Hypertrophic cardiomyopathy: New approaches and a time to reappraise older approaches

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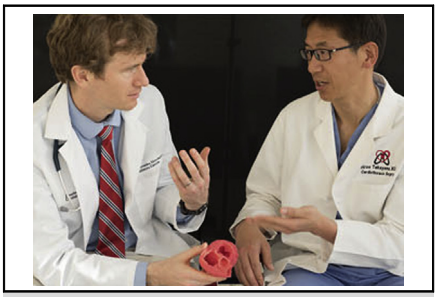

HCM program discussion on 3D printed heart.

Central Message

A small molecule prevents the development of HCM in a mouse model. Until its successful application in humans, the surgeon's role in treating obstructive hypertrophic cardiomyopathy remains critical.

See Editorial Commentary page 988.

In a recent issue of *Science*, Green and colleagues[1] described the successful application of a novel therapy for a mouse model of hypertrophic cardiomyopathy (HCM) with a mutant overactive form of the cardiac myosin heavy chain, the most common mutation affecting humans with this disorder. Their team designed a small-molecule (MYK-461) inhibitor of the abnormal protein that reduced excess sarcomere power output and thus successfully prevented the development of ventricular hypertrophy, cardiomyocyte disarray, and myocardial fibrosis. This important innovation sheds light on the unique pathophysiology of this disorder and may form the basis of treatment trials in humans, and it is therefore important to bring to the attention of the surgical community. We discuss the possible application of this therapy and use this as an opportunity to review the important surgical approaches to this disease and the competing procedures used by the interventional cardiology community.

MYK-461 AS A CURE FOR HCM?

It is well-established that patients with HCM tend to have hyperdynamic systolic function. It is known that this hypercontractility precedes the development of left ventricular hypertrophy (LVH).[2,3] Previous studies have shown that this hypercontractility is caused by mutant myosin proteins with enhanced ATPase activity, increased tension development, and/or increased unloaded actin-filament sliding velocities.[4] It is hypothesized that this hyperfunctioning protein, instead of being a beneficial mutation, leads to the development of hypertrophy, myocyte disarray, and fibrosis. This finding leads to the hypothesis that inhibition of the activity of these overactive proteins could be beneficial in the treatment of HCM. Green and colleagues hypothesized that a small-molecule inhibitor of myosin, MYK-461, in individuals with the abnormal overactive form of this protein would prevent the development of the pathologic abnormalities of HCM.[1] Using a mouse model, in which human-disease–causing mutations were introduced into the murine α-cardiac myosin heavy-chain gene,[5,6] they have elegantly demonstrated that early, chronic administration of MYK-461 does prevent the development of ventricular hypertrophy, cardiomyocyte disarray, and myocardial fibrosis, and attenuates hypertrophic and profibrotic gene expression in HCM mice. In addition, MYK-461 therapy in older mice with overt LVH showed partial regression of myocardial hypertrophy (Figure 1). Of importance, skeletal muscle function (grip strength or voluntary exercise capacity) was not impaired even though MYK-461 also inhibits the ATPase activity of skeletal myosin. The potential clinical implications of the study by Green and colleagues are multifold. Drug administration before the development of the HCM phenotype may prevent the development of the disease in patients with mutations in sarcomere protein genes, including *MYH7* and *MYBPC3* (the 2 commonest types of mutations in humans). Late administration might halt disease progression or induce regression. This discovery could potentially signify the dawn of a new era of treatment, although clinical trials will need to be performed to demonstrate safety and efficacy in humans.

MYK-461 has been tested in phase I clinical trials. Successful cure of HCM with MYK-461, as well as any other targeted pharmacologic therapies, however, will face a number of challenges. Despite tremendous efforts,

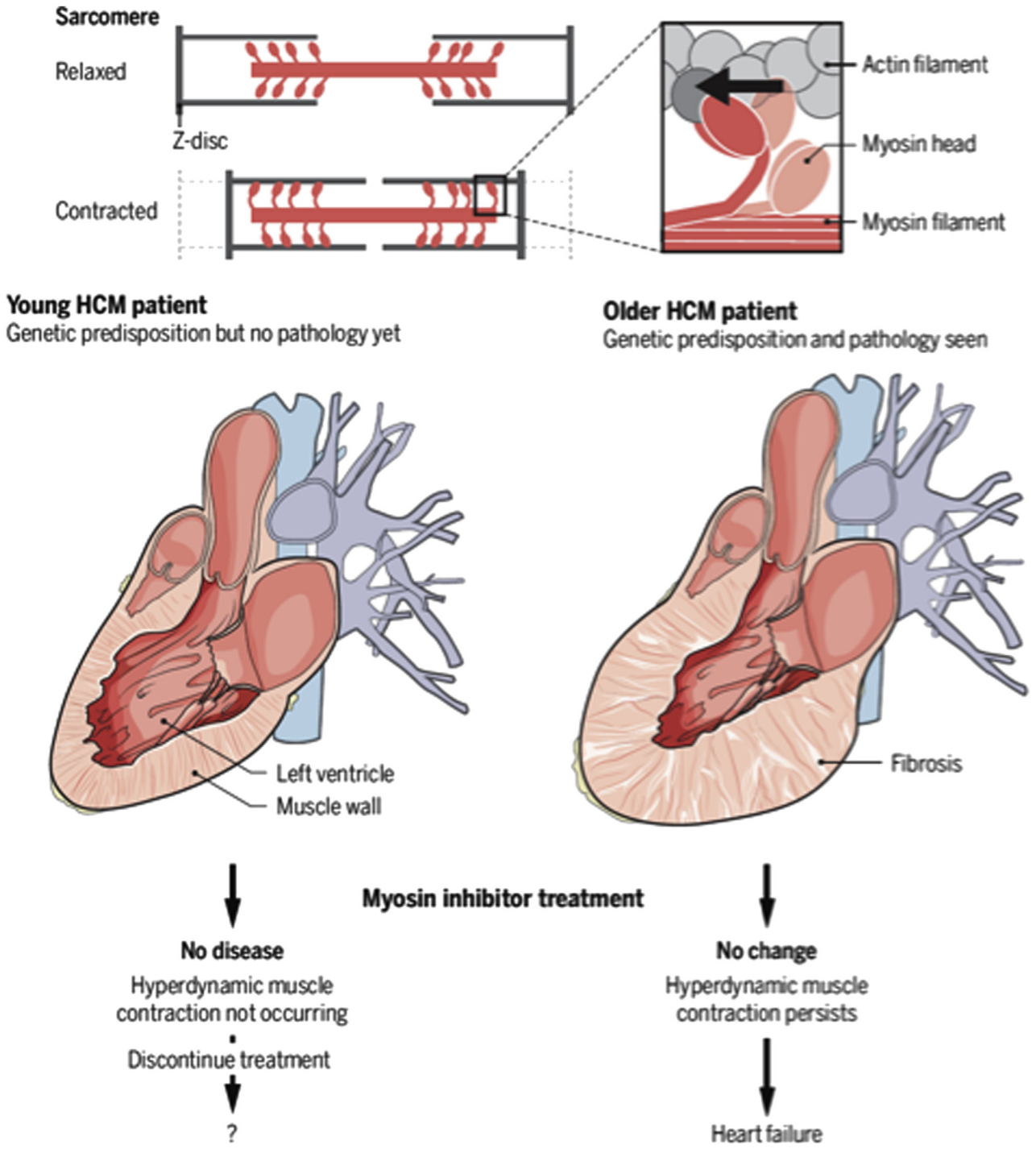

FIGURE 1. Mutations in myosin that increase power generation lead to hypertrophic cardiomyopathy (*HCM*). In a mouse model of HCM, early intervention with a small-molecule inhibitor of myosin reverses the disease (hypothetical patient scenario is shown). Such intervention could simplify treatment and become a generalized approach to control many contractile protein mutations that lead to HCM, or the use of myosin activators for dilated cardiomyopathy. (Adapted with permission from Warshaw,[7] Copyright © The American Association for the Advancement of Science.)

pharmaceutical innovations at the patient level are becoming rare events.[8] From 1991 to 2000, only 11% of all drugs tested in phase I trials were eventually successfully registered.[9] In addition to the obvious uncertainties with regard to the clinical effects and potential toxicities, successful application of MYK-461 will likely require