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EDITORIAL COMMENT

# Diffusion Tensor CMR

## A Novel Approach for Evaluation of Myocardial Regeneration*

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Multiple noninvasive imaging approaches have been proposed for the evaluation of the acute and chronic structural and physiological improvements following therapy directed at myocardial regeneration after myocardial infarction (MI) (1). In some instances, targeted molecular imaging has been applied in combination with viability and functional imaging to detect early molecular or cellular events associated with regenerative therapy (2). Most of the imaging approaches have focused on the evaluation of improvements in regional or global myocardial mechanical function. However, following MI, there are complex structural changes that occur that affect regional myocardial deformation. The left ventricle is a 3-dimensional structure that is composed of myocardial fibers interconnected with a dense collagen weave, which courses in different directions forming a helical structure. The myofibers change their angle in the left ventricle from the epicardial surface to the endocardial surface, and these cardiac fibers are organized into cohesive sheets with surface orientation varying throughout the ventricles. This complex myocardial structure facilitates a coordinated and efficient pattern of ventricular contraction, which can be significantly disrupted following MI within the infarct region, peri-infarct region, and remote myocardium. These changes in structure and regional mechanics are responsible for the adverse left ventricular remodeling. The goal of regenerative therapy is to optimally restore the injured and remote myocardial structure and function.

Invasive and noninvasive approaches have demonstrated that there is an epicardial to endocardial gradient in radial and circumferential strain throughout the ventricle. Increases in endocardial strain are associated with increases in cross-fiber strains, and radial-longitudinal and radial fiber shears in the endocardium. The changes in fiber and cross-fiber strain have been estimated by incorporating models of fiber architecture to magnetic resonance (MR)–derived strains. These early MR studies supported the previous theories that myocardial deformation is critically dependent on sliding between myocardial fibers (3). As mentioned in the previous text, myocardial infarction is characterized by marked changes in the fiber structure within the infarct area as well as changes in the peri-infarct and remote regions of the heart (4,5). Diffusion tensor cardiac magnetic resonance (DT-CMR) has the potential to evaluate the regeneration of myofiber structure following regenerative therapy and to help guide new treatment strategies.

The technique of DT-CMR is based on water diffusion in the intramyocellular space, as well as the intravascular and extravascular space. Therefore, the measure of diffusion with DT-CMR reflects all 3 compartments along with the microstructure of the heart. Some advanced techniques have allowed for separation of these compartments ex vivo, although these approaches have not been translated to the in vivo setting. (6)

The derivation of diffusion tensors requires a minimum of 6 linearly independent diffusion-encoding directions; however, for in vivo applications in the heart, up to 16 diffusion-encoding directions are performed with incorporation of

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several averages to improve the signal-to-noise ratio (SNR). Due to the complex motions of the heart, spatiotemporal registration is required to avoid partial volume artifacts.

Several relevant indexes can be derived from DT-CMR, including mean diffusivity, fractional anisotropy, myofiber helix angle, and myofiber sheet angle. Following myocardial infarction, there is myocellular injury, inflammation, activation of matrix metalloproteinases, and disruption of the fiber architecture, all of which result in increased free water movement within the infarct territory. This results in an increase in the mean diffusivity and a decrease in fractional anisotropy, which reflects alterations in myofiber structure. The changes in the infarct area have also been shown to result in changes in the fiber orientation in the remote areas of the heart, as reflected by a change in the myofiber helix angle (4).

Initial DT-CMR studies involved long ex vivo pulsed gradient spin-echo imaging sequences that allowed for careful characterization of the fiber structure within the heart. Sequences that were used for ex vivo imaging were not applicable for in vivo imaging due to their intrinsic motion sensitivity. Therefore, 3 primary strategies have been applied to address this issue (7). All approaches require breath-hold or respiratory-compensation (by registration or by navigator-gating), and electrocardiogram triggering in subjects with stable heart rates. The first and most widely applied is a dual-gated stimulated echo approach. This approach requires that the heart remains very static within the acquisition, and toward this goal, this approach uses 2 heartbeats for each diffusion encoding, with encoding in one and then decoding and imaging in the next. Any motion artifacts are reduced due to the halved encoding/decoding time. The second involves a velocity (M1) or velocity and acceleration (M2) compensated pulsed gradient spin-echo approach. The M1 compensated approach employs bipolar gradients, which results in longer echo times and lower SNR. This approach has been translated to clinical imaging with the advent of higher gradient strengths on 3-T magnets. The M2 compensation methods involve more complex gradient schemes (8,9). The study by Nguyen et al. (10) in this issue of *JACC: Basic to Translational Science* involves a breath-hold approach that compensates for M2 and employs a novel readout using a segmented balanced steady-state free precession sequence instead of echo-planar imaging. A third approach involves free-breathing, and an optimal time-window approach, with the use of principal component analysis for post-processing filtering to minimize the effects of motion (11). Bulk motion is corrected for by using nonrigid registration. Then, principal component analysis is used to improve SNR, and a temporal maximum intensity projection approach is applied to recover signal intensity. To compensate for respiratory motion, these DT-CMR methods commonly use either multiple breath-holds, as in the current study, or navigator-gating methods or free-breathing with registration.

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Although DT-CMR in the heart was first introduced over 20 years ago, the clinical translation of this approach has been challenging, and at first was only robust and reliable when performed ex vivo (12). By encoding the diffusion contrast in one heartbeat, and decoding it in the subsequent heartbeat (13), or by designing gradients with first (M1) (14) and/or second moment (M2) nulling (9), the artifacts of cardiac motion were reduced. These breakthroughs, further complemented by the availability of MR imaging systems with stronger gradients, high field strengths, multichannel receiver coils, dedicated high-order shimming, and acceleration techniques, has generated renewed interest (15). The unique strength of DT-CMR imaging is the ability to define the complex fiber architecture in the myocardium (7). However, limitations of DT-CMR remain for defining fiber structure in the setting of infarction and fiber disarray, or in areas where there is fiber crossing in different directions.

In the study by Nguyen et al. (10), DT-CMR provides unique information regarding the complex structural changes that occur following MI and those associated with regeneration therapy. The investigators performed DT-CMR in pigs 1 month after percutaneous balloon occlusion of the left anterior descending artery prior to intramyocardial catheter-based delivery of vehicle or CDCexo therapy to the peri-infarct region using electroanatomical mapping. Follow-up DT-CMR was performed again 1 month following the intervention. The study by Nguyen et al. (10) employed second-order motion compensated (M2), spin-echo B1-resistant (i.e., insensitive to B1 amplitude inhomogeneity), diffusion-prepared electrocardiogram-gated, cine-segmented, balanced steady-state free precession in the evaluation of therapeutic benefit of intramyocardial delivery of CDCexo to the peri-infarct area. They first demonstrate interscan reproducibility of this DT-CMR approach for determination of helical angle transmurality (HAT). They use this MR index of fiber architecture as a unique marker of post-MI remodeling in a remote location at the midventricular level. CDCexo therapy was associated with a reduction in scar size, preservation of left ventricular ejection

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fraction (LVEF), and no change in fiber architecture, whereas control pigs demonstrated no change in scar size, a decrease in LVEF, and a decrease in HAT. They also report a relationship between the change in HAT and the change in LVEF and scar size. The reduction in HAT reflects a loss of transmural variation in fiber angle in the remote area of heart. They infer a direct relationship between changes in fiber architecture and regional function, although they did not assess or demonstrate changes in regional myocardial function following their therapeutic intervention. In addition, the analysis of fiber architecture was restricted to the end-diastolic phase of the cardiac cycle, although fiber angle has been shown to change over the cardiac cycle (16).

Although DT-CMR may offer some important advantages in the evaluation of structural remodeling post-regenerative therapy, the study has several notable limitations. Delivery of the CDCexo therapy was via an electroanatomic mapping system to the infarct border region, which provides limited resolution for defining the peri-infarct region. Although late gadolinium enhancement was used to define scar size, it was not used to guide therapy. A potentially alternative approach would be to guide the intramyocardial delivery of therapy based on an MR map of the infarct and peri-infarct region. The additional structural MR indexes could be incorporated in the interventional suite by registering the MR images with a volumetric cone-beam computed tomography image acquired at the time of intervention. This alternative approach might provide better correspondence between the guided intramyocardial delivery and changes in fiber structure and function. Verification that therapy was specifically delivered to the targeted infarct border region would have further strengthened their observations. They acknowledge that DT-CMR was not adequate to evaluate the complex changes in the collagen architecture within the scar, and so all analyses are restricted to a single remote location at the midventricular level. They could have validated the fiber structure defined by their in vivo DT-CMR imaging by additional high-resolution ex vivo DT-CMR imaging of the entire heart. Future studies should relate the changes in regional fiber orientation to changes in regional function. Other investigators have used the information regarding fiber architecture to translate the myocardial deformations into the fiber domain to evaluate changes in fiber strain and cross-fiber strain (3).

DT-CMR has the potential to evaluate the regeneration of myofiber structure following regenerative therapy along with structural changes in the remote regions associated with remodeling. This noninvasive contrast free imaging approach may help guide new treatment strategies for the prevention of post-MI remodeling. However, DT-CMR imaging of the heart post-MI is challenging, particularly in this patient population that has underlying arrhythmias and may have difficulty with breath-holding. This approach will be facilitated by newer imaging systems with stronger gradients, and the development of novel acquisition sequences that allow for imaging with free breathing. Mekkaoui et al. (15) recently reported the feasibility of diffusion tractography of the entire left ventricle using free-breathing accelerated simultaneous multisection imaging in normal volunteers, and generated images that were quantitatively similar to those acquired with breath-hold techniques. Such advances may someday lead to in vivo DT-CMR imaging of the left atrium.

Future applications of this MR methodology should be incorporated with molecular imaging that could be acquired on newer hybrid PET/MR imaging systems. DT-CMR should also be integrated with conventional strain imaging to translate regional myocardial strains into fiber and cross-fiber directions. The integration of these methodologies will improve our fundamental understanding of normal myocardial mechanics; the changes that occur following MI in association with remodeling; and the effects of delivery of novel therapeutics, whether that be CDCexo or delivery of stem cells, gene therapy, or bioresponsive therapeutic hydrogels.

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