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Assessment of Myocardial Microstructural Dynamics by In Vivo Diffusion Tensor Cardiac Magnetic Resonance

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ABSTRACT

BACKGROUND Cardiomyocytes are organized in microstructures termed sheetlets that reorientate during left ventricular thickening. Diffusion tensor cardiac magnetic resonance (DT-CMR) may enable noninvasive interrogation of in vivo cardiac microstructural dynamics. Dilated cardiomyopathy (DCM) is a condition of abnormal myocardium with unknown sheetlet function.

OBJECTIVES This study sought to validate in vivo DT-CMR measures of cardiac microstructure against histology, characterize microstructural dynamics during left ventricular wall thickening, and apply the technique in hypertrophic cardiomyopathy (HCM) and DCM.

METHODS In vivo DT-CMR was acquired throughout the cardiac cycle in healthy swine, followed by in situ and ex vivo DT-CMR, then validated against histology. In vivo DT-CMR was performed in 19 control subjects, 19 DCM, and 13 HCM patients.

RESULTS In swine, a DT-CMR index of sheetlet reorientation (E2A) changed substantially (E2A mobility ~46°). E2A changes correlated with wall thickness changes (in vivo $r^2 = 0.75$; in situ $r^2 = 0.89$), were consistently observed under all experimental conditions, and accorded closely with histological analyses in both relaxed and contracted states. The potential contribution of cyclical strain effects to in vivo E2A was ~17%. In healthy human control subjects, E2A increased from diastole (18°) to systole (65°; $p < 0.001$; E2A mobility = 45°). HCM patients showed significantly greater E2A in diastole than control subjects did (48°; $p < 0.001$) with impaired E2A mobility (23°; $p < 0.001$). In DCM, E2A was similar to control subjects in diastole, but systolic values were markedly lower (40°; $p < 0.001$) with impaired E2A mobility (20°; $p < 0.001$).

CONCLUSIONS Myocardial microstructure dynamics can be characterized by in vivo DT-CMR. Sheetlet function was abnormal in DCM with altered systolic conformation and reduced mobility, contrasting with HCM, which showed reduced mobility with altered diastolic conformation. These novel insights significantly improve understanding of contractile dysfunction at a level of noninvasive interrogation not previously available in humans. (J Am Coll Cardiol 2017;69:661–76) Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

DCM = dilated cardiomyopathy

DT = diffusion tensor

E1A = primary diffusion tensor eigenvector angle

E1AR = E1 angle range

E2A = secondary diffusion tensor eigenvector angle

EF = ejection fraction

HA = helix angle

HAR = helix angle range

HCM = hypertrophic cardiomyopathy

IQR = interquartile range

LV = left ventricle

SA = sheetlet angle

WT = wall thickness

The microstructure of left ventricular (LV) compact myocardium in humans and other mammals consists of a continuously branching syncytium of cardiomyocytes embedded in a predominantly collagen matrix. The primary helical arrangement of cardiomyocytes through the depth of the LV wall (1,2) (**Figures 1A and 1B**) can be quantified by the helix angle (HA) (3,4). LV contraction entails both longitudinal and circumferential shortening of the ventricle (~10% to 25%, depending on direction and depth) accompanied by radial wall thickening (>35%), together with twisting of the apex relative to the base (5). Cardiomyocytes, the heart's fundamental contractile element, individually shorten by only ~15% and thicken by only ~8% during systole (5). Such conformational changes in cardiomyocytes in a helical arrangement alone are insufficient to explain the observed magnitude of systolic wall thickening (5). The secondary organization of cardiomyocytes consists of laminar microstructures, 5 to 10 cardiomyocytes thick, termed sheetlets (3,6). Reorientation of these sheetlets (7,8), quantified by changes in sheetlet angle (SA), has been proposed as the predominant mechanism associated with macroscopic LV wall thickening in vivo (9–12) (**Figures 1C to 1J**, Online Video 1).

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Cardiomyopathies affect both myocardial structure and function in the absence of coronary artery disease or abnormal loading conditions (13,14). In hypertrophic cardiomyopathy (HCM), there is an annual incidence of cardiovascular death of 1% to 2% due to heart failure and sudden cardiac death from arrhythmias (15). In dilated cardiomyopathy (DCM), 5-year mortality is up to 20% with a 14% risk of sudden or aborted cardiac death (16,17). Consequently, efforts are underway to better characterize these patient populations and direct appropriate therapies to those at risk. Cardiac magnetic resonance (CMR) is important to this process through improved phenotyping (18,19) and tissue characterization, particularly the detection and quantification of fibrosis through late gadolinium enhancement imaging (20,21).

Diffusion tensor (DT)-CMR potentially provides a novel approach for phenotyping through noninvasive interrogation of the 3-dimensional heart microarchitecture (22,23). In DT-CMR, the primary eigenvector (E1) corresponds to the local cardiomyocyte long-axis orientation, whereas the secondary eigenvector (E2) reportedly corresponds to the local within-sheetlet cross-cardiomyocyte orientation (6,24–34). The angle of E1 relative to the local wall tangent plane (E1A) is an index of mean intravoxel HA, and the angle of E2 (E2A) is an index of mean intravoxel SA (6,28) (Online Appendix). DT-CMR has been used to demonstrate the HA architecture in the normal beating heart (25,27) and in different pathological conditions (28,29), supported by studies validating ex vivo DT-CMR against histology (31–33). DT-CMR data supporting reorientation of laminar microstructures at different phases of the cardiac cycle have been reported in healthy rodent hearts imaged ex vivo in either contracted or relaxed states, with paired histology (6,34), as well as in vivo in healthy volunteers (30,35,36). Abnormal sheetlet dynamics have been demonstrated in dyssynchronous canine hearts (37,38) and in dystrophic rodent hearts (39) imaged ex vivo with paired histology.

In previous work, we implemented robust quantitative in vivo DT-CMR and confirmed its reproducibility in healthy subjects (40) and in HCM (41). We reported E2A changes from systole to diastole, which we hypothesized represented dynamic rearrangement of sheetlets in healthy subjects, as well as E2A changes in HCM, consistent with systolic hypercontraction and attenuated diastolic relaxation (28). However, the in vivo DT-CMR technique used encoded myocardial diffusion over an entire cardiac cycle, and so the influence of tissue deformation on the diffusion measurements has remained unclear (5,28,30,42).

To help understand the relationship of these in vivo findings to the actual underlying tissue microstructure, our study objectives included comprehensive validation of in vivo DT-CMR measures of cardiac microstructure against histology,

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