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Phenotyping of Cardiac Amyloidosis: Advancing from Macro to Micro?

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Amyloidosis is the exemplar restrictive cardiomyopathy in which mis-folded proteins deposit as amyloid fibrils in the interstitial space of the myocardium.[1] The most common types of cardiac amyloidosis (CA) are transthyretin (ATTR) amyloidosis and light chain amyloidosis (AL), due to misfolding of the amyloidogenic transthyretin protein in the former or immunoglobulin light chains in the setting of a plasma cell dyscrasia in the latter. Cardiac amyloidosis manifests as heart failure from biventricular myocardial thickening, biatrial enlargement, diastolic dysfunction and, in later stages, systolic dysfunction. Because there are no useful animal models of cardiac amyloidosis, much of our knowledge about this disease phenotype has been gained through cardiac magnetic resonance (CMR), echocardiography and radionuclide imaging.

A major focus of imaging studies of CA has been to distinguish left ventricular (LV) thickening of amyloid infiltration from left ventricular myocyte hypertrophy of hypertrophic cardiomyopathy, HCM or hypertensive heart disease. Cardiac structural and functional phenotype by echocardiography, including global longitudinal strain, cannot definitively distinguish LV hypertrophy from amyloidosis.[2] The identification, initially by Dr. Pennell's group[3], of a characteristic pattern of diffuse subendocardial or transmural late gadolinium enhancement (LGE) coupled with abnormal myocardial and blood-pool gadolinium kinetics that accurately distinguished amyloidosis from other causes of LV wall thickening brought CMR to the forefront in this disease. T1 parametric mapping before after gadolinium

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injection allows calculation of the extracellular volume (ECV), which provides a unique insight into the interstitial space. ECV, as quantitative marker, is useful for assessing response to therapy.[4] ECV values in advanced CA are generally far higher than in other etiologies of cardiomyopathy, but in the early stages CA cannot be distinguished from HCM by this modality.[5] Cardiac molecular phenotype imaged by ^{99m}Tc- bone-avid tracers[6] or by targeted ^{18}F-labeled (florbetapir,[7] flutemetamol, florbetaben) or ^{11}C-labeled (Pittsburgh-B compound) amyloid tracers provides the most specific tissue signal for amyloid fibrils.[1, 2]

In the current issue of *Circulation Cardiovascular Imaging*, Pennell et al.[8] propose another innovative CMR marker based on diffusion tensor cardiac magnetic resonance imaging (DT-CMR) to micro-phenotype myocardial structure and function. Before delving into the specific findings of this study, we provide a brief overview of DT-CMR technique and myocardial microarchitectural changes in amyloidosis and HCM.

Diffusion-weighted magnetic resonance imaging (DWI) is based on using bipolar magnetic field gradient pulses in a MR pulse sequence to produce image contrast that is proportional to the diffusional motion of water within tissues.[9] Diffusion tensor imaging (DTI) is derived from modeling of diffusion weighted images acquired for diffusion encodings in three orthogonal spatial directions. In bulk water diffusion is isotropic, but in tissue its architecture and structure result in diffusion anisotropy, making DTI a promising tool to study in vivo tissue microarchitecture and its integrity. Some of the key metrics derived from DT-MR that characterize myocardial structural integrity and organization include mean diffusivity (MD), fractional anisotropy (FA) and eigenvector angle (EA).[9] MD reflects the freedom of water diffusion within the myocardium. FA is a scalar value between 0 and 1; a value of zero means that diffusion is isotropic, i.e., it is unrestricted (or equally restricted) in all directions. EA primarily defines sheetlet orientation, as described. The primary helical arrangement of cardiomyocytes through the depth of the LV wall can be interrogated and quantified as the helix angle (HA). The secondary organization of cardiomyocytes consists of laminar microstructures, termed sheetlets, 5 to 10 cardiomyocytes thick, which reorient during left ventricular thickening. This reorganization can be quantified by changes in sheetlet orientation,[10–12] the components of which are the first eigenvector angle (E1A), an index of mean intravoxel HA, and the secondary eigenvector angle (E2A), an index of mean intravoxel sheetlet angle.[10]

Characterization of tissue microstructural features using DTI is not a novel concept; it was first described over 25 years ago and most of the work to date has been in neuroimaging. Application of DTI to cardiac imaging (DT-CMR) is relatively novel. DT-CMR has not, until now, been studied or considered for clinical adoption because of several technical challenges. These are listed below and summarized from a comprehensive review article by Basser and Pierpaoli in 1996.[9] DWI has low resolution. Low signal to noise ratio of DWI limits reproducibility of the method, although higher magnetic field strength improves the signal, and stronger MR gradient systems facility diffusion encoding. DWI is very susceptible to bulk motion of tissue including cardiac and respiratory motion of the heart, and rapid imaging sequences are preferred. Eddy current distortions may cause image distortions and misregistration between successive images. DWI images must be modeled in order to generate DTI, and inaccurate DWI can result in propagation of errors into DTI,

FA, and MD.[9] Some of these limitations may be overcome by novel and rapid imaging sequences, advances in image reconstruction from more sparsely sampled images, and potentially by machine learning methods. The current innovative study comes from a team with extensive expertise in cardiac DT-CMR technique development who have addressed some of the biggest limitations in this area.[10] Their results imply that DT-CMR offers the potential to provide unique insights into myocardial microstructure and cardiomyocyte organization.

Myocardial architecture is characteristically and distinctly altered in CA and HCM. Amyloidosis is typified by interstitial and peri-and intra-arterial amyloid infiltration, with amyloid accumulating around individual myocytes (pericellular pattern), in clumps (nodular pattern), or a combination of the two.[13] Myocardial deposition is initially nonuniform and patchy, tending to involve the subendocardial and mid-wall regions, but progresses to diffuse ventricular and transmural myocardial amyloid infiltration in advanced stages. HCM, on the other hand, is characterized by cardiomyocyte disarray with loss of normal parallel alignment, with the degree related to disease severity, leading to a swirling appearance of the myocardial architecture and interstitial fibrosis.[14] In early disease stages, heterogeneity of amyloid deposition in CA and disarray and fibrosis in HCM may be present. However, in advanced disease, myocardial histological patterns and microarchitectural changes in CA and HCM are distinct and make them excellent prototypes for evaluation with DT-CMR imaging.

In the current study, Pennell et al. evaluated DT-CMR in systole and diastole, and derived MD, FA and sheetlet orientation (E2A) in 20 subjects with CA (10 AL and 10 ATTR), 11 with hypertrophic cardiomyopathy (HCM), and 10 control subjects to assess the microstructural changes in CA and identify the potential role of DT-CMR in differentiating CA from HCM. Patients had advanced disease with median wall thickness 18 mm, IQR 15–21 mm in CA cohort and 21 mm (IQR 19–23 mm) in HCM cohort. MD was elevated and FA reduced in CA compared with both controls and HCM ($p<0.001$), and these changes in FA and MD were co-located with amyloid burden as measured by ECV. MD was directly correlated with ECV ($r=0.69$, $p=0.004$) and FA was inversely correlated with circumferential strain ($r=0.65$, $p=0.02$), the latter relationship reflecting the interaction of disrupted microstructural organization on gross myocardial function. In this study, diastolic helix angle gradient (HAG) in degrees per percentage wall thickness did not distinguish CA from HCM or controls throughout that cardiac cycle. Furthermore, the authors postulate that increasing amyloid burden causes greater limitation of sheetlet relaxation based on their finding of a strong correlation between diastolic E2A and ECV (a marker of amyloid burden) in ATTR, and that the lack of significant correlation with ECV in AL may reflect a different mechanism of amyloid infiltration on sheetlet impairment in AL. Given the small number of patients in this pilot study, however, it is premature to conclude that any differences between the AL and ATTR patients represent different pathological mechanisms.

DT-CMR, does not require gadolinium contrast, and MD (and FA) is highly specific (91%) and moderately sensitive (80% sensitive) to identify CA; it can therefore aid in distinguishing CA from other hypertrophic conditions when gadolinium use is contraindicated. Limitations of this study include its small sample size, the focus on

novel metrics without evaluation of incremental added value of these novel measures over existing clinical CMR metrics, the lack of reporting on reproducibility and image quality limitations from motion artifacts and limited signal. If, indeed, the reproducibility of DT-CMR metrics is validated, DT-CMR derived MD, FA, and E2A may serve as promising new investigational markers to monitor amyloid burden longitudinally, especially in patients with contraindication for gadolinium use. The need for custom-built software for modeling DTI currently precludes more widespread clinical and research application of this technique. Importantly, whether microstructural and functional phenotyping provides any added value to molecular phenotyping by targeted amyloid tracers remains to be determined.

Nevertheless, we congratulate Pennell et al. on this well-designed pilot study of the potential of DTI-CMR to microphenotype cardiac amyloidosis. The authors report several notable findings. First, they demonstrated feasibility of this challenging technique DT-MRI in cardiac application. Second, they showed that diffusion markers of MA and FA effectively discriminated CA from HCM. Finally, they showed that diastolic sheetlet orientation markers (E2A) distinguished CA from controls. Their study provides the foundation for future studies to measure DTI-CMR reproducibility, develop simpler and automated modeling methods to compute DTI from DWI, demonstrate incremental value to existing imaging biomarkers, and more. Whether micro-phenotyping is an advance over macro-phenotyping and molecular phenotyping only time and more studies will tell.

Conflicts of Interest

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