were tested and compared to a placebo group, with the high-dose group showing improvement or stabilization in each of the efficacy endpoints for the 6-month primary analysis. AAV1/SERCA2a was well tolerated with no reported adverse events (70). The study was limited by a small sample size and required screening of over 500 patients due to the presence of cross-reacting neutralizing antibodies to the viral vector capsid. The CUPID trial demonstrates that SERCA2a is a potential therapeutic target in patients with heart failure and provides supportive evidence for additional, larger randomized trials. Two clinical trials are currently targeting SERCA2a, one in patients implanted with left ventricular assist devices and another examining the effect on cardiac remodeling.

Istaroxime. Istaroxime is a novel intravenous drug that both inhibits the activity of sodium-potassium ATPase and stimulates sarcoplasmic reticulum calcium ATPase isoform 2a (SERCA2a) (75). This dual mechanism of action results in Istaroxime having both inotropic action by allowing the accumulation of cytosolic calcium during contraction and a lusitropic effect (improvement in diastolic relaxation) by sequestering calcium during relaxation (75). In an ischemic chronic heart failure animal model, Istaroxime improved both systolic and diastolic dysfunction without an increased incidence of arrhythmias (76). The HORIZON-HF (Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent: a Randomized Controlled Trial in Patients Hospitalized with Heart Failure) study assessed the hemodynamic effects of Istaroxime in a double-blind, placebo-controlled phase II trial in patients hospitalized with acute heart failure (75). The primary end point, reduction in pulmonary capillary wedge pressure, was improved for all 3 doses compared to placebo. A particularly notable secondary end point was a dose-dependent reduction in heart rate, a distinguishing feature from traditional intravenous inotropes. Additionally, there was an increase in systolic blood pressure but no effect on neurohormones, renal function, or troponin levels (75). Istaroxime is intriguing as a potential inotrope which avoids the adverse effects associated with conventional inotropic agents.

Selection of Patients for Home Inotropic Support

Patient preferences and goals of care should ideally be determined prior to any initiation of intravenous inotropic therapy. This should involve direct conversations with the patient and family discussing the available treatment options and possible outcomes. Various potential scenarios should be outlined such that expectations are established. For many

patients who are under consideration for inotropic agent therapy (milrinone or dobutamine), these discussions cannot be performed with the patient, as the patient may be too ill to participate in the discussion. In these cases, surrogate decision makers should be involved.

When one is unable to wean patients from inotropic support, many questions arise regarding its continued use. Discharging a patient with home inotropic therapy is complex and requires that the care team readdresses the goals developed during the acute use of inotropic agents while outlining discrete goals prior to discharge. Patients should also be instructed that further hospitalization is likely even with home inotropic therapy. For patients awaiting transplant, inotropes are meant to maintain hemodynamics and end-organ function and alleviate symptoms as a bridge to transplantation. For patients who are not likely to undergo further advanced therapies, inotropic agents may alleviate symptoms and should be provided based on the patient and family's preferences in close collaboration with hospice or end-of-life services (77).

Conclusions

End-stage heart failure is a progressive disease with high mortality and limited medical therapeutic options. Long-term use of conventional inotropic agents has been associated with no improvement or even increased overall mortality. This uncomfortable dilemma has led to expanded use of heart replacement therapy. Development of novel inotropes has been hindered in recent decades by the ambitious goal of achieving two seemingly opposing effects with a single molecule. Clinicians want to use drugs that increase cardiac output without increasing myocardial oxygen consumption. The inotropes in use in the United States today primarily increase cardiac output by amplifying the natural pathways for calcium entry into the cell. Calcium handling is energy intensive leading to adverse effects. The second goal of newly developed inotropes is to maintain stable levels of, or even reduce, myocardial energy consumption. The conserved energy may then be redirected for cellular repair and promotion of mitochondrial health with reduction of oxidative stress. Effectively, this requires that the inotropic agent does not result in increased chronotropy or calcium flux, as these processes may be the primary cause of the increased mortality associated with inotropic drugs. One would hope that the next generation of inotropic agents will achieve enhanced myocardial performance without altering the velocity of shortening or promoting excessive calcium modulation at the level of the SR or the L-type calcium channel.

New agents are on the horizon. However, the methods used to investigate their safety and efficacy can be challenging. Patients with end-stage heart failure are unstable by definition, thus presenting many additional challenges. These patients are also highly complex medically, providing multiple opportunities for confounding influences. Large patient populations are usually necessary to test survival outcomes. Clinical trials in this group of patients are likely to continue to be expensive, difficult, and uncertain with regard to proper end points. Nevertheless, the search for ideal inotropes should and will continue.

Reprint requests and correspondence: Dr. Gary S. Francis, University of Minnesota, Cardiovascular Division, MMC 508, 420 Delaware Street SE, Minneapolis, Minnesota 55455. E-mail: franc354@umn.edu.

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