The energetic cost of contraction is higher in the myocardium of patients with hypertrophic cardiomyopathy

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A missense mutation at residue 403 in the actin-binding loop of myosin was the first FHC-associated mutation to be identified, a seminal observation made by the Seidman Laboratory in nearly 25 years ago. The author’s laboratory studied a mouse bearing this mutation in the Seidman laboratory in the late 1990s. Using 31P NMR spectroscopy of the intact beating heart, we found that hearts bearing the heterozygous R403Q mutation in myosin heavy chain (MyHC) had normal systolic but abnormal diastolic function in the absence of hypertrophy, and that there were deficits in workload-induced energetics measured as a fall in phosphocreatine concentration (PCr) with unchanged ATP. About the same time, Jung et al. also using 31P NMR spectroscopy, reported that the PCr/ATP was decreased in young asymptomatic patients with HCM. In 2003, the Oxford group showed that the PCr/ATP was lower in 31 HCM patients with known FHC mutations (16 in MyHC), with and without hypertrophy. In 2005, Keller et al. described the properties of myosin isolated from the heart of a FHC patient who underwent transplantation. The myosin missense mutation was R403W; the patient also had a mutation in cMyBP-C. Using a motility assay, they found that myosin ATPase activity was disproportionately higher than the observed increase in motility. These early studies all suggested that the cost of contraction is higher in the myocardium bearing of HCM/FHC-associated mutations in sarcomeric proteins.

cMyBP-C is the most recent protein to be identified as an integral part of the sarcomere. A series of mini-reviews summarizing its structure–function, its role in regulating contraction, and its role in cardiac pathophysiology is currently being published in Pflugers Arch – Eur J Physiol, and is recommended. Briefly, cMyBP-C binds to MyHC and acts as a tether connecting the thick and thin filaments. Recent work suggests that, by binding to the thin filament, cMyBP-C physically alters the position of tropomyosin on the thin filament, thereby altering cross-bridge dynamics. About a third of all HCM mutations are in truncated mutants of cMyBP-C.

Witjas-Paalberends and Güclü and their colleagues measured the energetic cost of contraction in the myocardium of HCM patients in two ways. First, they isolated cardiac muscle strips from 26 patients undergoing surgery to relieve LV outflow tract obstruction or after heart transplantation and measured the cost of contraction as the ratio of...
maximal ATPase activity to maximum tension. The ratio was highest for the 9 patients with MyHC mutants, intermediate for the 11 patients with cMyBP-C, and lowest for the 6 patients with no known sarcomere mutations. These results show that tension cost was higher for patients bearing HCM mutations, and that the cost was higher for MyHC than for cMyBP-C mutant muscles. Secondly, they compared myocardial efficiency for 28 asymptomatic pre-hypertrophied mutation carriers and 14 genotype-negative relatives by measuring MVO$_2$ and external work. Consistent with the isolated muscle studies, efficiency was lowest for MyHC mutant carriers, intermediate for the cMyBP-C carriers, and highest for controls. MVO$_2$ was comparable among groups, but work differed. These results support the hypothesis that both missense and truncated mutations associated with HCM/FHC lead to lower efficiency (higher tension cost), and that the magnitude of the change is mutation-specific.

These conclusions extend earlier work studying both HCM/FHC patients and animal models in two important ways: first, they support the hypothesis that a common property of HCM/FHC mutant hearts is the lower efficiency of contraction (higher tension cost). Secondly, as the functional defect is present in asymptomatic carriers with no hypertrophy or other known cardiac disease, they support the conclusion that the cause of decreased cardiac efficiency is the sarcomere mutation. The consequences of these single amino acid substitutions (the missense MyHC mutants) and deletion of a portion of the peptide chain (the cMyBP-C mutants) profoundly affect the function of the sarcomere, which in turn affects the entire myocyte and the intact heart. Similar results, using different measures of energy cost, have been obtained for intact mouse hearts bearing mutations in the R92 hotspot located in the tropomyosin-binding domain of troponin-T.8

There is much work to be done in this field, both clinically with regard to diagnosis and treatment and fundamentally with regard to increasing our understanding of the biology of the sarcomere. One goal would be to identify the tension cost for specific mutations within MyHC and cMyBP-C, as well as other sarcomere proteins. Motility assays comparing mutant and normal peptides and molecular dynamics studies of peptide domains carrying specific mutations will allow us to identify how apparently diverse structures can lead to the common outcome of impaired myofilament efficiency. Another goal is that the mechanism(s) underlying the diastolic dysfunction would be identified. Finally, work should test whether early clinical intervention designed to alleviate increased tension cost would be beneficial for HCM/FHC mutant carriers as well as those suffering from disease.

References