Dama International Journal of Researchers (DIJR), ISSN: 2343-6743, ISI Impact Factor: 1.018
Vol 3, Issue 02, February, 2018, Pages 26 - 29, Available @ www.damaacademia.com

Cardiac Myosin Activator: A New Therapeutic Class Approach for a Treatment in Heart Failure

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Abstract
Heart failure commonly marked by cardiac systolic dysfunction, associated with the mortality and morbidity that remains high and has few therapeutic advances in decades. Impaired cardiac contractility is a central pathophysiological feature and may be a key therapeutic target. The inotropic agents increase cardiac contractility by altering intracellular calcium flux, but are associated with myocardial ischemia, hypotension, arrhythmias, and mortality. Adverse effects associated with the administration of current inotropic agents have stimulated research and development of novel drugs which would directly target the cardiac sarcomere. Direct activation of the cardiac sarcomere could be achieved in two ways: sensitizing proteins to calcium or activating cardiac myosin directly. A new class of pharmacologic agents, cardiac myosin activators, directly targets the kinetics of the myosin head, an inotropic property resulting in the improvement of systolic function of the heart without increasing energy demand and cellular calcium concentrations. It increases stroke volume, decreases filling pressures, and improves ventricular volumes by increasing the left ventricular systolic ejection time, without increasing the rate of left ventricular pressure development or heart rate, and without noticeable effect upon myocardial oxygen uptake, blood pressure, or coronary blood flow. They still a challenge developing a novel mechanism in heart failure.

Key words: *heart failure, cardiac contractility, cardiac myosin activator, inotropic.*

I. INTRODUCTON

Heart failure (HF) is a clinical syndrome representing the end-stage of a number of different cardiac diseases commonly marked by cardiac systolic dysfunction. HF associated with the mortality and morbidity that remains high and has few therapeutic advances in decades.[1,2] In systolic HF, the left ventricle loses its ability to contract normally. The heart can't pump with enough force to push enough blood into circulation, and hence the left ventricular ejection fraction is reduced.[2] Impaired cardiac contractility is a central pathophysiological feature in at least one-half of these patients and may be a key therapeutic target. Inotropic agents can worsening HF. The agents increase cardiac contractility by altering intracellular calcium flux, but are associated with myocardial ischemia, hypotension, arrhythmias, and mortality.[3] Consequently, recent guidelines limit the use of these agents to patients with cardiogenic shock or evidence of marked end-organ hypoperfusion.[4,5] Currently available cardiac function improving agents (inotropic drugs), such as adrenergic receptor agonists (i.e. dobutamine), phosphodiesterase inhibitors (i.e. milrinone), and levosimendan increase cardiac contractility via cyclic adenosine monophosphate and intracellular calcium-handling mechanisms, but these compounds are associated with increased oxygen consumption, intracellular calcium, increased heart rate, hypotension, arrhythmias, and mortality.[6] Increasing the speed or velocity of muscle contraction may also shorten the duration of systolic ejection time, the time it takes for the blood to leave the heart chamber and enter systemic circulation.[7] Inotropes should be considered only in such patients with systolic dysfunction who have low cardiac index and evidence of systemic hypoperfusion and/or congestion. To minimize adverse effects, lower doses are preferred. Similarly, the ongoing need for inotropic support and the possibility of discontinuation should be regularly assessed.[5] Due to multiple risks associated with current inotropes being used in clinical practice, there have been many efforts in the last few years to develop safe and efficacious inotropes. There is newer agents and works as a cardiac specific myosin activator, an inotropic property resulting in the improvement of systolic function of the heart without increasing its energy demand.[8]

II. CARDIAC CONTRACTILITY

Myocardial contractility is produced at the cellular level by the interaction of myosin and actin filaments, with their relationship dynamics modulated by ATP, calcium, and regulatory proteins.[9] Myosin is a molecular motor, which interacts with actin to convert the energy from ATP hydrolysis into mechanical work. In cardiac myocytes, two myosin isoforms are expressed and their relative distribution changes in different developmental and pathophysiologic conditions of the heart.[10] The cardiac sarcomere, the fundamental unit of cardiac muscle contractility, is an elegantly organized cellular structure made up of interdigitating thin and thick filaments. The

force generating enzyme, cardiac myosin, is the main component of the thick filament. The thin filaments are composed of cardiac isoforms of actin and the troponin-tropomyosin regulatory complex.[12,13]
In the resting state, there are low calcium concentrations in the myocyte, and the troponin–tropomyosin complex blocks cross-bridge formation between actin and myosin.[14] During each cardiac cycle, the sarcoplasmic reticulum is triggered by depolarization of the myocyte to release transiently calcium ions (Ca^{2+}) into the cytoplasm.[11,12] In the sarcomere, these calcium ions activate the thin filament by binding to troponin, shifting tropomyosin to uncover the myosin binding sites of the actin filaments. Upon binding to the actin filament, cardiac myosin undergoes a power stroke, pulling on the thin filaments and shortening the sarcomere. Cardiac myosin powers contraction of the myocardium by cyclically converting the chemical energy of ATP into the mechanical force. This cycle may be viewed as starting with the hydrolysis of ATP by myosin into ADP and inorganic phosphate (Pi) that provides the potential energy for myosin. The cleavage of this ATP enables myosin to weakly bind to the actin filaments; this ATP ultimately is consumed by myosin regardless of whether it generates any force. Once fully engaged with its actin binding site, myosin transitions to a strongly-bound state, releasing Pi from the myosin head and bending its head in a force-generating power stroke, pulling on the actin filament. Subsequently, ADP is released and ATP binds rapidly to myosin, resulting in the detachment of myosin from actin. This cycle, which takes approximately 100 msec to complete, is then again ready to repeat. Only a minority of myosin heads produce a power stroke during a cardiac cycle, potentially representing some degree of energetic inefficiency.[12,13] When calcium is removed from the cytoplasm, cardiac muscle relaxes again.[12] The cardiac actin–myosin cycle is central to this process of myocardial force generation and continued research has elucidated important details of the cycle.[14]

III. ENHANCEMENT OF MYOCARDIAL CONTRACTILITY

Positive inotropic agents (PIAs) increase the strength of myocardial contraction and have beneficial hemodynamic effects in patients with acute systolic HF due primarily to a direct increase in cardiac output. PIAs are typically classified into the following four classes: (A) digitalis (e.g., digoxin), (B) β-adrenergic receptor agonists (e.g., dobutamine and dopamine), (C) PDe3 inhibitors (e.g., inamrinone and milrinone), and (D) calcium-sensitizing agents (e.g., levosimendan, not approved for use in the United States).[2]

A. Digoxin

Cardiac glycosides inhibit the monovalent cation transport enzyme–coupled Na^+, K^+-ATPase and increase intracellular [Na^+]; in turn, increases intracellular [Ca^{2+}] through a Na^+-Ca^{2+} exchange carrier mechanism. The increased myocardial [Ca^{2+}] augments Ca^{2+} released to the myofilaments during excitation and invokes a positive inotropic response.[15] It tends not to increase myocardial oxygen demand and does not reduce coronary perfusion.[16]

B. Adrenergic receptor agonists

Dopamine and dobutamine improve myocardial contractility and are effective in the management of severe acute HF. They increase cAMP through receptor-mediated increases in cAMP production with multiple downstream signaling effects. This mechanisms result in increased intracellular calcium, which in myocytes increases contractility. The increased intracellular calcium needs to be actively transported back into the sarcoplasmic reticulum with each cardiac cycle, markedly increasing the ATP required to maintain calcium homeostasis. This increased energy utilization results in increased myocardial oxygen demand. Myocardial oxygen demand is further exacerbated by an increased heart rate. Elevations in intracellular calcium concentrations and increased calcium transients are also considered to play a role in the increased arrhythmogenicity of these agents. These effects contribute to the observed clinical increase in arrhythmias and mortality with these drugs, especially in the setting of myocardial ischemia.[14] Dopamine is a naturally occurring, immediate precursor of norepinephrine and has a combination of actions that makes it particularly useful in the treatment of a variety of hypotensive states and HF. In low dose, it dilates renal and mesenteric blood vessels through stimulation of specific dopaminergic receptors, thereby augmenting renal and mesenteric blood flow and sodium excretion. In the range of 2 to 10 g/kg per min, dopamine stimulates myocardial β_1 receptors but induces relatively little tachycardia, while at higher doses it also stimulates α-adrenergic receptors and elevates arterial pressure. Dobutamine acts on β_1, β_2, and α_1 receptors. It exerts a potent inotropic action, has only a modest cardio accelerating effect, and lowers peripheral vascular resistance.[15]

C. Phosphodiesterase inhibitors

These bipyridines, amrinone and milrinone, are noncatecholamine, nonglycoside agents that exert both positive inotropic and vasodilator actions by inhibiting phosphodiesterase III, an enzyme that breaks down intracytoplasmic cyclic AMP, the second messenger which is critical to adrenergic stimulation and consequently also increase intracellular concentrations.[14,15] These agents are administered intravenously; by simultaneously stimulating cardiac contractility and dilating the systemic vascular bed they reverse the major hemodynamic

abnormalities associated with HF. Amrinone and milrinone may be administered for the same conditions in which dopamine or dobutamine are useful; they may be employed together with and potentiate the sympathomimetics.[15]

D. Calcium-sensitizing agent

Levosimendan is a calcium sensitizing agent which can exert its inotropic effect by increasing the sensitivity of cardiomyocyte to intracellular calcium by binding to troponin C. An inotropic effect without increasing intracellular calcium levels can prevent an increased risk of cardiac arrhythmia with this agent. Levosimendan also has vasodilatory properties by opening adenosine triphosphate (ATP)-sensitive potassium channels in vascular smooth muscle, causing their relaxation. It may also have some phosphodiesterase (PDE) inhibitor activity.[8]

E. Cardiac myosin activator

Adverse effects associated with the administration of current inotropic agents have stimulated research and development of novel drugs which would directly target the cardiac sarcomere. Direct activation of the cardiac sarcomere could be achieved in two ways: sensitizing proteins to calcium or activating cardiac myosin directly.[17] Another new target for treatment of HF is to improve myocardial contractility. It is being investigated as a potential treatment for heart failure, a novel activator of cardiac myosin, the motor protein that powers cardiac muscle contraction.[18] These new agents directly modulate the myosin and actin mechanism by accelerating the rate-limiting step of the myosin cycle, actin binding coupled to phosphate release. Although the force generated by each myosin head does not change, overall contractile function improves. Normally only a fraction of available myosin heads participate in each cardiac cycle; by speeding up the rate-limiting step, cardiac myosin activators allow a greater fraction of myosin to bind actin for each cycle, producing an augmented power stroke.[9]

The cardiac muscle activator stimulates cardiac myosin to increase cardiac performance without increasing cellular calcium concentrations. It increases stroke volume, decreases filling pressures, and improves ventricular volumes.[20] It does so by increasing the left ventricular systolic ejection time, without increasing the rate of left ventricular pressure development or heart rate, and without noticeable effect upon myocardial oxygen uptake, blood pressure, or coronary blood flow.[14,17,19,20] Animal models have shown that this novel mechanism increases the systolic ejection time, resulting in improved stroke volume, fractional shortening, and hemodynamics with no effect on myocardial oxygen demand, culminating in significant increases in cardiac efficiency. A first-inhuman study in healthy volunteers with the lead cardiac myosin activator, CK-1827452 (omecamtiv mecarbil), as well as preliminary results from a study in patients with stable chronic heart failure, have extended these findings to humans, demonstrating significant increases in systolic ejection time, fractional shortening, stroke volume, and cardiac output.[14]

The safety, tolerability, pharmacokinetics, and pharmacodynamics of the new cardiac myosin activator have been studied across nine Phase 1 clinical trials, which enrolled over 200 healthy volunteers. This cardiac myosin activator was the subject of four Phase 2 clinical trials that enrolled more than 1,300 people with heart failure, including a trial called COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) that evaluated oral cardiac myosin activator in patients with chronic heart failure and left ventricular systolic dysfunction and ATOMIC-AHF (A Trial of Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure), a Phase 2 trial that evaluated intravenous dosage form. Based on the strength of results from this Phase 2 program, this drug ran into a Phase 3 clinical development program to evaluate clinical efficacy and establish safety and tolerability.

Table 1. Positive inotropic drugs

Drug	Mechanism	Intracellular calcium concentration effect
Digoxin	Na-K pump inhibitor	Increase
Dopamine	Dose related action. High dose stimulate adrenergic snd low dose stimulate dopaminergic receptors	Increase
Dobutamine	Pure adrenergic; $\beta1 > \beta2 > \alpha$ receptor agonist	Increase
Milrinone	Phosphodiesterase inhibitor	Increase
Levosimendan	Calcium sensitizer	Not increase
Omecamtiv mecarbil	Activate cardiac myosin by enhances myosin and actin cross-bridge formation	Not increase

CONCLUSION

Cardiac myosin activator might be implicated as a novel therapeutic approach to improve cardiac function in systolic heart failure patients, without the adverse events associated with current indirect inotropes. The overall

treatment effect of cardiac myosin activator is an improvement of systolic function by increasing left ventricular systolic ejection time. These new agent is still a challenge developing a novel mechanism in heart failure and ran into Phase 3 trial so the benefit and safety to improved clinical outcomes needed to investigate. The search for ideal inotropes should and will continue.

Conflict Of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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