Clinical dilemmas in predicting the progression of pre-clinical hypertrophic cardiomyopathy—is MRI strain the solution?

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Provenance: This is an invited article commissioned by the Academic Editor Dr. Hao Cui (Department of Cardiovascular Surgery, Mayo Clinic, Rochester, MN, USA).


Submitted Jul 15, 2019. Accepted for publication Jul 24, 2019.

Hypertrophic cardiomyopathy (HCM) is one of the commonest inherited cardiac diseases, with an estimated prevalence of 1 in 500 (1). It is characterized by unexplained myocardial hypertrophy, which occurs in the absence of pressure overload (e.g., hypertension, aortic stenosis) or infiltration (e.g. amyloidosis) (2,3). Myocardial hypertrophy in HCM typically occurs in the interventricular septum but can also be apical, segmental, or concentric. HCM is primarily a genetic disease involving mutations in at least 14 genes (2,4). Its inheritance is autosomal dominant but with incomplete penetrance. There is commonly a silent compensatory period, which may be followed by the development of a variable phenotypic expression of disease (5).

Advances in genetic testing has broadened our understanding of the molecular processes underpinning HCM, as well as providing an opportunity to perform cascade testing of at-risk family members. This has led to the recognition of a novel patient subset within the vast and ever-expanding HCM spectrum, that is the genotype positive-phenotype negative (G+P−) or pre-clinical HCM (5,6).

There are clinical challenges that have emerged in the management of G+P− patients. One question is whether G+P1 patients should be considered for primary prevention implantable cardiac defibrillator therapy especially for those with a strong family history of sudden death (5). Indeed, sudden death has been described in G+P− individuals suggesting that the non-hypertrophied myocardium in these individuals can in fact be functionally abnormal and harbor arrhythmogenic substrates capable of triggering life-threatening ventricular tachyarrhythmias (7). Second is whether these patients should be disqualified from participation in strenuous competitive sport (5). Improved recognition of early myocardial structural or functional alterations that reflect effects of sarcomere mutations is therefore needed to allow targeting of at-risk G+P− individuals with early preventative strategies. With these dilemmas in mind, we turn to advances in cardiac imaging to improve our understanding of early effects of HCM sarcomere mutations, before pathological remodelling ensues to define clinically overt disease.

Traditional assessment of left ventricular (LV) function using echocardiographic ejection fraction is often limited by image quality and significant measurement variability. Recently, myocardial strain assessment has garnered interest as a novel imaging technique to more sensitively assess myocardial contractile performance (8). Myocardial strain refers to the degree of deformation of a fixed material point within the myocardium from its initial length throughout the cardiac cycle (9). In the early stages of adoption, myocardial strain assessment was performed using tissue Doppler imaging to measure strain rate (10). This approach was limited by the angle dependency of Doppler imaging. The development of speckle tracking was a leap forward which allowed the angle independent measurement of strain using echocardiography in circumferential, longitudinal...
and radial directions. It was then identified in a range of cardiovascular disorders including aortic stenosis and HCM, that, abnormal LV global longitudinal strain was associated with increased adverse cardiovascular outcomes such as death and ventricular arrhythmias (8,11). Importantly, speckle tracking imaging is still subject to all the inherent limitations of ultrasound including image quality and operator dependency. The utility of strain imaging has now evolved into the field of cardiac magnetic resonance (CMR) (9,12,13).

Feature tracking cardiac magnetic resonance (FT-CMR) is one of several CMR imaging techniques used to assess myocardial strain (9). It tracks features of interest along contour lines on routinely acquired cine images, following the same basic premise of speckle tracking echocardiography. More precisely, it is based on defining small square windows, centred around a feature, on a first image and then searching for the most similar greyscale pattern on the following cine image (9). It’s a main advantage, relevant for clinical adoption, is that, as a post-processing CMR technique of routinely acquired steady-state free precision sequences, there is no need for additional image acquisition. The diagnostic and prognostic utility of myocardial strain have already been reported in other cardiovascular disorders such as ST-elevation myocardial infarction and dilated cardiomyopathy (12,13).

In the December 2018 edition of Radiology, Vigneault et al. (14) contribute valuable findings, paving the way towards the use of FT-CMR in patients with HCM. The study cohort comprised 99 participants who were prospectively recruited as part of a multicentre observational study of participants with HCM and their family members. Genetic testing and CMR was performed in all participants which comprised 23 control participants, 34 participants with preclinical HCM (G+P−) and 42 participants with overt HCM (G+P+). Using feature-tracking software, circumferential strain was measured at the epicardial and endocardial surfaces and their difference computed to yield the circumferential transmural strain difference (cTSD). The main finding of the study was that FT-CMR identified increased systolic dysfunction as assessed by epicardial and endocardial circumferential strain in HCM participants with confirmed sarcomere mutations, regardless of the presence of hypertrophy. Remarkably, cTSD was not only significantly higher in those with overt HCM (22±7) but also in those with pre-clinical HCM (17±4) compared to control participants (14±4, P<0.001). There were also significant differences in segmental cTSD between those with overt HCM and pre-clinical HCM compared to control participants. For example, there was higher cTSD in the antero-septal wall in those with HCM (26±9, P<0.001) and pre-clinical HCM (20±5, P=0.011) compared to the control group (16±5). In multivariable models (controlling for septal hypertrophy and N-terminal brain-type natriuretic peptide), cTSD was independently predictive of preclinical (OR: 1.28, P<0.01) and overt HCM disease status (OR: 1.41, P<0.01). Notably, analogous contractile abnormalities were not detected by conventional myocardial tagging, though details of the analysis are not provided by the authors.

The study by Vigneault et al. (14) broadens our understanding of the fundamental contractile abnormalities observed in HCM, demonstrating an abnormally high difference in circumferential strain between the endocardial an epicardial surfaces. In health, it is known that a small cTSD exists (15,16), probably contributed by a gradient in the myocardial fiber angle across the thickness of the LV wall. In pre-clinical and overt HCM, the pathophysiological mechanisms behind a high cTSD are unclear but possibly reflect a combination of increased wall thickening, myocardial fibrosis or subendocardial dysfunction. Notably in this study, there were no differences in wall thickness between participants with preclinical HCM and seemingly healthy controls (9.5 vs. 9.8 mm, respectively; P=0.496). This implies that differences in cTSD seen in preclinical HCM cannot be explained by changes in cardiac contraction caused by increased wall thickness alone. The authors sensibly hypothesize that functional myocardial abnormalities may therefore precede anatomic changes as early phenotypic manifestations of sarcomere mutations. What remains certain is that, there is considerable interest in identifying the patients likely to progress to overt HCM, especially given the emerging evidence that pre-clinical treatment may attenuate early LV remodelling in HCM (17).

The major limitations of this study include its small sample size and the lack of data on hard cardiovascular outcomes. Additionally, the differences in strain values between the groups were small relative to biologic and technique variability. Although the study participants were recruited prospectively, it is unclear if the investigators performing the analysis of CMR-FR were blinded to the participant study groups. For these reasons, it remains uncertain if utilization of parameters such as cTSD will demonstrate any meaningful impact on therapeutic decision making in the future. Furthermore, given the incomplete penetration and variable expressivity of HCM, the ability
to accurately identify those with pre-clinical HCM who are most likely to develop overt disease, cannot be resolved without longitudinal follow-up studies. Lastly, as a post-processing method, FT-CMR may also lack the sensitivity of dedicated CMR strain acquisition methods such as CMR tagging (9). Unlike myocardial tagging, feature tracking is unable to measure mid-wall strain because of the paucity of cardiac MRI features in the mid-wall of the myocardium. The question thus remains as to the most optimal technique to measure myocardial strain in HCM, and ultimately for practical reasons, a balance will need to be struck between the diagnostic accuracy of the ideal strain technique and acceptable acquisition times.

Overall, this study suggests that strain as measured by CMR-FT has the potential to allow additional characterization of subtle abnormalities in myocardial function that appear to be an early manifestation of sarcomere mutations. This may allow identification of early disease and thus facilitate targeting of at-risk individuals in the pre-clinical stages of disease. Further, larger-scale, prospective studies are warranted to further explore the utility of CMR-derived strain in HCM.

Acknowledgments
None.

Footnote
Conflicts of Interest: Dr. Desai is on the steering committee of the HC MR (hypertrophic cardiomyopathy registry) trial sponsored by the National Institutes of Health. He also acknowledges Haslam Family Endowed Chair in Cardiovascular Medicine. Dr. Ramchand has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Ramchand J, Desai MY. Clinical dilemmas in predicting the progression of pre-clinical hypertrophic cardiomyopathy—is MRI strain the solution? Ann Transl Med 2019. doi: 10.21037/atm.2019.07.82