Myocardial dynamics in subclinical genetical hypertrophic cardiomyopathy

Running Title: Myocardial dynamics in subclinical HCM

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INTRODUCTION

Genetic hypertrophic cardiomyopathy (HCM) is caused by pathological mutations in sarcomere or sarcomere-related genes (G+). A diagnosis of HCM is established in the presence of a left ventricular (LV) maximal wall thickness >15mm in probands or >13mm in familial disease, capturing the presence of left ventricular hypertrophy (LVH).However, not all variant carriers develop LVH or clinically overt HCM (G+LVH+) since penetrance is age- and context-dependent, and influenced by genetic and environmental factors[1]. However, the absence of LVH in sarcomere variant carriers, or subclinical HCM (G+LVH—), is not equivalent with the absence of a phenotype as they may have a constellation of subtle manifestations. Cardiovascular MRI (CMR) can identify in subclinical HCM: (1) a higher prevalence of myocardial crypts[2], mitral valve (MV) abnormalities[3] and increased trabeculation[4] potentially suggesting deficient embryonic cardio-morphogenesis; (2) regional and global impaired myocardial perfusion potentially suggesting microvascular dysfunction[5]; (3) higher extracellular matrix volume (ECV) potentially suggesting fibrotic remodelling[6]; (4) abnormal diffusion on cardiac diffusion tensor imaging (cDTI) potentially suggesting myocardial disarray[7]; (5) a lower phosphocreatine to adenosine triphosphate ratio potentially suggesting altered myocardial energetics[8], and (6) a supranormal systolic function[9] potentially suggesting abnormal calcium signaling[4]. However, the impact of these subtle phenotypic manifeststations on myocardial dynamics is yet to be elucidated.

Myocardial dynamics in subclinical HCM

What the study of Negri *et al* published in this issue of *Circulation: Cardiovascular Imaging* adds to the literature is that subclinical HCM may also be characterized by abnormal myocardial dynamics[10]. The study recruited 38 G+LVH— individuals and 42 healthy individuals which were similar in terms of mean age, percentage of males and body surface area. In all participants, balanced stead-state free precession cines were acquired, including three long axis view (2-chambers, 3-chambers, and 4-chambers) as well as a complete LV short axis stack. CMR feature tracking analysis using a 3D deformable model of the myocardium was performed[11] which allowed the derivation of the global longitudinal, radial, and circumferential strains. Compared with healthy control subjects, sarcomere variant carriers had worse myocardial dynamics suggested by the presence of smaller absolute strain values across all three directions despite the absence of LVH and regardless of the ejection fraction.

The mechanism underpinning the worse myocardial dynamics in sarcomere variant carriers has not been established. However, it might be related to myocardial fibrosis, disarray, and ischemia altering the degree of myocardial deformation during the cardiac cycle. Indeed, CMR perfusion[5] and oxygen-sensitive CMR sequences[12] can identify reduced perfusion and impaired tissue oxygenation in +LVH— individuals. In addition, pro-fibrotic pathways are known to be already activated in sarcomere variant carriers (e.g. increased serum levels of C-terminal pro-peptide of type I procollagen [PICP] and PICP-to-C-terminal telopeptide of type I collagen ratios[13] indicating more collagen synthesis than degradation leading to its extracellular matrix deposition). CMR data in G+LVH— corroborate this profibrotic milieu given the reportedly higher ECV[6]. Lastly, the lower diffusivity, higher mean diffusivity and elevated absolute second eigenvector angle identifiable using cDTI in G+LVH— suggest a microscopic architecture characterized by myocardial disarray.

There are also more complex ways to assess myocardial dynamics. In contrast with conventional strains (i.e., longitudinal, radial, and circumferential), principal strains capture the deformation along the natural directions (i.e., direction of strongest systolic compression)[14]. Using Procrustes motion analysis, higher-order mechanics metrics such as Procrustes trajectory size, Procrustes trajectory distance from diastole, tensor determinant or squared norm of the second gradient[14] can be calculated. An advantage of this methodology is that Procrustes analysis is free of confounding by non-shape variations and is able to capture pure shape deformation patterns[15]. However, their utility in subclinical HCM is yet to be explored.

Transition from subclinical to clinically overt disease

Given the absence of extensive hypertrophy and fibrosis, the subclinical phase of genetic HCM may be more amenable to interventions aiming to decrease or even halt disease projection. The EXPLORER-HCM (Clinical Study to Evaluate Mavacamten [MYK-461] in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy) [16] and VANISH (the Valsartan for Attenuating Disease Evolution in Early Sarcomeric Hypertrophic Cardiomyopathy)[17] suggested that mavacamten (a myosin inhibitors) and ,valsartan (an angiotensin II receptor blocker) respectively, may have beneficial effects on cardiac remodeling in overt HCM. Thus, biomarkers

which track disease progression from subclinical to clinically overt disease are urgently needed, so future clinical trials evaluating the ability of these potential disease-modifying therapies to halt progression of HCM can accurately be evaluated. For this purpose, myocardial dynamics metrics are potential candidates, but it is currently unclear whether they track disease progression.

On average, 60% of sarcomere variant carriers will develop overt HCM[1]. Currently, those who are older, have an abnormal ECG[18], abnormal MV[19], and evidence of diastolic dysfunction on Doppler echocardiography[19] appear to be more likely to develop penetrant disease during longitudinal follow-up in small cohorts of G+LVH—. As we are unable to predict who will develop over disease, all variant carriers require life-long surveilance[20]. However, whether the presence of myocardial dynamics abnormalities in subclinical variant carriers predicts the development of LVH and can be used to guide surveillance strategies remains elusive.

Conclusion

Phenotypic conversion biomarkers are urgently needed to guide surveillance strategies and treatment response in clinical trials evaluating potential disease-modifying therapies in sarcomere variant carriers. Myocardial dynamics abnormalities may be present in subclinical sarcomere variant carriers prior to developing LVH in the form of reduced absolute global longitudinal, radial, and circumferential strain. However, their clinical utility remains to be stablished.

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