

# **Automated Non-Contrast Myocardial Tissue Characterization For Hypertrophic Cardiomyopathy – Holy Grail Or False Prophet?**

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Non-invasive cardiovascular imaging is fundamental to diagnosis, surveillance, risk stratification and management of patients with hypertrophic cardiomyopathy (HCM). While transthoracic echocardiography more frequently identifies or confirms the presence of HCM, cardiovascular magnetic resonance (CMR) is increasingly recommended to exclude phenocopies, screen family members, and make decisions concerning implantable cardiac defibrillator (ICD) implantation to prevent sudden cardiac death.

Alongside improved delineation of cardiac structure and left ventricular (LV) myocardial function to measure LV myocardial mass, wall thickness, and systolic-diastolic function, CMR offers the potential to characterize the LV myocardial tissue and thereby identify the presence and extent of underlying disease processes. To date, much of this identification relies on gadolinium-based contrast agent (GBCA) administration to appreciate late gadolinium enhancement (LGE) which can detect extracellular pathology including replacement fibrosis and infarction, necrosis, extracellular edema, microvascular obstruction, hemorrhage and infiltration.

Similar to the established relationship between myocardial scar and arrhythmogenicity in ischemic heart disease, there is evidence that significant myocardial scar observed with LGE portends a poor prognosis in HCM. As a result, international HCM guidelines<sup>1,2</sup> now include recommendations to consider CMR to identify LGE within the hypertrophied LV myocardium to improve risk stratification. Observing >15% of the LV myocardium with LGE portends an increased risk of future sudden cardiac death.

Acquiring and assessing LGE images during CMR has some limitations including requirement for GBCA contrast administration which lengthens the CMR procedure for the patient. The presence of LGE in those with HCM provides important prognostic information

yet may underestimate potentially harmful underlying myocardial pathophysiology. HCM is characterized by diffuse LV myocardial interstitial fibrosis alongside myocardial hypertrophy and myocellular disarray, with islands of denser focal scar present only in more advanced disease. LGE imaging relies on regional heterogeneity in myocardial signal intensity to identify focal fibrosis, but cannot discriminate diffuse fibrosis. Thus correlation of LGE with histological fibrosis is weaker than in ischemic cardiomyopathy where focal infarcts are generally surrounded by relatively unaffected LV myocardium. Also, LGE quantification in those with HCM is highly dependent on the thresholding technique used, making it a less robust tool for risk stratification.<sup>3</sup>

T1 mapping is a CMR technique that provides quantitative pixel-wise measurements regarding LV myocardial tissue composition without the requirement for GBCA with the signal influenced by both myocyte and extracellular interstitial compartments. T1 values are elevated in sarcomeric HCM (including phenotype negative gene carriers), and the use of T1 mapping can discriminate HCM from other hypertrophic phenotypes.<sup>4</sup> Unfortunately, there has been lack of standardization of T1 mapping sequences and thresholds for health and disease commonly overlap. Therefore, the initial promise of T1 mapping has not translated into routine clinical use as an independent diagnostic or prognostic biomarker aside from limited extreme phenotypes (e.g., cardiac amyloidosis, iron deposition and Fabry's disease). T1 map analysis involves manual post-processing to calculate the average T1 in a specific region of interest. While this gives a measure of the fibrosis severity within a myocardial area, it provides little information regarding the affected myocardium volume and reproducibility remains limited.

Over the last five years, automated analysis techniques using artificial intelligence (AI) and machine learning have become more prevalent in cardiovascular research (**Figure 1**). As the era of tracing of regions of interest comes to a close, the resultant improvements include accuracy and precision of AI-contoured quantification of myocardial structure and function.<sup>5</sup> In this issue, Zhang, *et al.*, developed an AI-based deep learning technology ‘Virtual Native Enhancement’ (VNE) from CMR non-contrast T1 maps and cine images, to produce synthetic images that closely resemble conventional LGE scar images.<sup>6</sup> They trained and validated a neural network on the large international multicenter Hypertrophic Cardiomyopathy Registry (HCMR) cohort,<sup>7</sup> demonstrating strong agreement with LGE and better image quality. Furthermore, this new method demonstrated increased sensitivity for detecting relatively mild fibrosis regions, a feature particularly valuable in the context of sarcomeric HCM as it may facilitate earlier diagnosis during family screening or in pre-phenotypic gene carriers. The automated analysis used in VNE is based on the full-width-at-half maximum quantification method and T1 measurements were quality controlled using phantom calibration. Together these advances could further improve measurement standardization, thereby permitting direct comparison between scans acquired at different times or on different scanners – of particular importance for detecting serial imaging changes or combining datasets from different centers for clinical research.

The authors suggest that VNE analysis may obviate the requirement for contrast administration and could be applied across a broad range of cardiac pathologies. The potential advantages of widespread adoption of a non-contrast approach to CMR using automated analysis are clear as GBCA administration has some drawbacks including: (1) GBCA are not well suited for some patient groups including those with severe renal dysfunction, allergies to GBCA, or where there are concerns related to gadolinium

accumulation in the brainstem; (2) GBCAs require intravenous cannulation and physician supervision in case of allergy; and (3) LGE images must be acquired five to 10 minutes after GBCA administration which, when combined with image acquisition, prolongs scan duration. Incorporating VNE imaging as opposed to GBCA-based LGE methods could reduce procedural length and provide faster and more reproducible post processing via automated analysis as observer variability may strongly influence CMR-derived measures such as wall thickness in HCM.<sup>8</sup>

Importantly, there are still areas for future study and points worth highlighting. First, the improved visual image quality with VNE compared with the standard LGE images is unsurprising given that the VNE deep learning generator inputs a co-localized pre-contrast cine image alongside the T1 mapping data. CMR cine images have higher signal to noise than LGE images and significantly higher (approximately 5-fold) temporal resolution. This means the cardiac motion blurring seen in the longer LGE acquisitions is not found on the VNE (cine-based) images. In addition, as the authors themselves acknowledge, there needs to be comparison of VNE with contemporary improved LGE techniques. The sequences used for LGE identification in HCM have now been replaced by motion corrected averaged sequences in many centers. Hence, some observed LGE image artifacts would not be found using newer sequences. Similarly, applying VNE to non-hypertrophic phenotypes may be more challenging; further model training is likely required to detect small subendocardial scars in thinned myocardium.

Second, although replacing LGE imaging with VNE imaging may reduce scan duration, this potential reduction may be less pronounced than suggested by the authors. Individual sequence acquisition times for T1 (required for VNE) and LGE are broadly similar, and

although LGE images are acquired ten minutes following contrast administration, most centers use that time interval to acquire the short axis cine images. Currently almost all CMR protocols include whole heart coverage for myocardial tissue characterization using LGE, including three long axis images and a 8-12 image short axis stack. The author's current study acquired only three short axis T1 maps, hence should VNE replace LGE imaging routinely in clinical practice, the protocol would need to be expanded significantly to attain equivalent whole heart imaging.

Finally, it is important to remember that T1 mapping (and hence VNE) and LGE CMR are not imaging equivalent myocardial disease processes, and precise correlation between the two techniques should not be expected. Given that T1 mapping (and hence VNE) derives signal not only from the interstitium (enabling measurement diffuse fibrosis) but also from the cardiac myocytes, it is likely to be able to detect acute myocardial injury including intracellular edema and inflammation with greater sensitivity than LGE imaging. For many cardiomyopathies, including HCM, there is increasing recognition that inflammation plays a key role in the underlying pathophysiology,<sup>9</sup> and that this can be acute, chronic or relapsing-remitting and likely impacts prognosis. The holy grail in HCM management is to transition towards stratifying patients by myocardial biology. This will provide personalized targeted therapies based not on clinical scenario (heart failure, outflow tract obstruction, arrhythmia) but on the underlying pathophysiology (myocyte hypertrophy, inflammation, fibrosis). While the authors focus on replacing LGE imaging with VNE, further post processing of VNE and LGE images together to identify and quantify differences in signals between the two sequences may offer additional information related to the myocytes and intracellular disease processes including edema. Indeed, with the advent of multiparametric mapping and MR

fingerprinting, VNE has the potential to become a generative imaging technique providing novel insights into underlying myocardial biology.

In summary, CMR using LGE imaging has been transformative for non-invasive myocardial tissue characterization thereby helping diagnose and risk stratify cardiomyopathies including HCM. Zhang, *et al.*, have provided valuable evidence that applying deep learning automated analysis techniques to standard non-contrast CMR sequences generates synthetic LGE images that correlate strongly with conventional LGE images, demonstrating their clinical utility in HCM. More importantly, the VNE technique has the potential to improve feasibility and reduce overall CMR procedural time, which should further increase demand of this currently under-utilized modality. The first major test for VNE will be its performance as a prognostic marker within the HCMR Study itself – we await the outcome with much anticipation.



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**Figure 1. Timeline of Cardiovascular Magnetic Resonance (CMR) Biomarkers.** A timeline depicts the evolution of CMR biomarkers, with key milestones indicated including the new potential role of VNE.<sup>6</sup> A case example of a 26 year old female with asymmetric

HCM is shown in short-axis (left image) and 4 chamber views (right image) demonstrating cine images with increased wall thickness of 3.7 cm in the inferoseptal wall (green boxes), LGE images with extensive patchy LV enhancement in areas of hypertrophy (blue boxes), and diffusely elevated T1 values on T1 mapping (yellow boxes). *Abbreviations: American Heart Association (AHA), artificial intelligence (AI), extracellular volume (ECV), gadolinium-based contrast agent (GBCA), hypertrophic cardiomyopathy (HCM), Hypertrophic Cardiomyopathy Registry (HCMR), implantable cardioverter defibrillator (ICD), late gadolinium enhancement (LGE), magnetic resonance imaging (MRI), virtual native enhancement (VNE)*