Hypertrophic cardiomyopathy (HCM), an inherited disease of the heart muscle, is among the most common Mendelian cardiac diseases, occurring in 1 in 500 people (1). Advances in genetics have facilitated identification of a subpopulation of patients with pathogenic variants in cardiac sarcomere genes. The earliest family mapped by positional cloning had a disease-causing mutation at position 403 of the β-myosin heavy chain (MHC) protein (2). A knock-in mouse model of this variant recapitulated aspects of human disease (3); many other sarcomere genes have been implicated subsequently (4). In clinics today, coding regions of numerous cardiac sarcomere genes are routinely sequenced, and, excluding those patients with discrete upper septal thickening, clearly pathogenic variants are identified in 30% to 50% of patients (5), thus marking a subset of “sarcomeric” HCM.

Current therapy for HCM is primarily palliative. Beta-blockers, nondihydropyridine calcium channel blockers, and the class Ia antiarrhythmic agent disopyramide are used for their negative inotropic and chronotropic and positive lusitropic effects (6,7). When these medications fail to alleviate symptoms, more invasive options for obstructive patients are recommended, such as surgical septal reduction or alcohol septal ablation (8). In patients at sufficiently high risk of sudden cardiac death, cardioverter-defibrillators are implanted.

Given this limited treatment armamentarium, there is renewed focus toward investigating therapies targeting the underlying pathophysiology of HCM. Novel approaches based on promising preclinical data showing prevention or regression of phenotype have led to ongoing clinical trials of angiotensin receptor blockade, statins, moderate-intensity exercise, and N-acetylcysteine. These therapeutic approaches have been joined in recent years by interest in gene silencing (9–11) and targeting the late sodium current (12) or the molecular motor itself (13). A critical question for all these approaches is as follows: Can treatment be given at any time, or is administration necessary before disease is established? Essentially, is the disease reversible? Or does the fact that HCM tends to progress during the growth spurt of the teenage years suggest an “irreversible” pathophysiological state?

In this context, the paper from Cannon et al. (14) in this issue of the Journal is of particular interest. These investigators created a new transgenic mouse model of the MHC R403Q mutation and tied it to a doxycycline-responsive element in a “gene-off” configuration. During placebo treatment, transgenic animals carrying 2 endogenous copies of the mouse α-MHC, as well as transgenes expressing mutant α-MHC under control of the doxycycline-responsive element, experienced progressive hypertrophy as well as dilation and reduction in ventricular function. Normal, nontransgenic mice did not. The investigators studied the effect of giving doxycycline to suppress the αMHC transgene at 3 time points: 20 to 40 weeks, 6 to 40 weeks, and 0 to 6 weeks (from the time of conception, which is possible because doxycycline crosses the placenta). These investigators found that disease manifestations were suppressed only in the group treated from conception.

This study is notable because it provides one of the first insights into the timing of murine disease onset. A lack of reversibility of human disease would have...
important implications for disease-modifying drugs currently in development. There may also be translational relevance for proactive family screening; for early identification, screening with genetic testing, echocardiography, and electrocardiography would be required more consistently at a younger age than guidelines currently endorse.

Given these far-reaching implications, can we assume that such an effect extends to humans? Although the study investigators showed the effects of treatment on transgene suppression and normalization of transgene protein at one time point, we cannot tell from the presented data whether there is treatment escape with age. In other words, was the doxycycline dose given later in adulthood adequate to suppress transgene expression at that time? We also do not know whether mutant transgene protein persisted in the myocardium of adult mice treated with doxycycline starting at 6 or 20 weeks. The investigators noted a variable effect of the transactivator system on left ventricular hypertrophy in mice, but these mice did not serve as comparator controls.

In assessing translational relevance, we must remember that mice and humans differ greatly. Notably, none of the HCM mouse models displays asymmetric hypertrophy or a left ventricular outflow tract gradient, 2 pathognomonic features of the disease. Further, mice express a different dominant MHC chain gene missense mutation. Cell 1990;62:999–1006.

What about reversibility itself? In fact, we are accustomed to expect reversibility given our experiences with reverse remodeling in patients with treated valvular disease, treated hypertension, or chronic kidney disease treated with renal transplantation. Decades of work show that inhibiting the renin-angiotensin-aldosterone system reverses cardiac fibrosis. Previous investigators demonstrated an ability to prevent or reverse fibrosis in HCM (15–17). In a bigenic mouse model with expression of the R92Q variant of troponin T type 2 (18), for example, removal of stimulation with mifepristone during adulthood led to fibrosis regression and a change in pathological markers. Importantly, drug treatment was required for expression, not suppression, of transgene activity. The same group examined 2-year-old rabbits that, like humans, express predominantly the cardiac β-myosin. After 12 months of therapy with N-acetylcysteine, these investigators observed reversal of established cardiac hypertrophy and interstitial fibrosis (17).

Currently, it is unclear how to resolve these apparently disparate observations. Maybe, for certain mutations, an abnormal transcript or protein leads to a state shift in cardiomyocytes or fibroblasts from normal to pathological and that suppressing gene expression and a change in pathological markers. Importantly, drug treatment was required for expression, not suppression, of transgene activity. The same group examined 2-year-old rabbits that, like humans, express predominantly the cardiac β-myosin. After 12 months of therapy with N-acetylcysteine, these investigators observed reversal of established cardiac hypertrophy and interstitial fibrosis (17).

Candidates for such processes could include calmodulin kinase II or chromatin remodeling. Such a construct could explain why treatment with N-acetylcysteine or exercise may lead to reversal, whereas allele silencing or transgene suppression alone did not in these studies. Perhaps adjunctive therapies focused on pushing downstream gene expression programs or protein signaling networks back to a steady-state normal may be required for treatment of disease in adults.

The current work lends important insight to our understanding of the pathophysiological basis of this disease, and it is especially timely as we move with cautious optimism toward targeted therapies.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Euan A. Ashley, Stanford University Falk CVRC, 300 Pasteur Drive, Stanford, California 94305-5406. E-mail: euan@stanford.edu.

REFERENCES


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