At the Source: Treating Heart Failure by Altering Muscle Motor Function

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Cardiac Myosin Activation: A Potential Therapeutic Approach for Systolic Heart Failure
Malik et al

A new study in Science provides proof of the principle for directly modulating the cardiac muscle’s motor, myosin, as a therapeutic target in heart failure.

The human and economic tolls from heart failure (HF) are significant in both developed and undeveloped countries.1-3 Although HF can take many forms,4,5 it is most commonly associated with decreased cardiac contractility and is, therefore, referred to as systolic HF (sHF).6 Current therapeutic strategies rely on blocking neurohormonal activation by inhibiting associated pathways or by receptor blockade using either β-adrenergic or aldosterone blockers.7,8 Alternatively, some therapies are directed at increasing cardiac contractility in an effort to restore sufficient blood flow, usually by activating second messenger signaling pathways that increase cardiomyocyte calcium levels and augment sarcomere contraction.9 Both strategies suffer from a lack of specificity in that they target proteins upstream of the actual contractile events that underlie force production. Affecting important signaling pathways or receptor-ligand interactions can impact cellular function and perturb homeostasis in ways unrelated to the contractile apparatus, leading to undesirable side effects, such as hypotension, tachycardia, and even arrhythmias that can lead to sudden death.10

Recognizing the significant limitations of current therapeutic modalities, Malik and co-workers have directed their efforts at directly modulating cardiac contractility by tuning motor function at the source, the myosin heavy chain. The cardiac myosin heavy chains are encoded by two genes, MYH6, which encodes α myosin heavy chain, and MYH7, which encodes β myosin heavy chain, the latter being the predominant isoform in human ventricle. Although having greater than 90% amino acid homology, the two proteins differ significantly at the biochemical level. In comparison with α myosin, β myosin is relatively more efficient in force production as a function of energy consumption, with a lower rate of ATP gamma phosphate catalytic removal. As the high-energy phosphate is removed, the energy is stored in the myosin-actin-ADP-Pi intermediate, such that upon phosphate release, chemical energy is transduced into the mechanical movement that underlies cardiomyocyte contractility and, ultimately, cardiac output.

Recognizing the therapeutic potential for directly affecting the cardiac motor’s function, Malik’s group initially screened an extensive small molecule library for compounds that increased myosin ATPase activity and identified a compound that effectively activated the heavy chain’s enzymatic activity.11 Further development directed at improving the molecule’s efficacy, specificity, and pharmacokinetic profile resulted in a slightly modified compound, CK-1827452, named omecamtiv mecarbil.

The effects of omecamtiv mecarbil were assessed in two canine models of sHF: myocardial infarction, followed by rapid ventricular pacing and aortic banding-induced left ventricular (LV) hypertrophy (LVH), followed by rapid ventricular pacing (LVH-sHF).12 In both models of sHF, before omecamtiv mecarbil treatment, there were significant increases in nonpaced heart rate, mean left atrial pressure, and left ventricular end-diastolic pressure——, as well as a significant decrease in LV dP/dt max, systolic wall thickening, and cardiac output. In both models, intravenous infusion of omecamtiv mecarbil for twenty-four hours resulted in significant improvements in nonpaced heart rate, LV systolic ejection time (LVSET), left ventricular end-diastolic pressure, systolic wall thickening, cardiac output, stroke volume, and total peripheral resistance. These effects were first noted after 15 minutes of infusion and were sustained over the twenty-four-hour study period, suggesting that desensitization did not occur. Importantly, the improvements in cardiovascular function occurred without an increase in myocardial oxygen consumption and persisted in a subset of dogs maintained on omecamtiv mecarbil for seventy-two hours.

Early clinical trials (published to date only in abstract form) have been conducted to begin to address questions of safety, efficacy and pharmacokinetics. Healthy male volunteers demonstrated increases in LVSET and LV systolic function directly proportional to escalating doses of intravenous omecamtiv mecarbil, with no adverse effects. Increases in LVSET were found to be highly correlated with increases in LV ejection fraction and shortening fraction and, thus, may provide a simple method to indicate drug effect.13 A phase II safety study was performed in patients with ischemic cardiomyopathy and angina to test the hypothesis that prolongation of the LVSET by omecamtiv mecarbil might adversely limit

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coronary flow and ventricular filling. Subjects performed treadmill exercise testing before and during a twenty-hour infusion of placebo or omecamtiv mecarbilin at rates titrated to achieve one of two target serum omecamtiv mecarbil levels. The primary safety endpoint was angina-induced cessation of exercise at a stage earlier than the patient’s baseline. Only one placebo-treated subject (and none of the omecamtiv mecarbil subjects) demonstrated the primary endpoint. There were no clinically significant changes in vital signs, electrocardiograms, or cardiac biomarkers in patients randomized to omecamtiv mecarbil.14

In the Science article, Malik et al make major strides in understanding the mechanistic basis for omecamtiv mecarbil’s effectiveness in increasing cardiac output.15 Using a combination of isolated systems and stop-flow kinetic analyses, they define the compound’s effects on the different steps of the mechanochemical cycle of myosin, as ATP is split and the energy translated into movement of the myosin lever arm, resulting in sarcomere contraction as myosin translocates across the actin filament. For actual force development, myosin and actin must strongly interact, and this “strong interaction” does not occur upon initial myosin-actin interaction, which is characterized by an electrostatic contact “weak-binding” state of myosin, actin, and ADP-Pi. Rather, a second, stereospecific contact involves additional hydrophobic residues from both actin and myosin. Upon release of inorganic phosphate, the energy of hydrolysis is stored in a high-energy intermediate state, while myosin, ADP, and actin tilt, twist, and rotate to a strongly bound state. Concomitant with inorganic phosphate (Pi) release, the myosin lever arm undergoes a conformational switch and the myosin and actin filaments move relative to one another, resulting in a translocation of the actin filament toward the center of the sarcomere.

Malik et al showed that omecamtiv mecarbil increases the actin-dependent rate of Pi release from cardiac myosin. Molecular modeling based on affinity labeling of a benzophenone derivative of omecamtiv mecarbil showed that the probable binding site was located in a cleft in the myosin head only 3.5 nm from the ATP binding domain and 6.5 nm from the actin binding site. The authors also note that the cleft lies within the structural elements of the myosin head thought to mediate the conformational changes producing the actual motion underlying the power stroke. They hypothesize that omecamtiv mecarbil acts to lower the energy barrier between the weakly and strongly bound states, accelerating the release of Pi and the actual power stroke. Important for specificity of any eventual therapeutic application in human shF, a single molecule of omecamtiv mecarbil binds to a single myosin head, and this interaction appears to be restricted to cardiac myosin.

If omecamtiv mecarbil is, indeed, affecting the power stroke at the weakly to strongly bound transition, then its therapeutic target is fundamentally different from classic inotropes. The authors confirm this in a brief but elegant series of experiments in which they compare the effects of omecamtiv mecarbil and isoproterenol in isolated cardiomyocytes. Although omecamtiv mecarbil clearly increased cell contractility, in comparison with isoproterenol, it had no effect on the calcium transient. Consistent with the proposed mechanism of action, the β adrenergic blocker carvedilol had no effect on the action of omecamtiv mecarbil.

What are the potential therapeutic implications of these studies? Clearly additional work is required to optimize the route of administration, dosing, and the duration of therapy. Moreover, the safety and efficacy of omecamtiv mecarbil in human heart failure is yet to be determined. Certainly, the initial data are promising, and the heart appears to be quite robust in terms of tolerating myosin motor tuning over the long term. Indeed, in rabbit models in which the normal complement of β myosin has been altered via cardiomyocyte-specific transgenesis, such that the ventricle contains approximately equal amounts of α- and β-myosin, there was no overt cardiomyopathy and the transgenic animals were, in fact, cardioprotected in a pacing-induced heart failure model.16 Indeed, echocardiography and cardiac catheterization showed that α-myosin heavy chain transgenic rabbits aged to 56 ± 11 months were anatomically and functionally indistinguishable from NTG littermates (James and Robbins, unpublished data). Thus, in a long-term animal model, significant alterations in the overall ATPase activity of the myosin complement was completely benign and even protective under certain conditions of cardiac stress. However, our current understanding of failing myocardium as “energy starved” raises concern as to whether the human heart could keep pace with a potential need for increased ATP production. Although it is reassuring that there was no increase in myocardial oxygen consumption in the canine models of shF treated with omecamtiv mecarbil, careful study of myocardial energetics is warranted both in animal models and ultimately in clinical trials. Regardless, direct manipulation of contractility at the motor level offers a potentially precise therapeutic avenue for increasing cardiac output. Although the downstream effects have yet to be determined, this strategy offers the promise of a novel and effective therapeutic alternative for shF.

References


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