Exploiting Differences in Myocardial Compartments With Native T1 and Extracellular Volume Fraction for the Diagnosis of Hypertrophic Cardiomyopathy

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The detection of hypertrophic cardiomyopathy (HCM) is important. It is the most common genetic cardiomyopathy usually caused by autosomal-dominant mutations in the proteins of the cardiomyocyte sarcomere. (1) The diagnosis carries important implications for the patient and family. Although most people with HCM have normal life expectancy, a minority do not and are prone to heart failure, stroke, and sudden death. HCM is the most common cause of sudden death in young people. Genotyping may help with diagnosis, but the cardiology community requires more robust tools to (1) characterize phenotypes and their stages of evolution and (2) understand the underlying disease processes, particularly as new therapeutic approaches are being considered.

See Article by Hinojar et al

Clinicians often face the challenge of distinguishing HCM from hypertensive heart disease (HHD). This overlap in phenotype creates a diagnostic dilemma. Both exhibit left ventricular hypertrophy with HCM frequently having specific features, such as asymmetrical hypertrophy or other functional and morphological abnormalities (dynamic left ventricular outflow tract obstruction, elongated mitral valve leaflets, aberrant papillary muscle configuration, apical aneurysms, and myocardial crypts). Nevertheless, ascertaining early or morphologically mild HCM may still be difficult.1

In this issue of Circulation: Cardiovascular Imaging, Hinojar et al2 analyze data from the International T1 Multicenter Cardiovascular Magnetic Resonance (CMR) Study and report that myocardial tissue characterization with CMR T1 mapping may help. Tissue characterization with late gadolinium enhancement is familiar, but why go beyond it? Although HCM is fundamentally a cardiomyocyte disease (sarcomere protein mutations), myocardial fibrosis characterized by disproportionate collagen accumulation is a key pathogenic process, associated with systolic and diastolic dysfunction, arrhythmias, capillary rarefaction, and decreased perfusion reserve.3 LGE detects fibrosis, but the technique depends on regional heterogeneity. It cannot depict diffuse interstitial expansion. LGE is a detector of focal fibrosis only. Focal and diffuse fibrosis often coexist in a continuum in HCM and many other cardiomyopathies. Therefore, LGE cannot quantify myocardial fibrosis well, and it is not validated against the histological gold standard of the collagen volume fraction. For example, areas of fibrosis depicted by LGE vary up to 2-fold depending on the thresholding technique used.4 This limitation significantly undermines LGE as a risk stratifier and as a method to quantify diffuse interstitial fibrosis, a promising target for therapy.5

CMR is introducing new techniques that go beyond LGE. Here, the authors used T1 mapping to measure 2 principal parameters: native myocardial T1 (precontrast) and the extracellular volume fraction (ECV) after contrast administration. Compared with healthy volunteers, both native T1 and ECV were normal in HHD, but were elevated in HCM, even in those patients without LGE.2 Of particular interest was the finding by Hinojar et al2 that native T1 was significantly higher in the septum in genotype-positive/phenotype-negative (n=23) participants (P<0.0001), whereas ECV values were not (P=0.49).

What might these findings mean? The link between genetic mutations (of which there are >1400) and overt phenotype in HCM still remains poorly understood. Regardless of the genotype, it is useful to conceptualize myocardial remodeling in terms of its compartments.6 Any increase in myocardial thickness may reflect growth of the cardiomyocyte compartment (eg, cellular hypertrophy or cellular edema), disproportionate expansion of the interstitial compartment and its constituents (eg, fibrosis), or some combination of both. Fibrosis is familiar as a replacement for cardiomyocyte loss in myocardial infarction, but for many diseases, areas of fibrosis positively associate (correlate) with hypertrophy (the hypertrophy triggering the fibrosis or the fibrosis triggering the hypertrophy in compensation). For example, in cardiac amyloidosis, often conceptualized as a purely interstitial infiltrative disease, there is early suggestion that the transthyretin subtype demonstrates triggered cardiomyocyte hypertrophy.7 Interactions between the cardiomyocyte compartment and interstitial compartments remain incompletely understood.

T1-mapping techniques can probe these myocardial compartments. Native T1 signal arises from the entire

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myocardium permitting disease detection if reference values are established (as with all assays). At present, establishing native T1 reference ranges is needed for each particular scanner and software version because small variations in T1-mapping methodology can exert significant influence on normal reference ranges. Native T1 decreases with some diseases (fat infiltration and iron overload) and increases in others (fibrosis, edema, and amyloid). In myocardial fibrosis, the native T1 elevation is likely from the interstitial compartment rather than cardiomyocyte compartment, but not definitively known.

In contradistinction to native T1, ECV detects diseases limited to the interstitium (including myocardial vasculature). ECV exploits the extracellular nature of gadolinium contrast agents. The concentration of contrast in myocardium relative to the concentration in plasma (not whole blood) is a direct measure of the interstitial space after equilibration, as long as contrast agents are not protein-bound. The relative concentrations are derived from the change in relaxivity (ie, 1/T1) for myocardium and whole blood before and after contrast administration and then multiplying the resultant partition coefficient by (1 - hematocrit). The latter term accounts for the displacement of plasma by erythrocytes and enables computation of plasma contrast concentration from the whole-blood measurement from regions of interest measured from the T1 images.

ECV and T1 have their respective limitations. The signal to noise ratio of the biological signal to be detected may be massive in some diseases (iron, Fabry, and amyloid) but smaller in diffuse fibrosis. Small signals are intrinsically harder to detect and more prone to potential biases and difficulties with quality control, particularly between centers. There is some evidence that measurement errors are lower at 1.5T than 3T. Because T1 and ECV measures are ratios, some systematic T1 biases may cancel. However, ECV requires precise T1 measurement over a broader range of values and relies on a second measurement system for the hematocrit (Coulter counter), another potential source of error. ECV also varies slightly with contrast concentration possibly from water exchange effects in and out of cells. Therefore, variations in gadolinium contrast concentration (which relates to choice of contrast timing and dose) can yield slight differences in ECV values, for example, if double-dose or single-dose contrast is used or if time intervals between contrast bolus and post contrast T1 measures vary significantly. Both T1 and ECV can be prone to partial volume error from adjacent tissues (eg, blood) and off resonance, so care must be taken in their measurement.

What might occur in myocardial compartments with HCM, particularly early HCM? The authors demonstrate early native T1 changes. This finding, in part, agrees with previous HCM studies, one measuring circulating peripheral biomarkers of fibrosis (presumably myocardial), and another indicating elevations in myocardial ECV associated with increased pro-brain natriuretic peptide levels and decreased mitral annular E' velocities. The authors did not find these changes in HHD—also concordant with 2 studies where native T1 and ECV only increased in the setting of frank left ventricular hypertrophy, suggesting that cellular hypertrophy may develop without disproportionate fibrosis in early HHD yielding normal ECV. But if fibrosis seems early in HCM, why did native T1 increase alone, without an associated ECV increase? Indeed, ECV seems to yield more robust validation data as a fibrosis metric against the histological gold standard of the collagen volume fraction than native T1. Reviewing the above conceptual framework may provide answers.

Biologically, native T1 could plausibly increase with expansion of the myocyte compartment (edema/cardiomyocyte disarray) without interstitial expansion, or extracellular fibrosis may be balanced by capillary rarefaction. Another possibility is that native T1 has been measured better than ECV. This difference could occur if the particular T1-mapping sequence is better tuned for the long T1 values in native T1, rather than for both long (pre contrast) and short (post contrast) T1 values needed for ECV, or because of other measurement flaws in the ECV approach used. The authors acknowledge limitations in their ECV measures: (1) hematocrit measures were noncontemporary, (2) hematocrit were only available in 34% and imputed in 66% (methodology not described), and (3) variable doses of gadolinium contrast were used at different centers. The discrepant coefficients of variation (expressed as SD/mean) between native T1 and ECV in their control population suggest their findings relate to decreased measurement reliability with ECV. The healthy control native T1 mean was 1044 ms, SD was 18 ms, that is, coefficient of variation = 1.7%, whereas the ECV mean was 23%, SD was 7%, coefficient of variation = 30%. Most papers have healthy populations with the same or lower variability for ECV compared with native T1, suggesting that ECV was not well measured compared with native T1.

So how shall the reader interpret these data? Methodologically, the data emphasize the importance of consistent and standardized approaches for ECV measurement as recommended in the first T1 and ECV-mapping Consensus Statement. Biologically, these data seem broadly supportive of earlier findings in HCM and HHD. A future study might involve patients with 12 to 15 mm wall thicknesses where discerning HCM from HHD can be challenging.

T1 and ECV mapping are coming of age. Meticulous quality control and standardized approaches are still developing. Various T1 approaches are converging and gradually being replaced by consensus, and experts have advocated locked protocols to address some of these issues, but not (yet) specified precisely what these protocols should be. However, the data now seem to exist, and interscanner calibration has begun with 2 global projects using phantoms to measure stability, accuracy, and precision. We congratulate the authors for creating a T1-mapping network and executing one of the first multicenter center T1/ECV studies and generating novel and provocative data, an important achievement. We are cautiously optimistic that native T1 can be an imaging biomarker of HCM to help clinicians distinguish it from HHD, but as the authors rightly claim, prospective studies in large and broad populations are required to validate our findings for widespread use.

Disclosures

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References


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