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EDITORIAL COMMENT

Can an Energy-Deficient Heart Grow Bigger and Stronger?*

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Since its initial description by two French pathologists more than a century ago (1), hypertrophic cardiomyopathy (HCM), a genetic model of cardiac hypertrophic response (2), has remained an intriguing disease that has fascinated clinicians and scientists alike. While it is easy to fathom a hypertrophic cardiac response to an external stressor, a myocyte loss, or gross cardiac dysfunction, there is no increase in external load, no discernible myocyte loss, or no gross cardiac dysfunction in HCM. Thus, how would one explain the development of cardiac hypertrophy in HCM? As early as in 1975, Grossman et al. (3) proposed enhanced myocardial contractility alone, evidenced by an increased left ventricular ejection fraction, could be responsible for the development of cardiac hypertrophy. Accordingly, increased

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contractility, conferred by the underlying genetic defect, could increase wall stress by shifting the force to an earlier time point in systole before thickening of the left ventricular wall (force-thickness mismatch). Increased systolic wall stress stimulates parallel replication of sarcomeres and hypertrophy. Nevertheless, despite preserved left ventricular ejection fraction, there is considerable evidence to suggest myocardial contraction and relaxation in HCM are reduced, even in the absence of discernible cardiac hypertrophy (4–6). Thus, alternatively, impaired myocardial contraction and relaxation could provide the stimulus for the development of hypertrophy in HCM. To resolve the apparent conflicting hypotheses, elucidation of the molecular pathogenesis of HCM is necessary. Since HCM is a genetic disease, identification of the primary defect that instigates the development of cardiac hypertrophy had to await elucidation of the molecular genetic basis of HCM.

The seminal discovery of an arginine to glutamine mutation in amino acid position 403 in the β-myosin heavy chain (MyHC) about 12 years ago in the affected members of a family with HCM led to elucidation of the molecular genetic basis of HCM (7). Subsequently, a large number of mutations in 11 genes encoding sarcomeric proteins were identified that encompass missense, deletion, and truncation mutations in the β-MyHC, cardiac troponin T (cTnT), and myosin binding protein-C (MyBP-C), the three most common causal genes for HCM (2). Today, HCM is a considered a disease of contractile sarcomeric proteins. However, since hypertrophy is a common response of the myocardium to a variety of external and internal stimuli, it is not surprising that a gross phenotype similar to HCM (i.e., cardiac hypertrophy in the absence of an increased external load) could also arise from defects in non-sarcomeric proteins. Examples are several and include expansion of trinucleotide repeats in myotonin protein kinase (myotonic dystrophy) (8) and frataxin (Friedrich's ataxia) (9), and mutations in mitochondrial deoxyribonucleic acid (Kearns Sayre syndrome) (10) and in the γ2 subunit of adenosine monophosphate kinase (11,12). While gross cardiac phenotype in sarcomeric and non-sarcomeric HCM appears similar, pathologic phenotype as well as the pathogenesis of cardiac hypertrophy are expected to differ. This notion is supported by the results of a recent study of mutations in γ2 subunit of AMP kinase, suggesting cardiac hypertrophy, due in part at least to storage of glycogen in the myocardium, is not associated with myocyte or myofibrillar disarray, the hallmark of HCM due to defects in sarcomeric proteins (13). Whether such a pathologic distinction is a consistent feature of cardiac hypertrophy caused by mutations in non-sarcomeric proteins remains to be determined.

Identification of the molecular genetic defects in HCM was soon followed by a large number of in vivo and in vitro functional studies with the goal of delineating the primary defect and, hence, the molecular pathogenesis of HCM phenotypes. In view of the diversity of the causal mutations, not surprisingly a diverse array of initial defects was described reflective of differences in the function of the causal proteins and topography of the mutations as well as differences in the experimental conditions (14). Despite the wealth of data, a fundamental issue of whether mutations afford gain-of-function, as one would speculate from the Grossman et al. (3) hypothesis 27 years ago, or loss-of-function, as some experimental data would suggest, remains unsettled. Similarly, whether cardiac myocyte dysfunction results from impaired contractile performance or altered calcium homeostasis in the sarcomere or a bioenergetic deficit also remains to be proven. We have proposed that the primary structural defect incites a functional defect in the responsible sarcomeric protein and myocytes leading to increased myocyte stress (15). Increased myocyte stress, whether mechanical, biochemical, or bioenergetic leads to expression and activation of a variety of stress-responsive molecules and intracellular signaling molecules that instigate gene expression and induction of diverse histological and structural phenotypes including cardiac hypertrophy, interstitial fibrosis, and myocyte disarray. The presence and severity of phenotypic expression are determined not only by the topography of the causal mutations and their impacts on

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the function of the sarcomeric proteins and myocytes, but also by the modifier genes as well as non-genetic and environmental factors (16).

In this issue of the *Journal*, Crilley et al. (17) provide evidence suggesting insufficient utilization of adenosine triphosphate (ATP) in the myocardium of patients with HCM provides the stimulus for the development of cardiac phenotype. Evidence for the "energy compromise" in the myocardium is based on demonstration of a 30% difference in the resting ratio of cardiac phosphocreatine (PCr) to ATP between 31 patients with mutations in either the β-MyHC or cTnT or MyBP-C gene and 24 control subjects. There were no significant differences in the PCr/ATP ratios among HCM subjects who had β-MyHC, cTnT, or MyBP-C mutations, and there was no significant correlation between PCr/ATP ratio and the maximum wall thickness. Another interesting finding of the study was a reduced PCr/ATP ratio in seven subjects who had the HCM mutations but did not have echocardiographic or electrocardiographic evidence of cardiac hypertrophy. The authors suggest that the underlying defect in HCM due to sarcomeric mutations is inefficient utilization of ATP, which increases the cost of force production putting excess demand to the myocyte and, thus, compensatory cardiac hypertrophy.

The results of the current study (17) complement the results of previous studies (18–22), including the presence of reduced myocardial PCr/ATP ratio in patients with Friedrich's ataxia irrespective of the presence or absence of cardiac hypertrophy (22). The strengths of the present study (17) are: 1) knowing the specific genetic mutation in each HCM individual included in the study; 2) inclusion of mutation carriers without cardiac hypertrophy; and 3) mutations in three major causal genes responsible for HCM are represented. The findings of reduced PCr/ATP ratio in those with cardiac hypertrophy is not surprising and has been shown previously in pathologic cardiac hypertrophy including fully evolved HCM (18–21), as well as in heart failure and in myocardial ischemia (23). However, the finding of a reduced PCr/ATP ratio in subjects with sarcomeric protein mutations but no discernible cardiac hypertrophy is novel. This is in accordance with the results of a previous study (22) in Friedrich's ataxia of subjects harboring frataxin mutations with no significant cardiac hypertrophy but who had abnormal PCr/ATP ratios. These findings collectively implicate altered myocardial bioenergetics in the development of cardiac hypertrophy, as proposed by the authors of the present (17) and previous (22) studies. However, review of data shown in Figure 1 of Crilley et al. (17) subdues the enthusiasm for the proposed hypothesis. Despite the mean values being statistically different, there is a significant overlap in the PCr/ATP ratio between normal individuals and those with HCM, including subjects with causal mutations but no cardiac hypertrophy. Table 1 of Crilley et al. (17) shows two possible outliers in the HCM group that probably account for the major portion of the differences in the mean values of PCr/ATP ratios. The presence of a significant degree of overlap in the PCr/ATP ratio of half of all study subjects shown in Figure 1 of Crilley et al. (17), along with the presence of normal PCr/ATP ratios in several subjects with HCM, do not support a direct causal role for myocardial energy deficit in the pathogenesis of cardiac hypertrophy in HCM. The absence of a correlation between PCr/ATP levels and the maximum wall thickness also diminishes the possible contribution of reduced myocardial bioenergetics in affecting expression of hypertrophic phenotype. In addition, the potential confounding effects of medications and dietary supplementation in cardiac high-energy phosphate levels are unclear. The finding of a reduced PCr/ATP ratio in those without cardiac hypertrophy raises the possible utility of this noninvasive technique to detect mutation carriers. Table 1 of Crilley et al. (17) shows 11 of 31 HCM subjects did not have the pre-defined criteria for left ventricular hypertrophy (a maximum wall thickness of ≥13 mm). The PCr/ATP ratios in seven of these subjects, shown in Figure 1 of Crilley et al. (17), unfortunately exhibit significant overlap with the values for the controls. While receiver-operator characteristics curves are required for the proper analysis, given the limitations cited in the preceding text, one would expect low sensitivity for detecting pre-clinical HCM even when restricted to screening family members of affected pro-bands.

Another interesting aspect of the results of the present study is absence of a significance difference in the PCr/ATP ratio among HCM patients with mutations in three different causal genes, as shown in Figure 1 of Crilley et al. (17). This finding, along with the observation that hypertrophy of any cause reduces the PCr/ATP ratio, and heart failure associated with other causes may have a decreased PCr/ATP ratio suggest decreased PCr/ATP is a consequence rather than a primary defect. The authors appropriately claim that decreased PCr/ATP is a primary defect based on the observation that decreased PCr/ATP is observed in individuals with HCM mutations without hypertrophy. Nevertheless, the significant overlap in the PCr/ATP ratio between normal individuals and those with HCM makes this claim less enticing. Secondly, the specific molecular defects known for some of the mutations are quite diverse, namely, altered myosin actin binding, altered calcium affinity, and altered adenosinetriphosphatase activity are unlikely to lead to the same specific primary defect in bioenergetics. The absence of a significant difference among the three groups of HCM patients may reflect the relatively small number of subjects in each group and, hence, the possibility of a statistical type II error cannot be excluded. While the PCr/ATP ratio is considered a well-established indicator of cardiac energy status, data are needed to show how diverse mutations, located in different domains and different sarcomeric proteins affect myocardial PCr/ATP ratio and whether reduced PCr/ATP ratio reflects lower (PCr) or higher (ATP) concentrations in the myocardium or a combination of both. The need for further delineation in

the components of the PCr/ATP ratio is demonstrated by data in the GLUT4 null mice, whereby an increase in myocardial PCr/ATP ratio is associated with severe cardiac hypertrophy but a depressed myocardial function (24). In addition, since mutant β-MyHC protein is also expressed in slow skeletal muscles of patients with HCM, an energy deficit in skeletal muscle of these muscles in pre-clinical stage would be expected, which would be unexpected since significant number of HCM subjects succumb to sudden cardiac death during highly competitive sport activities. It would be also interesting to determine whether PCr/ATP ratios were different between interventricular septum, site of predominant hypertrophy, and other walls, or if a gradient existed between the subendocardium and the epicardium. Furthermore, HCM patients could suffer from myocardial ischemia because of a relative capillary paucity as well thickening of the media of intramural coronary arteries; the potential confounding effects of myocardial ischemia, a major determinant of PCr/ATP ratio, deserve to be explored. Finally, additional studies are needed to characterize functional and biological significance of changes in different components of myocardial bioenergetics, such as transport of creatine to myocytes via creatine transport uptake protein, production of ATP in the mitochondria through oxidative phosphorylation, and/or hydrolysis of ATP to ADP and Pi by the β-MyHC during cardiac cycle.

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