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Imaging Myofibrillar Disarray and Microvascular Dysfunction in Hypertrophic Cardiomyopathy: Novel Imaging Biomarkers for a New Era in Therapeutics

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Hypertrophic cardiomyopathy (HCM) is a heterogeneous disease unified under the broad umbrella of increased left ventricular thickness in the absence of another cause[1]. Long before unravelling the genetic underpinnings, first as a monogenic disorder of the sarcomere[2] and more recently in sarcomere mutation negative patients as a polygenic predisposition with environmental triggers such as hypertension[3], the histologic hallmark of HCM has been myofibrillar disarray.. As the microscopic disorder progresses, so too do varying degrees of microvascular dysfunction, fibrosis, both replacement and interstitial, and myocyte and left ventricular hypertrophy[4]. The exact interrelations between these factors, however, are non-linear and challenging to tease apart[4]. In the end, what is left is behind is both substrate and trigger for arrhythmias and heart failure. Predicting risk of sudden cardiac death (SCD) are the goals of recently updated European Society of Cardiology guidelines[5] (a quantitative score) and ACC/AHA guidelines[1] (more qualitative). None of the presently used risk models are aimed at predicting the risk of heart failure or other causes of mortality in HCM.

Many well-established predictors of SCD in HCM reflect higher burdens of fibrosis[6]. Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) directly measures replacement fibrosis *in vivo*. Extensive LGE (>15% of LV mass) is a marker of increased risk of SCD[7] and is now a class IIb indication for an implantable cardioverter defibrillator in the most recent ACC/AHA guidelines[1], but is not included in the ESC guidelines[5]. Higher levels of biomarkers such as NT-proBNP and hs-cTnT increase in a graded fashion with both interstitial and replacement fibrosis as measured by CMR[8], and these blood biomarkers portend increased risk of adverse events[9], although are not presently included in risk prediction algorithms. The SHaRE registry demonstrated that patients with identifiable sarcomere mutations have worse outcomes relative to those without[10]. The Hypertrophic Cardiomyopathy Registry (HCMR), a large NHLBI funded project to delineate the relative role of genetics, biomarkers and CMR in risk stratification, revealed that genotype positive patients have more LGE relative to those without[8]. Worse outcomes in sarcomere mutation positive may relate, at least in part, to the greater amount of scar found in this subgroup.

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These markers and others underscore that scar in HCM is an important prognostic risk marker. However, what initiates scar formation? Is microvascular disease and ischemia an inciting factor? Many hypothesize that myofibrillar disarray and microvascular health are the earliest bad actors in HCM. These processes have been elusive both to detect and to quantify to this point.

In this issue of *Circulation,* Joy et al[11] report on quantitative CMR myocardial perfusion as a marker of microvascular disease (MVD) in HCM and an emerging and innovative CMR technique known as cardiac diffusion tensor imaging (cDTI). cDTI measures the diffusion of water within an imaging voxel to quantify the extent of myocardial microstructural pathology. In this case, cDTI measures the degree of myofibrillar disarray and was first applied to HCM patients almost a decade ago[12]. The manuscript defines three groups: 51 HCM patients without an identifiable genotype (G-LVH+), 50 HCM patients with an identifiable sarcomere mutation (G+LVH+), and 77 patients with an identifiable sarcomere mutation that do not have phenotypic criteria for a diagnosis of HCM (G+LVH-), as well as 28 normal controls. Patients with overt HCM, independent of genotype, had abnormal microstructure and MVD compared to healthy volunteers. Within the two groups of overt phenotypes, the G-LVH+ group had elevated absolute second eigenvector angle (E2A) relative to the G+LVH+ group. E2A is a component of cDTI thought to correspond with increased cardiomyocyte tension and worsened lusitropy. Perhaps most thought provoking were the results of the G+LVH- group. Compared to normal controls, G+LVH-had worse cDTI and MVD, though not to the extent of those with overt phenotype. This data supports the potential of cDTI and quantitative perfusion as early-phenotype biomarkers in HCM. The question remains whether these findings add prognostic import to the presence of the sarcomere mutation in G+LVH- individuals.

The authors should be commended for performing the largest study to date on cDTI techniques in combination with quantitative CMR myocardial perfusion imaging in a broad population of HCM patients. The study did show an independent association of abnormal cDTI with having an abnormal ECG, but the prognostic importance of the findings remain unclear. The size of the present study is not conducive to uncovering prognostic markers given that the hard outcome event rate in HCM is <1% per year and thus prognostic studies require thousands of patients followed for several years to uncover relevant risk markers[8, 10]. However, potential intriguing future applications of these techniques would involve tracking changes in cDTI metrics and quantitative perfusion in patients on cardiac myosin inhibition (CMI) before and after treatment, or in patients pre- and post-septal reduction therapies (SRT). What do these metrics look like before and after intervention? How do these therapies work on the myocardial structural level?

CMIs have burst onto the HCM scene in the last few years, first in clinical trials and then with the FDA-approval of mavacamten in April 2022. In patients with left ventricular outflow tract obstruction (LVOTO), CMIs robustly reduce LVOTO gradients, improve symptoms of heart failure, and increase exercise tolerance[13]. Even more strikingly, a sub-study of the EXPLORER-HCM trial demonstrated that CMIs reduce LV mass, LV maximal thickness, and left atrial size[14] and thus are the first medical therapies to demonstrate reverse remodeling in HCM. The question remains whether this is simply an effect of

reducing LVOTO or there is a direct effect of CMI's on myocardial structure, including myofibrillary disarray, the microvasculature, and myocyte hypertrophy. CMR studies of CMI's in nonobstructive HCM may shed some light on the aforementioned question. The role of CMIs in non-obstructive HCM remains less clear than in obstructive HCM, with phase 3 trials ongoing. The phase 2 MAVERICK trial of mavacamten showed improvement in biomarkers in a small cohort of HCM patients[15]. Many see CMIs as heralds of disease modification, though direct head-to-head comparisons with SRT are lacking, and cost-effectiveness remain in question given their high cost at present. Building upon the groundwork laid by Joy et al[11], a logical extension of their work would be to examine changes in cDTI in patients on CMI. These findings might identify patients more or less likely to respond to CMI's, or even identify higher risk G+LVH- patients that might benefit from treatment before development of overt LVH. Understanding which processes are reversible and in what order will help elucidate the relationship between myocyte disarray, fibrosis, increased thickness, and microvascular health.

The authors of the present study have brought forth an important work at an important time in HCM care. The ability to image myocardial fibrosis has already added to prognostication and care of this population; cDTI and quantitative perfusion may well be a useful tool to examine the microstructure and microvasculature before fibrosis develops. In the new era of disease modification in HCM, identifying early markers of high risk phenotypes has become a priority. The authors have identified another set of imaging biomarkers that, in the future, may help get the right treatment to the right HCM patient at the right time.

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