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EDITORIAL COMMENT

Moderating the Myosin Motor to Treat Hypertrophic Cardiomyopathy*

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Limiting cardiac contractility by small molecules that directly inhibit the myosin motor protein is a revolutionary new concept for the treatment of familial hypertrophic cardiomyopathy (HCM). Cardiac pump function can be dysregulated by structural and functional myocardial alterations during HCM, where mutations of genes encoding mostly sarcomeric proteins are responsible for disturbances in cardiomyocyte signaling rendering the left ventricle (LV) hypercontractile. In addition, ventricular hypertrophy and fibrosis of the septal myocardium may pose obstruction of blood outflow from the LV, requiring interventions (surgical myectomy or alcohol septal ablation) to prevent the progression of this condition to overt heart failure. Of note, current pharmacologic approaches cannot prevent or substitute invasive treatments (including the cardioverter-defibrillator implantation and heart transplantation) in a number of HCM patients.[1]

In this issue of *JACC: Basic to Translational Science*, Malik et al[2] report on a phase 1 double-blind, randomized, placebo-controlled, first-in-human study that used aficamten, a second-generation cardiac myosin inhibitor drug developed for the treatment of HCM. After years of preclinical and clinical screening of cardiac myosin inhibitors, the clinical applicability of aficamten now appears to be superior to that of mavacamten (a first-generation cardiac myosin inhibitor). In the present study, the safety, pharmacokinetic, and pharmacodynamic profiles of aficamten were tested, while also paying attention to potential confounding effects of food intake or a CYP2D6 (a cytochrome P450 mixed-function oxidase) poor metabolizer phenotype. To these ends, healthy adults were enrolled to receive single ascending doses or multiple ascending doses of aficamten or placebo. Doses of oral aficamten up to 50 mg during single applications or up to 10 mg following once daily repeated administrations evoked small but significant reductions in left ventricular ejection fraction (LVEF). Aficamten was well tolerated in healthy participants, and similarly to preclinical data, no substantial CYP induction or inhibition were observed. Taken together, results of this study extend and confirm earlier investigations, and thus hold a promise for the safe applicability of aficamten in humans.[2]

Cardiac systolic contractions are brought about by an ATP-driven molecular interaction between 2 sarcomeric myofilament proteins: myosin and actin. Nonetheless, concerted actions of an additional set of cardiomyocyte proteins are required to coordinate the contractile process, referred to as excitation-contraction coupling. In short, electrical excitations in the surface cell membrane elicit transient elevations in cytoplasmic Ca^{2+} concentration during each heartbeat, and this signal controls force production through the myosin motor. It follows that the magnitudes and time courses of cardiac contractions are the function of those of intracellular Ca^{2+} transients. Accordingly, a number of drugs with distinct molecular mechanisms of action have been used to augment intracellular Ca^{2+} transients and thereby counter systolic dysfunction (eg, during heart failure with reduced ejection fraction). Nevertheless, the clinical applicability of the above classic positive inotropic approach is compromised by the tight connection between increases in intracellular Ca^{2+} concentration and

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myocardial oxygen demand. Consequently, novel pharmacologic strategies aiming at targets more distal from cellular Ca^{2+} cycling (eg, by Ca^{2+} sensitization or by direct myosin activation) were sought to avoid alterations in intracellular Ca^{2+} handling when modulating cardiac contractility. Of note, cardiac myosin inhibition also develops in the absence of intracellular Ca^{2+} concentration changes, thereby implicating no adverse consequences for myocardial energetics.[3]

Characterization of the quantitative aspects of cardiac sarcomeric force production typically requires in vitro investigations of simplified biological systems, eg, physiologic measurements in single isolated cardiomyocytes or biochemical assays on myofilament proteins. Previous preclinical studies of these kinds provided evidence for the potential applicability of direct myosin inhibitors during HCM. Direct myosin inhibitors decreased myosin ATPase activity along with concentration-dependent reductions in systolic cardiomyocyte cell length changes and LV fractional shortenings. In addition, the pharmacokinetic and pharmacodynamic characteristics of aficamten have been assessed in several species (including mice, rats, dogs, and monkeys), predicting favorable features for humans as well.[3]

The molecular interaction between omecamtiv mecarbil, a cardiac myosin activator, and the myosin heavy chain (MHC)-β is thought to stabilize the prepower stroke state of myosin to evoke the positive inotropic effect. Cardiac responses on omecamtiv mecarbil administrations involve the increase in systolic ejection time, and this effect is considered to be a hallmark of myosin activation. Nevertheless, this alteration also predicts a proportional decrease in the duration of diastole at a given heart rate. Interestingly, omecamtiv mecarbil shifted the Ca^{2+}-force relationship to the left in permeabilized cardiomyocyte-sized preparations of the rat under isometric conditions, and thus suggested that the molecular mechanisms of direct myosin activation and myofilament Ca^{2+} sensitization represent different, though interrelated, facets of the same molecular interaction between omecamtiv mecarbil and MHC-β. Moreover, omecamtiv mecarbil increased cardiomyocyte force production at diastolic Ca^{2+} concentration levels as well. Furthermore, the Ca^{2+}-sensitizing effect of omecamtiv mecarbil was demonstrated not only in cardiomyocytes, but also in the skeletal muscle fibers of the rat diaphragm, because the slow-skeletal muscle fibers co-express the same MHC isoform (ie, MHC-β) as found in the heart.[4] Taken together, direct myosin activation affects cardiomyocyte force production in a way that may influence not only the systolic but also the diastolic function of the heart, and it may affect the function of other systems (eg, skeletal muscles) as well.

Similarly to omecamtiv mecarbil, the molecular target of aficamten is the same MHC-β molecule, but in contrast to omecamtiv mecarbil, aficamten decreases contractile force by slowing phosphate release from the myosin and by stabilization of the weak actin-binding myosin conformation.[5] It is important to stress that neither myosin activators nor myosin inhibitors suspend Ca^{2+} regulation of the contractile protein machinery, but they merely modulate the coupling process, whereby the magnitude and kinetics of Ca^{2+}-dependent myofilament force production will differ in their presence from conditions when they are absent. Accordingly, and also based on previous findings with omecamtiv mecarbil, it would be interesting to see if aficamten also affected the Ca^{2+}-force relationship of isometric force production in cardiomyocytes and skeletal muscle fibers. Moreover, it is to be determined how aficamten administration alters the extents and kinetics of systolic and diastolic phases of cardiac contractions in HCM patients. These data will certainly aid future efforts in optimizing the application of myosin inhibitors in clinical settings.

A current hypothesis links HCM-associated sarcomeric mutations to myocardial hypercontractility and consequently to the activation of signaling pathways that cause cardiac hypertrophy, fibrosis, and myofilament disarray.[5] Therefore, reducing myocardial contractility by pharmacologic agents appears as an attractive strategy in HCM, where direct myosin inhibition would not only inhibit hypercontractility, but also forecasts the prevention of pathologic cardiac remodeling. Nevertheless, therapeutic application of myosin inhibitors (which by definition evoke negative inotropy) will certainly need careful considerations, because major reductions in LVEF may inevitably culminate in heart failure. The shallower concentration-response profile of aficamten than that of mavacamten is an obvious advantage and implicates easier dosing by aficamten than by mavacamten.[3] All in all, verification of the hypercontractile state of HCM-associated ventricles and threshold LVEF values before and during aficamten administrations will probably be considered during the

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clinical application of direct myosin inhibitors. Current and future clinical trials are expected to elucidate these technicalities and will hopefully support the clinical introduction of direct myosin inhibitors to the treatment of HCM.[5]

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