Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease; yet, despite several decades of research, there is no specific disease-modifying therapy. Patients most often present with reduced exercise tolerance, heart failure, and cardiac arrhythmias. The discovery of specific HCM-causing mutations, advances in molecular medicine, and improved diagnostic techniques have generated substantial interest in identifying new HCM-specific therapies and more importantly determining the optimal timing for initiation of such therapy. Research into mechanisms underlying the clinical symptoms and complications in HCM has varied from genetics to molecular and cellular pathways. For some time, there has been burgeoning evidence that cardiac metabolism may play an important role in mediating the clinical consequences of HCM.1,2

See Article by Güçlü et al

Decreased efficiency in adenosine triphosphate utilization is a common feature of cardiomyocytes carrying diverse mutations. Crilley et al1 reported a decreased phosphocreatine-to-adenosine triphosphate in 7 HCM carriers without left ventricular hypertrophy by the use of 31P spectroscopy, suggesting that a compromised energetic state may play a role in the early manifestation of hypertrophy. We previously demonstrated that myocardial phosphocreatine was significantly decreased by 24% in HCM patients with a β-myosin heavy chain mutation compared with controls; pseudo-first-order creatine kinase rate constant was 26% lower and the forward creatine kinase flux 44% lower in HCM.3 However, in this study, myocardial strain did not correlate with the metabolic indexes. Investigations of cardiac energetics have generally used magnetic resonance spectroscopy.

Positron emission tomography (PET) introduces a new level for imaging cardiac pathophysiology using physiological tracers labeled with C-11, N-13, O-15, and F-18, which allow the synthesis of naturally occurring and biologically active compounds. Use of radiolabeled compounds allow for better in vivo quantification of specific biological processes. These PET techniques have unique advantages while investigating the role of cardiac energy metabolism in maintaining cardiac performance as a pump.4 A direct estimate of the tricarboxylic acid cycle using C-11 acetate as a PET tracer can offer insights into myocardial oxidative metabolism. C-11 acetate is rapidly absorbed by myocytes, converted to acetylCoA, and metabolized to CO₂ and water through the tricarboxylic acid cycle via oxidative phosphorylation.5 The myocardial clearance rate after intravenous administration of C-11 acetate correlates closely with myocardial oxygen consumption measured by arterial-venous difference of oxygen.6 While metabolic studies with C-11 palmitate or FDG studies are dependent on plasma substrate levels, C-11 acetate metabolism is independent of concentration of energy substrates for the myocardium.7 In the heart, there is close coupling between myocardial oxygen consumption (MVO₂) and its mechanical function. Mechanical efficiency is defined as the ratio of useful energy (eg, stroke work) to oxygen consumed and is ≥25% under normal conditions.8 Mechanical efficiency is reduced in heart failure, and increased energy expenditure relative to performed work likely contributes to disease progression.9 Mechanical efficiency is calculated by dividing the estimates of external work (mean arterial pressure, stroke volume, and heart rate) by the product of MVO₂ and left ventricular mass. The numerator is obtained via imaging such as magnetic resonance or echocardiography and the denominator (MVO₂) by PET-based C-11 assay.

In this issue of Circulation: Cardiovascular Imaging, Güçlü et al10 report investigate myocardial efficiency and energetics in genotype-positive-phenotype-negative HCM subjects (G+P−) versus obstructive HCM patients using cardiac magnetic resonance and 11C-acetate PET imaging. Myocardial external efficiency (MEE) was reduced in G+P− compared with normal controls but was further decreased in obstructive HCM. The authors demonstrate that reduced MEE at the early stage of HCM (G+P−) is largely caused by a decrease in cardiac external work and slight increase in MVO₂. At the advanced stage of HCM (hypertrophic obstructive cardiomyopathy [HOCM]), MEE was reduced because of a significant decrease in oxygen consumption per gram tissue.

In this study, a reduction in MEE was not accompanied by regional contractile abnormality early in the disease (G+P− had similar peak systolic circumferential strain to controls) but was reduced in HOCM, interestingly, only in the septal but not in the lateral wall. The authors postulate that these nonuniform changes in contractile efficiency were related to the secondary negative remodeling effects of the septal hypertrophy. The authors further investigated the impact of outflow tract obstruction by monitoring changes in myocardial geometry, contractility, and mechanical efficiency pre- and
post-myectomy. Compared with aortic stenosis patients undergoing aortic valve replacement, patients with HOCM undergoing septal myectomy had less reverse remodeling, as evidenced by a smaller decrease in left ventricular end-diastolic volume, left ventricular end-systolic volume, and left ventricular mass. Furthermore, there was no significant change in global systolic circumferential strain, MVO₂, and MEE post-myectomy, while all parameters improved postaortic valve replacement. The deterioration of MEE post-myectomy was largely related to adverse changes in the septal wall, with small yet significant improvements in the lateral wall.

The present study provides a comprehensive profile of energetics, mechanics, and mechanical efficiency, using sophisticated techniques, at different stages of HCM. The authors have significant expertise in this field. They have published several papers on the topic with regards to mutation carriers and HCM patients with consistent results. The current study complements their previous studies and provides unique incremental insights. Although performed in a cross-sectional design, the authors demonstrate the apparently progressive impairment of myocardial efficiency from genotype-positive carriers to phenotype-positive patients. The current study also enlightens us that reduced efficiency coupled with hypertrophy possibly underlies the wall-to-wall differences in contractile efficiency in HCM.

Another incremental piece of information is the issue of the primary myopathy in HCM. Their investigation of post-myectomy and postvalve replacement patients highlights the differences between hypertrophy and secondary myopathy related purely to afterload (aortic stenosis) versus a primary myopathy (HCM). Relief of afterload resulted in significant reverse remodeling in aortic stenosis. Relief of afterload in HCM, on the other hand, did not because factors other than afterload, namely, including the primary myopathy, continue to negatively impact the myocardium.

In many aspects, this body of work is personally rewarding because it dovetails well with findings from our HCM cohort. We have independently demonstrated concepts germane to this discussion without the advantage of ¹⁴C acetate imaging. We have argued for some time that the primary myopathy in HCM is often ignored. In over 100 post-myectomy HCM patients with significant reductions in left ventricular outflow tract gradients, we demonstrated lack of substantial changes in global systolic strain, despite improvements in symptoms and exercise time. The present work showing no change in MEE after myectomy fits well with our findings.

There are some issues to be mindful of while interpreting the results of the Güçlü study. The sample size is small particularly for the HOCM subgroup. Given the variability in presentation and post-myectomy evolution, one could suspect that postsurgical remodeling likely encompasses a wider range of response than that seen in the presented cohort. Scar burden (=4% left ventricular mass in HOCM) is smaller than that noted in our experience and in several other large cohorts. Again, this is likely a function of the small sample size, and in defense of the authors, a larger scar burden would most likely only magnify the lack of reverse remodeling and inability to improve MEE postsurgery. Diastolic strain rates by magnetic resonance are technically challenging, and their value is uncertain. We do not know the temporal resolution of the scans and, therefore, unsure of the reliability and validity of the diastolic strain data. Echo-derived E/E′ data are similarly controversial. There is evidence that E/E′ does not closely correlate with left atrial pressure. On an examination of our cohort of >600 patients, we found that E/E′ was not valuable in predicting clinical outcomes in HOCM but useful in nonobstructive HCM at baseline and in HOCM patients after myectomy. Therefore, we feel only the post-myectomy E/E′ data in Table 3 are informative. Overall, their conclusions on diastolic function may need further validation. Mean arterial pressure may not represent true afterload and may underestimate external work in obstructive HCM. Inclusion of nonobstructive and labile-obstructive HCM patients who had similar resting left ventricular outflow tract gradients as controls would have been additionally informative.

The issue of microvascular ischemia remains a significant confounder. Others and we have shown significant microvascular ischemia in HCM. Our previous work demonstrates that a nonobstructive HCM cohort with high rates of adverse clinical outcomes had large scar burden and high prevalence of microvascular ischemia. Not knowing the ischemia burden and distribution particularly in the HOCM cohort, pre-and post-myectomy, makes it challenging to understand the implications of the MEE and strain findings. While it is the most feasible method to noninvasively measure MVO₂,¹¹C acetate provides only a semiquantitative index of oxidative metabolism. Formulae converting clearance rate constants to equivalents of absolute units were derived from small sample sizes in predominantly normal physiological conditions and, therefore, may not accurately extrapolate to pathological states. Furthermore, factors unrelated to oxygen utilization may influence tracer kinetics. Finally,¹⁵O₂ is considered the gold standard for noninvasive estimation of MVO₂ because oxygen is the final electron acceptor in all pathways of aerobic metabolism. This approach yields absolute values of MVO₂ and is impervious to the confounding influence of pathological disease states. However, availability, logistics, and data analysis are challenging, making it unreliable and difficult to apply widely.

The authors raise the possibility of early detection of metabolic abnormalities that may prompt early, prephenotype initiation of metabolic modulators that hold out the promise of modifying the course of disease. In that regard, perhexiline, a metabolic modulator that prompts carbohydrate utilization as the preferential substrate by the cardiomyocyte, has shown some promise in HCM. In 46 nonobstructive HCM patients, perhexiline ameliorated cardiac energetic impairment, corrected diastolic dysfunction, and increased exercise capacity. Unfortunately, a larger perhexilene clinical trial was recently terminated, and its wider impact on symptomatic HCM patients may have to wait.

Disclosures
None.

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A Good Heart Is Hard to Find: Even Early in Hypertrophic Cardiomyopathy
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