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JACC REVIEW TOPIC OF THE WEEK

Cardiac Calcitropes, Myotropes, and Mitotropes

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ABSTRACT

The term "inotrope" is familiar and intimately connected with pharmaceuticals clinically used for treatment of low cardiac output with cardiogenic shock. Traditional inotropic agents exert their effect by modulating calcium signaling in the myocardium. Their use is associated with poor long-term outcomes. Newer molecules in development intend to break from calcium mediation and the associated detrimental long-term effects by targeting distinct mechanisms of action to improve cardiac performance. Thus, "inotropy" does not sufficiently describe the range of potential novel pharmaceutical products. To enhance communication around and evaluation of current, emerging, and potential therapies, this review proposes a novel nuanced and holistic framework to categorize pharmacological agents that improve myocardial performance based on 3 myocardial mechanisms: calcitropes, which alter intracellular calcium concentrations; myotropes, which affect the molecular motor and scaffolding; and mitotropes, which influence energetics. Novel chemical entities can easily be incorporated into this structure, distinguishing themselves based on their mechanisms and clinical outcomes. (J Am Coll Cardiol 2019;73:2345–53) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Inotrope derives from Greek, meaning "sinew" and "tropic" meaning changing or affecting. The term inotropy has been broadly used for many years to describe treatments that directly improve the contractile function of the heart (1,2). The concept is familiar and broadly used by both specialists and general medical practitioners because of the worldwide substantial disabling and mortality

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ABBREVIATIONS AND ACRONYMS

ADP = adenosine diphosphate

ATP = adenosine triphosphate

Ca^{2+} = calcium ion

cAMP = cyclic adenosine monophosphate

HFrEF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

SR = sarcoplasmic reticulum

burden from heart failure with reduced ejection fraction (HFrEF) (3). Because of this vernacular, inotrope has become interchangeable with available pharmacological agents that alter cardiac performance by changing cardiac myocyte calcium ion (Ca^{2+}) balance and flux (4). The improvement in contractility from these agents can be manifested by increased left ventricular systolic pressure generation per unit time (dP/dt) and augmented hemodynamic performance, including cardiac output and stroke volume. This improvement can be visualized on imaging by an elevated left ventricular ejection fraction (LVEF) or, in some cases, by subsequent reduction of cardiac biomarkers, including natriuretic peptides. Some of these agents may have additional secondary effects, such as changes to vascular tone that may contribute to their cardiac activities, although the focus here is the load-independent effects of these drugs. Unfortunately, the detrimental long-term effects of these agents on clinical outcomes for patients with HFrEF are a direct consequence of their mechanisms of action and have sullied the term inotrope as a potential long-term therapeutic option.

With continued use, conventional inotropic agents—including catecholamines, phosphodiesterase-3 inhibitors, sodium-potassium adenosine triphosphatase (ATPase) inhibitors, and mixed-mechanism calcium sensitizers and phosphodiesterase-3 inhibitors—detrimentally alter myocardial energetics, decrease the adenosine triphosphate (ATP)/adenosine diphosphate (ADP) ratio, and have been associated with clinical outcomes that are at best neutral and at worst deadly, including malignant arrhythmias (4). The underlying Ca^{2+}-centric mechanism of these agents may be the dual-edged sword that causes both their inotropic and detrimental effects. In contrast, well-established HFrEF medical therapies improve myocardial contractility and mortality over time without increasing cardiomyocyte Ca^{2+} fluxes (5). New pharmacological agents that alter myocardial performance and contraction by novel means may be able to further improve myocardial energetics and clinical outcomes for patients with HFrEF. Direct contraction–promoting agents may avoid adverse clinical effects by targeting new mechanisms of action separate from conventional Ca^{2+}-acting medications.

Inotropy as currently used is an overly broad and ill-defined concept to describe therapies that improve the pumping function of the heart. We therefore propose a novel, more nuanced and holistic framework for drugs that directly improve myocardial performance to facilitate improved clinical and scientific communication, augment pharmaceutical development, and hopefully enhance clinical care. The suggested schema categorizes these entities in a manner that incorporates future therapeutic agents with distinct mechanisms of action, hemodynamic consequences, and potential clinical benefits. The 3 broad conceptualized areas (**Table 1**) that can mechanistically be targeted are intracellular Ca^{2+}, the physical sarcomere, and myocardial energetics. We propose cardiac calcitropes, myotropes, and mitotropes to describe these categories, respectively.

HIGHLIGHTS

- Traditional inotropic agents modulate calcium signaling in the myocardium but are associated with poor long-term outcomes.
- Mechanistic nomenclature could improve communication and recognize therapeutic advances in myocardial functional enhancement.
- Calcium-independent pharmaceuticals may demonstrate better efficacy and safety than available agents and should continue to be developed.

INOTROPY, CONTRACTILITY, AND CONTRACTION

Typical definitions of inotropy refer to the function of the myocardial contractile apparatus that is load-independent. Two attributes can increase the physical impulse produced, the force–time product: increased force or longer contraction time.

- Cardiac contractility is conventionally manifested by accelerated myocardial fiber shortening that increases the rise in ventricular dP/dt and leads to an elevated peak tension. Contractility is load-independent and defined as the ability of the myocardium to generate force per unit time.
- In contrast, contraction is the measure of shortening of the underlying myocardial structure, the sarcomere. Although increased contraction can occur because of augmented contractility, contraction can also increase independently of load or dP/dt by mechanisms that prolong the duration of contraction.

Loading changes can also affect cardiac function; for instance, vasodilation and decreased afterload can increase contraction speed with stable contractility. Many typical measurements of ventricular function,

TABLE 1 Currently Available and Developmental Direct Inotropic Agents

Pharmacological Agent	Mechanism	dP/dt	Hemodynamic Effects	Patient Outcomes
Cardiac calcitropes				
Dobutamine	Catecholamine: β-adrenergic receptor→ cAMP → ↑ Ca^{2+}	↑	↑ Cardiac output	↑ Mortality
Dopamine	Catecholamine: β-adrenergic receptor→ cAMP → ↑ Ca^{2+}	↑	↑ Cardiac output	↑ Mortality
Epinephrine	Catecholamine: β-adrenergic receptor→ cAMP → ↑ Ca^{2+}	↑	↑ Cardiac output	↑ Mortality
Milrinone	Phosphodiesterase-3 inhibitor: cAMP→ ↑ Ca^{2+}	↑	↑ Cardiac output	↑ Mortality
Levosimendan	Phosphodiesterase-3 inhibitor (and calcium sensitizer): ↓ Troponin and tropomyosin inhibition; cAMP → ↑ Ca^{2+}	↑	↑ Cardiac output	?↑ Mortality
Cardiac glycosides	Na^{+}-K^{+} ATPase inhibitor: ↓NCX Ca^{2+} extrusion → ↑ Ca^{2+}	↑	↔ Cardiac output	? ↔Mortality ↓ Hospitalizations
Istaroxime	Na^{+}-K^{+} ATPase Inhibitor & SERCA2a Activator: ↓Ca^{2+} extrusion → ↑ Ca^{2+}, ↑ SERCA2a → ↑ Ca^{2+} in SR	↑	↑ Cardiac output	?
Cardiac myotropes				
Omecamtiv mecarbil	Direct myosin activator ↑ Myosin participation in systole	↔	↑ Cardiac output	?
Cardiac mitotropes				
Perhexiline	Carnitine palmitoyl transferase inhibitor: ↓ Mitochondrial fatty acids → ↑ Glucose metabolism	↔	↑ Cardiac output	?
Trimetazidine	Thiolase I inhibitor: ↓ Fatty acid oxidation → ↑ Glucose metabolism	↑	↑ Cardiac Output	?
Elamipretide	Cardiolipin stabilizer ↑ Adenosine triphosphate synthesis	?	?	?

↑ = increase; ↓ = decrease; ↔ = no change; ? = unknown or possible; ATPase = adenosine triphosphatase; Ca^{2+} = calcium ion; cAMP = cyclic adenosine monophosphate; K = potassium; Na = sodium; NCX = sodium ion/calcium ion exchanger; SERCA2a = sarcoplasmic/endoplasmic reticulum calcium ATPase; SR = sarcoplasmic reticulum.

such as measurement of LVEF by imaging or hemodynamically measured cardiac output, are load-dependent. Although these can be useful clinical metrics, they are often conflated with contractility in clinical settings, and they fail to assess the isolated contractile status of the myocardium. Thus, although pure vasodilators may improve LVEF or stroke volume, they cannot be considered inotropes.

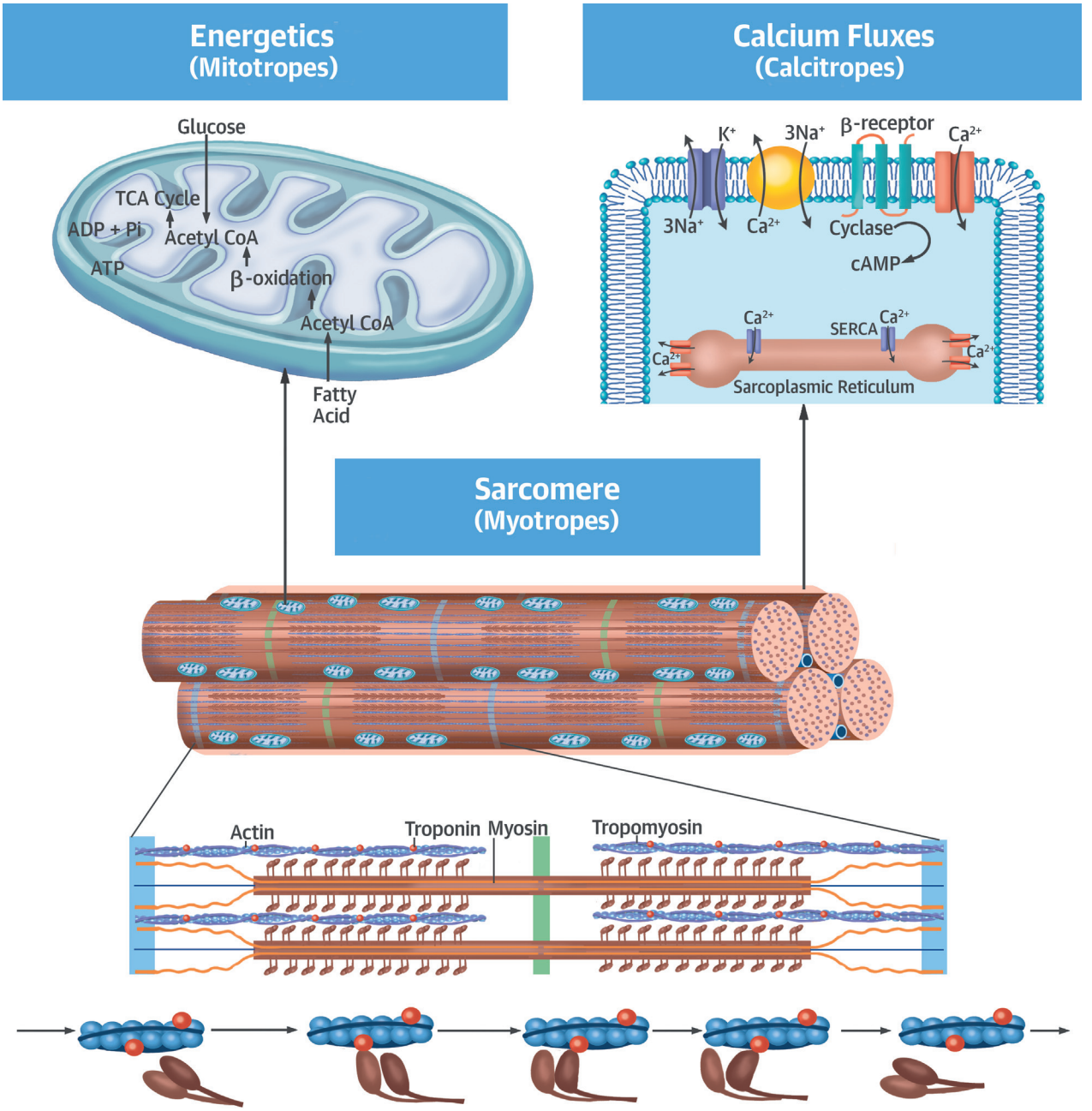
MYOCARDIAL CONTRACTILE APPARATUS AND ENERGETICS

Available inotropic agents and those currently in development alter ventricular systolic performance by affecting the myocardial machinery. The 3 broad components of this machinery are: 1) the contractile elements that consist of the myosin motor, actin filaments, and the regulatory proteins, including the troponin–tropomyosin complex that impede actin and myosin interactions; 2) the Ca^{2+} cycling elements responsible for the storage and flux of myocardial Ca^{2+}; and 3) the energetic elements that include ATP produced by the mitochondria required for myosin activity (**Central Illustration**).

Myosin is the critical molecular motor that converts energy stored as ATP into contractile force. It is the active enzyme of the myocardial force–producing structure, the sarcomere. Sarcomeric myosin exists as thick filaments interdigitated between the thin filaments of actin on which it pulls to mediate contraction (6,7). Actin-associated troponin and tropomyosin enable the intracellular Ca^{2+} status and other factors to regulate the myosin–actin interaction. At basal intracellular Ca^{2+} levels before contraction, tropomyosin complexed with troponins blocks actin–myosin crossbridge formation. When stimulatory electrical action potentials activate cardiac myocytes, Ca^{2+} enters the cell by sarcolemmal L-type Ca^{2+} channels and triggers secondary larger Ca^{2+} release from the sarcoplasmic reticulum (SR) through ryanodine receptors (8). The elevated Ca^{2+} binds to troponin C and induces a positional change in tropomyosin that disinhibits actin–myosin cross bridging.

Once actin is available for binding in response to increased cytosolic Ca^{2+} and troponin and/or tropomyosin movement, the myosin mechanochemical cycle can proceed (7). Myosin in the primed state, which is associated with a lone phosphate moiety following hydrolysis of ATP to ADP, weakly interacts with the actin filaments. Myosin only enters the contractile cycle from this primed state, because release of the phosphate transitions the myosin to a strong interaction with actin. The power stroke that occurs, the mechanical transduction of the myosin lever arm, generates force and moves the actin myofilament approximately 10 nm (9). Following the power stroke, ATP rapidly binds to myosin and dissociates it from the actin myofilament to reset the lever arm for another power stroke.

CENTRAL ILLUSTRATION **The Myocardial Contractile Apparatus and Classes of Therapeutic Agents**



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The 3 broad components of the myocardial machinery are the contractile elements and regulatory proteins in the sarcomere, the calcium ion (Ca^{2+}) cycling elements in the cell and sarcoplasmic reticulum membranes, and the energetic elements, including adenosine triphosphate (ATP) produced by the mitochondria. Pharmacological agents that improve myocardial performance can be described by this framework: calcitropes alter intracellular calcium concentrations; myotropes affect the molecular motor and scaffolding; and mitotropes influence energetics. ADP = adenosine diphosphate; cAMP = cyclic adenosine monophosphate; CoA = coenzyme A; K = potassium; Na = sodium; Pi = inorganic phosphate; SERCA = sarcoplasmic/endoplasmic reticulum calcium ATPase; TCA = tricarboxylic acid cycle.

Concomitantly, following cell depolarization, Ca^{2+} is returned to the SR by the sarcoplasmic/endoplasmic reticulum calcium ATPase 2a (SERCA2a) and passed into the extracellular space by the sodium–calcium exchanger and a calcium ATPase. The power stroke occurs during cardiac systole following the electrocardiographic QRS as the correlate of the Ca^{2+} influx. The resetting of the molecular motor takes place during diastole, and the Ca^{2+} efflux is visualized as the electrocardiographic T-wave.

Myocardial excitation–contraction coupling, as described previously, and the resulting ventricular systole requires substantial ATP; without regeneration, the process would use all intracellular ATP within 1 min (10). The intramyocardial power source responsible for providing energy to the myocardial contraction apparatus is the mitochondrion (11). The intracellular processing of fatty acids and glucose produces carrier molecules that deliver electrons to the mitochondrial electron transport chain, establishing a proton gradient and driving mitochondrial ATP synthase to produce ATP. In normally functioning myocardium, fatty acids are the primary energy source. Elevated intracellular and mitochondrial Ca^{2+} participates in regulation of energy production by activating enzymes for fatty acid processing and thus increasing delivery of electrons required for ATP production (12). However, additional stimuli such as elevated intracellular ADP also accelerate the production of ATP to maintain sufficient energetic reserve.

TRADITIONAL INOTROPES: CARDIAC CALCITROPES

Inotropy produced by conventional agents, including catecholamines, phosphodiesterase-3 inhibitors, and cardiac glycosides (e.g., digitalis), all increase myocardial force production by altering the concentration of intracellular Ca^{2+}. The augmented Ca^{2+} by these agents offsets the observed decrement of Ca^{2+} in the SR of patients with HFrEF caused by ryanodine receptor leak (8). Because the effects are all mediated by altered Ca^{2+}, these agents are proposed to be called cardiac calcitropes. The calcitropes are defined by their direct myocardial action rather than their secondary effects on vascular tone and chronotropy, both of which may also alter cardiac performance.

Catecholamines such as dobutamine, dopamine, epinephrine, and norepinephrine activate membrane-bound, G-protein coupled adrenergic receptors that stimulate adenylyl cyclase to transform ATP into cyclic adenosine monophosphate (cAMP) (4,13). Protein kinase A activated by cAMP phosphorylates multiple downstream targets, including phospholamban (which increases SR Ca^{2+} uptake by SERCA2a), the ryanodine receptors (which then release more Ca^{2+} during depolarization), and troponin C (which facilitates actin exposure for myosin). These Ca^{2+}-mediated effects increase cardiac contractility.

The phosphodiesterase-3 inhibitors (e.g., milrinone) also exert their effects through cAMP, by blocking its degradation and stimulating protein kinase A to activate the same downstream Ca^{2+} cascade as catecholamines (4). Levosimendan is a phosphodiesterase inhibitor, although it also sensitizes the troponin and tropomyosin complex to facilitate unmasking of the myosin-binding site on actin, and has distinct vasodilatory effects mediated by potassium channel activation (14–16). The cardiac glycosides are sodium–potassium ATPase inhibitors that impede establishment of the sodium gradient used by the sodium–calcium exchanger to extrude Ca^{2+}. This shift increases intracellular Ca^{2+} to facilitate contraction. Although cardiac glycosides do increase dP/dt, they do not markedly change cardiac output in clinical studies, perhaps due to concomitant vasoconstriction and slowing of the heart rate (17–19). Istaroxime is a nonglycoside sodium–potassium ATPase inhibitor that may also improve SERCA2a activity. Although it elevated cardiac output in a phase 2 randomized controlled trial, its development program was halted by the manufacturer (20).

Although these cardiac calcitropes can improve symptoms and may have a role in acute shock, bridging to transplantation, and for palliation, observational cohorts and randomized clinical trials have shown that long-term use of catecholamines and phosphodiesterase-3 inhibitors is associated with increased mortality in patients with HFrEF (21–27). Levosimendan has been associated with similar mortality as the catecholamines (28–30). In 1 large-scale trial, the cardiac glycosides decreased heart failure hospitalizations, but did not improve mortality in HFrEF patients and were associated with harm in some modern observational cohorts (31). The unifying mechanism by which each of these agents enhance cardiac contractility is increased intracellular Ca^{2+}, and this mechanism may be why they have been unable to improve long-term survival of patients with HFrEF.

CARDIAC MYOTROPES

Because myosin is the central actor of the sarcomere, therapeutics that target the myosin, actin, the associated regulatory proteins, or other structural

elements of the sarcomere through calcium-independent mechanisms are proposed to be called cardiac myotropes. Calcium sensitizers acting on regulatory troponin and tropomyosin independently of Ca^{2+} fluxes would be considered cardiac myotropes, and the calcitrope levosimendan also has this myotropic activity. Myosin is an attractive therapeutic target because it performs the work of myocardial contraction and may participate in wasteful actin-independent ATP hydrolysis outside of the myosin mechanochemical cycle. The myotrope currently under study, omecamtiv mecarbil, directly activates cardiac myosin in a calcium-independent manner by allosterically modulating its activity (32). By binding to myosin and stabilizing the pre-powerstroke energetic state, omecamtiv mecarbil increases the number of myosin heads that enter the force-producing state that are able to pull on actin filaments during depolarization; it also appears to decrease inefficient actin-independent noncontractile energy usage. Omecamtiv mecarbil does not alter Ca^{2+}-dependent second messenger signaling to alter contractile function (32).

Direct myosin activation by omecamtiv mecarbil raises the total amount of time spent in contraction and systole without increasing the rate of force generation (dP/dt). Conceptually, cardiac myotropes and cardiac calcitropes both increase the force–time product, but although calcitropes increase the force generated per unit time, known myotropes increase the time spent expending a given force. At stable loading conditions, elevated cardiac myotropy augments the duration of ventricular systole, the systolic ejection time, and thus, aortic blood flow for each contraction. Myotropes also appear to be energetically distinct from calcitropes. Although calcitropes require increased oxygen use to augment the dP/dt, myotropes appear to increase contraction without greater oxygen consumption; thus, they improve the overall efficiency of the mechanochemical system (9,32).

The clinical usefulness of the myotrope omecamtiv mecarbil is currently being evaluated in a phase 3 randomized controlled multicenter clinical trial (GALACTIC-HF [Registrational Study With Omecamtiv Mecarbil/AMG 423 to Treat Chronic Heart Failure With Reduced Ejection Fraction]; NCT02929329). Data from earlier investigations suggest that its alternative mechanism of action may improve clinical outcomes compared with the cardiac calcitropes (33,34). Long-term oral dosing of the compound to patients with stable HFrEF decreases natriuretic peptide biomarkers and improves ventricular dimensions (5,35). This agent is the first in the class of pure cardiac myotropes. Nevertheless, even if omecamtiv mecarbil was unable to improve or even impair clinical outcomes for patients with HFrEF, the premise of increasing myocardial contractile performance by targeting the myosin motor or other sarcomeric elements would remain an intuitive therapeutic target that justifies appropriately descriptive terminology.

CARDIAC MITOTROPES

Myocardial energetics are centered around mitochondrial energy production, and drugs acting at the mitochondria are therefore proposed to be called mitotropes. Myocardial energetics are an attractive target because of the energy dependence of myocardial contraction and the metabolic derangements present in the myocardium of patients with HFrEF. The primary oxidation substrates transition from fatty acids to glucose, and there is a reduction in myocardial ATP (36,37).

Multiple chemical entities that affect the mitochondrion or alter myocardial metabolism are in various stages of pre-clinical and clinical development and clinical use. Perhexiline inhibits the protein that translocates fatty acids into the mitochondria under the premise that the shift to the more efficient ATP production through glucose is beneficial (38). Changes in myocardial contractile activity have been variable in small clinical studies with perhexiline, although it does appear to improve myocardial energetics in patients with HFrEF (38,39). Alternatively, trimetazidine blocks the mitochondrial oxidation of fatty acids by the enzyme thiolase and similarly shifts metabolism towards glucose (40). Small cohorts and open-label randomized studies suggest trimetazidine improves myocardial performance and contractility as measured by increased LVEF, tissue Doppler velocities, and cardiac output, and that it clinically benefits patients with HFrEF (41–44). However, these results have not been reproduced in more appropriately sized randomized controlled trials. Coenzyme Q10 is a component of the mitochondrial electron transport chain that appeared to decrease cardiovascular and all-cause mortality in a small HFrEF trial with a low event rate (45). No adequately sized trial has confirmed these results. Elamipretide stabilizes the essential phospholipid cardiolipin within the ATP-producing inner mitochondrial membrane, which is believed to enhance ATP synthesis. Elamipretide seemed to increase left ventricular function, as manifested by elevated LVEF and cardiac output in dogs with HFrEF, although it was also associated with vasodilatory effects and upregulation of

SERCA2a (46,47). A small placebo-controlled, dose-ranging study in patients with HFrEF demonstrated acute reductions in left ventricular volumes with the highest dose of elamipretide; however, LVEF and global longitudinal strain were unchanged (48).

CLASSIFICATION OF CURRENT HEART FAILURE MEDICAL THERAPY

Current guideline-directed neurohormonal antagonists for HFrEF improve myocardial activity over time through load-dependent and load-independent actions, including by ventricular remodeling (5,49). The inotropic subclassifications introduced previously can enhance mechanistic evaluation of these neurohormonal agents. Focusing on these concepts suggests that specific combinations of calcitropic, myotropic, and mitotropic activities may be more likely to provide survival and myocardial performance benefits similar to neurohormonal antagonism. For instance, beta-adrenergic receptor antagonists directly decrease contractility in the first few months of therapy by blocking cAMP formation and the Ca^{2+} cascade, although LVEF improves in that time due to remodeling and loading changes (50). Beta-adrenergic antagonists can therefore be classified as direct negative calcitropes. Myocardial contractility rebounds between 3 to 6 months, with continued treatment associated with improvements in myocardial energy efficiency, which suggests that beta-adrenergic receptor antagonists also act as indirect positive mitotropes (50,51).

Antagonists of the renin-aldosterone-angiotensin system can also be characterized by these concepts. Mineralocorticoid receptor antagonists appear to reduce Ca^{2+} fluxes and function as negative calcitropes (52). These agents may improve contractility by increasing myosin ATPase activity in addition to their effects on loading and remodeling, and thus they may also be positive myotropes (5,53). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers inhibit the increase in Ca^{2+}-mediated myocyte contractility induced by angiotensin 2 (54,55). Although it remains unclear whether this suppression is due to antagonism of angiotensin 2–augmented Ca^{2+} fluxes (calcitropy) or increased Ca^{2+} sensitivity (myotropy), it is possible that each major class of HFrEF therapeutics directly antagonizes calcitropy. This activity of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers is in addition to blocking the fibrotic, hypertrophic, ventricular loading, and apoptotic effects of angiotensin 2 (56). Because established therapeutics for HFrEF commonly function as negative calcitropes, albeit with concomitant beneficial changes on ventricular loading, remodeling, and noncalcitropic myocardial performance enhancement, it may be that avoidance of calcitropic activity should be sought in developing new HFrEF therapeutics.

CONCLUSIONS AND FUTURE DIRECTIONS

The goal of optimizing cardiac function, the load-independent contractile activity of the myocardium, is a valuable target for novel therapeutics to treat HFrEF. It remains unclear whether pharmaceuticals that use mechanisms other than Ca^{2+} to directly boost myocardial contractile action will demonstrate better efficacy and safety than currently available agents. To improve communication around current agents, to revise the clinical concept of improved myocardial performance, and to permit and to encourage accurate evaluation of potential new therapies that enhance myocardial contractility and contraction, we have proposed a framework based on mechanisms of action. These mechanisms include 3 basic myocardial processes: Ca^{2+}-based regulation; the molecular motor and sarcomeric scaffolding; and energetics. Agents that primarily alter Ca^{2+} intracellular concentrations should be called cardiac calcitropes, those that directly affect myosin or other components of the sarcomere should be called cardiac myotropes, and those that alter myocardial energetics should be called cardiac mitotropes. Novel chemical entities can easily be incorporated into this structure, distinguishing themselves based on their mechanisms of action and effects on clinical outcomes. The reviewed data suggest that therapeutic pathways that avoid or perhaps antagonize calcitropy may be more likely to improve long-term myocardial function and clinical outcomes, and should be targeted for development. This classification will enhance communication during drug discovery, facilitate investigation into mechanisms of action and efficacy, and inform clinical discussions even if the agents currently under evaluation fail to demonstrate clinical benefit.

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